The future of cancer, as told through the story of Renee

Explaining in everyday language how the science that brought us the Human Genome Project is giving hope to cancer patients of today and tomorrow is no easy task. **Mark Henderson**, science editor for *The Times* in London, won a Best Cancer Reporter Award for this piece, which was originally published under the title, 'Making cancer history: killing tumours'.

Merrimack, New Hampshire, usually gets a white Christmas. And when Renee Weaver felt a pain in her back over the holiday season, she assumed she must have pulled a muscle while shovelling snow.

When her sight became blurred a few weeks later, there also seemed to be a logical cause. "I'm about to be 40," she thought. "I must need glasses." But her optician revealed that neither ailment had so benign an explanation. A mass was pressing on Renee's right eye but, doctors told her, its cells hadn't started out there. Though just 39, and a non-smoker since her twenties, Renee had advanced lung cancer. It had already spread to her brain, bones and liver.

For the mother of Emily, 13, and Jacob, 10, the diagnosis could hardly have been more devastating. Median life expectancy for a patient with so many metastases is just eight months, and the five-year survival rate is lower than 10%. "The doctor, when she told us, I really think she thought I was headed for death," she said. "Like any mother, I just thought of my children. My God, I won't see them grown." A serendipitous coincidence, however, has thrust Renee to the heart of a gathering medical revolution that is starting to give patients like her genuine hope of beating cancers that would once have carried the bleakest prognosis.

Mark Henderson

With the help of a surgeon who was treating her husband, Tