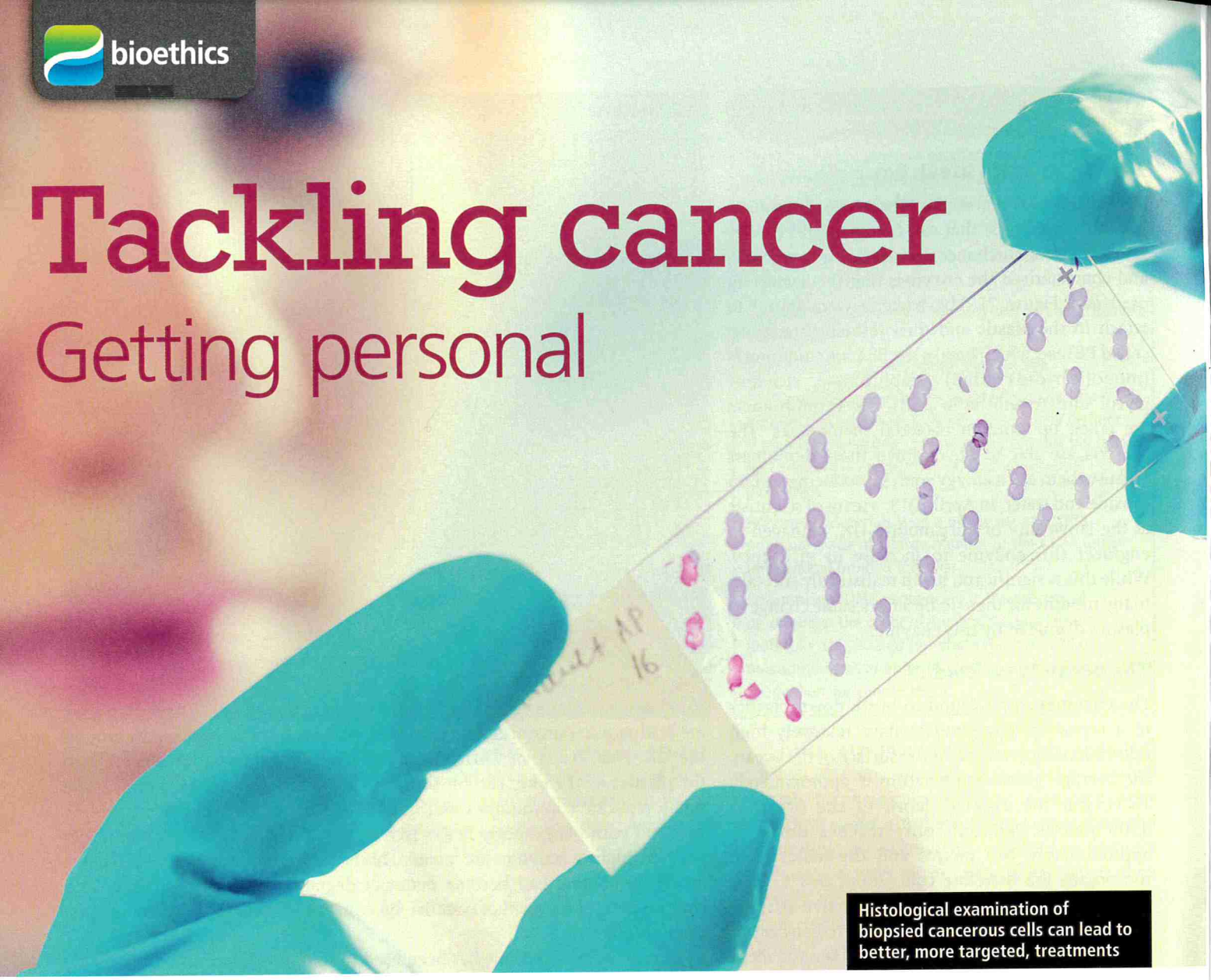
bioethics

Tackling cancer

Getting personal



Histological examination of biopsied cancerous cells can lead to better, more targeted, treatments

Bioethicist Chris Willmott explains that understanding the diversity of cancer is crucial to the application of personalised treatments, tailored to challenging the characteristics of the specific cancer

Current estimates suggest that half of the UK population will be diagnosed with cancer at some point in their lives. Cancers can vary considerably in both the underlying cause (the aetiology) and the likelihood of recovery (the prognosis).

Key words

Cancer
Genomics
Next generation sequencing
Oncogene
Personalised medicine

DNA damage

All cancers involve a loss of control of cell division and an accumulation of genetic errors. Although some inherited mutations make it more likely to develop cancer, these are relatively uncommon. Instead, it is DNA damage in the tissues of the body over the course of our lives that has the most important role in cancer development.

Mutations in two classes of gene are especially significant. The first are oncogenes. These genes encode proteins normally involved in promoting cell division. In cancers, one or more genetic change leaves oncogenes permanently switched on. The second class of genes are tumour suppressors. The proteins encoded by these genes normally act as gatekeepers. Mutations that stop tumour suppressors working allow for unrestrained cell division.

Mutations

Genetic changes can result from exposure to environmental factors, including ultraviolet radiation and **carcinogenic** substances — for example, those found in cigarette smoke. They can also arise from mistakes made during DNA replication. Some of those changes play a major role in cancer development while others have little or no effect. As we try to understand more about cancers, we need to be able to distinguish between the significant mutations that cause the cancer, known as driver mutations, and those that are less important, referred to as passenger mutations.

Changes to the DNA associated with development of cancer can take a variety of forms. There may be alteration of the sequence of a gene, and the corresponding amino acid sequence of the protein it encodes, as a result of base substitutions (a single nucleotide polymorphism), or by

insertion or deletion of larger sections of DNA ('indels'). Alternatively, there may be more radical structural changes, with whole chunks of DNA swapped between different chromosomes (translocations).

Other cancers are associated not so much with a change in the DNA sequence of the gene itself but a change in the amount of protein being produced. This in turn may be due to having more copies of the gene within the chromosomes (copy number alterations) or higher levels of expression of the existing genes.

The power of sequencing

Our understanding of cancers has been progressed by the development of new technologies that allow us to rapidly acquire the DNA sequence of entire genomes. Although the original human genome project, first drafted in 2001, was an amazing achievement, it took over 10 years to complete and cost more than $2 billion. To make **genomics** useful for personalising cancer diagnosis and treatment, a radically different, and very much cheaper, approach was needed.

Creative minds have come up with several new methods to sequence DNA more quickly, and for a tiny fraction of the cost. By 2010, it was possible to sequence DNA 50 000 times faster than it had been a decade earlier, and the latest methods are faster still. These techniques, sometimes collectively referred to as 'next generation sequencing' (NGS) share the fact that they achieve 'massively parallel sequencing', allowing millions of sequencing reactions to be carried out simultaneously.

Comparison is the key

Crucially for cancer genomics the faster and cheaper methods allow us to make three different sorts of comparison.

- Comparing the DNA sequence in tumour cells with that of normal cells from the same patient reveals specific changes that have happened as the cancer developed.
- Comparing variations within a tumour as it develops. These can be changes over time, e.g. as the cancer becomes a more **malignant** form, or differences — heterogeneity — between cells within a particular tumour. This is why taking only one **biopsy** sample may provide an inaccurate or incomplete picture of the genetic alterations that have been taking place.
- Comparing mutations in the 'same' cancer in different patients lets you see whether the underlying causes really are identical. If you looked at the DNA in only one cancerous cell, you would not be able to tell which changes were crucial driver mutations and which were passengers. But if you look at the DNA in hundreds of cells with the same cancerous morphology, you can start to see which changes are shared across a wide variety of the cancers tested.

There will be distinct patterns of mutations — many will have the same genetic alterations, but others share a different set of characteristic changes. It is this third type of comparison that offers the greatest potential for cancer treatments to become more tailored to the individual patient.

When the 'same' cancers are actually different

Until the advent of genomics, people generally described cancers based on the tissue within which the disease was found, for example bowel cancer or brain cancer. Doctors might also talk about the type of cell that had become mutated (e.g. **carcinomas** originate in epithelial cells, sarcomas develop in connective tissues, and leukaemias affect leukocytes). Discussing the tissue and the type of cell involved remains useful, but genomics allows a closer look at the underlying cause of the cancer in a particular patient.

It has long been known that some patients respond well to a specific drug, while others do not. A major part of this different response stems from the fact that cancers that appear similar may actually have quite different genetic changes.

Breast cancer, for example, can be diagnosed histologically, by examining biopsied cells under a microscope. Traditional treatment options were then a combination of surgery, chemotherapy and/or radiotherapy. But now, we can offer more refined treatments.

Even before genomics had become established, it was known from genetic studies that breast carcinoma was associated with **upregulation** of two proteins — oestrogen receptor and human epidermal growth factor receptor 2 (HER2). Patients with high blood concentrations of the latter, roughly a quarter of all breast cancers, are said to be HER2-positive and this was associated with poor survival rates.

Trastuzumab, better known as Herceptin, is a **monoclonal antibody** that targets the HER2 protein. This drug significantly improves outcomes but only for patients overproducing HER2. 'HER2-negative' women do not benefit from Herceptin. This was among the earliest examples of tailored treatment based on genetic information.

NGS allows deeper analysis of the molecular causes of cancers and more specific classification of disease types. There are at least ten subtypes of breast cancer, with associated differences in prognosis and responsiveness to particular therapies. Armed with this information, doctors can pick the most appropriate treatment for the individual.

Terms explained

Biopsy A sample taken from a patient to look for the presence, cause or extent of a disease.

Carcinogenic A substance or agent that has the potential to cause cancer.

Carcinoma A cancer originating from epithelial cells in the skin or the lining of an internal organ.

Genomics Broadly, the study of the structure and function of the genome, but particularly used to mean sequencing of multiple genes in an organism simultaneously.

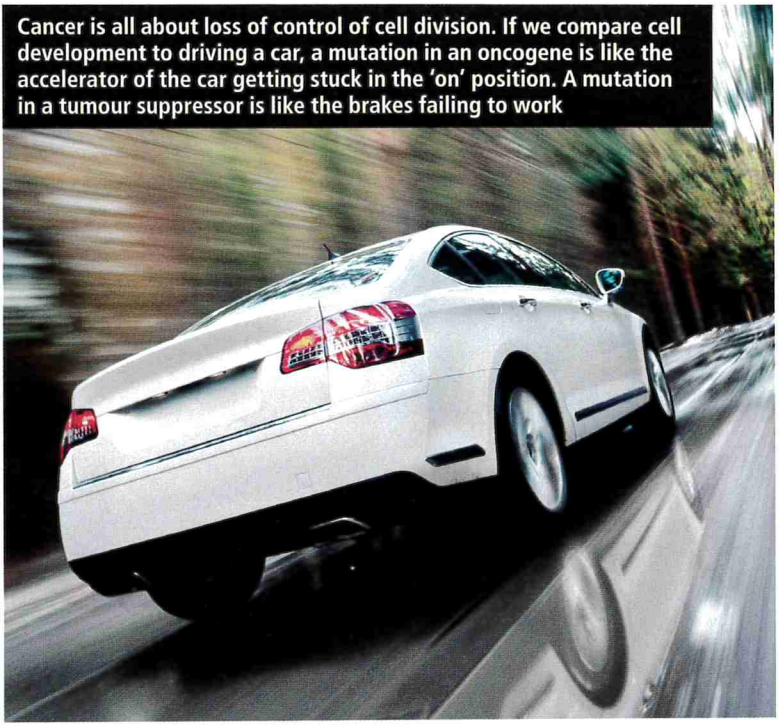
Malignant A tumour that is capable of spreading to other tissues in the body.

Metastasis The spread of a cancer from the original site (the primary tumour) to a different region of the body (a secondary tumour), possibly a long way apart.

Monoclonal antibody Purpose-made antibody that recognises a specific target molecule (e.g. a protein found on the surface of a cancerous cell).

Oncology The study and treatment of cancers.

Upregulation A protein (e.g. a cell surface receptor) is said to be upregulated if there is an increase in the number of copies of that protein (due to there being more copies of the gene for that protein, and/or the gene being transcribed more frequently than usual).



Cancer is all about loss of control of cell division. If we compare cell development to driving a car, a mutation in an oncogene is like the accelerator of the car getting stuck in the 'on' position. A mutation in a tumour suppressor is like the brakes failing to work

Ethics

The ability to identify differences in cancers that would previously have been grouped together (and treated the same) is one of the most important outcomes of cancer genomics, and is the cornerstone of personalised **oncology**. This means both that the right treatment goes to the patients who will benefit from it, and that time is not wasted giving patients a drug that would not work for them.

Genomics is also leading to other fundamental changes in both the diagnosis and treatment of cancer. At its most radical, this could lead to a shift from reactive approaches (treating an existing cancer) to a proactive model, in which genetic knowledge facilitates prediction and prevention of cancers. An early example of this would be the choice of women, most famously the actor Angelina Jolie, to have an elective mastectomy based on the fact they have a mutated copy of a BRCA gene, known to give a high chance of breast cancer.

Particular excitement is focused on the emerging use of a simple blood test that can reveal whether someone is developing cancer. The test — a liquid biopsy — relies on the fact that tumours release fragments of DNA into the blood. With NGS approaches it is possible to pick out these genetic signals. Most of these tests are not currently accurate enough to be rolled out into the clinic but, once validated, will offer several advantages over existing biopsies.

1 They are less invasive than taking tissue samples from a patient, meaning less pain and less risk of accidentally dislodging cancerous material, which might cause spread to other locations.

2 They can reveal signs of cancer development much earlier, meaning that the disease can be tackled in a more timely fashion, ideally before **metastasis**. The test can look for the presence of specific changes associated with certain stages of the disease, giving useful information about prognosis and the likely success of treatment.

3 Ongoing blood testing after treatment will be an easy way to monitor whether there has been any return of the cancer.

Working together

The key to the success of cancer genomics is comparison of normal versus tumour DNA for an individual patient, of tumour development over time, and of molecular differences in the 'same' cancer. The more available data, the better. This has driven large collaborations such as The Cancer Genome Atlas and the International Cancer Genome Consortium (ICGC). The ICGC is well on the way to fulfilling its ambition to complete a comprehensive description of 500 genomes from each of 50 different types of cancer. The pooling of this information is an example of the potential for 'big data' projects to maximise their impact.

However, there are some difficulties with cancer genomics. One concern about a shift to personalised oncology is the expense. The price of sequencing has fallen rapidly but remains costly. The medicines used for tackling a specified cancer tend to be far more expensive than traditional therapies. Bodies such as the National Health Service have finite resources, so decisions about costs versus benefits have to be made. Money spent here cannot be used for other treatments.

On balance, however, the opportunity that genomics offers to make earlier, more accurate diagnosis of the molecular basis of an individual's cancer, and to follow this up with medicine tailored to tackling their specific disease, means that cancer genomics is going to become an ever more important tool in the battle against 'the big C'.

Things to do

- Watch one of the short videos listed in Further reading (or, if you are particularly interested in the topic, the longer more detailed one).
- What are the main ethical issues with cancer genomics? What advantages does cancer genomics bring? What are the potential downsides?

Further reading and viewing

Cancer Genomics Overview (from the website of the US National Cancer Institute, introductory): **https://tinyurl.com/yb3gj5gl**

Video: 'Genomics and personalised medicine', NHS Alliance (4.5 min, introductory): **https://youtu.be/X8eNFa6fpLs**

Video: 'Personalised medicine could lead to a breakthrough in cancer in 2017' (3 min, introductory): **https://youtu.be/JGk2k1mWMk8**

Video: 'Personalized medicine in cancer: what does it mean and how is it done?' (6 min, introductory): **https://youtu.be/5iNV8Fuc8pk**

Video: 'Introduction to cancer genomics' (90 min, advanced): **https://youtu.be/9mKkQOf1Qxs**

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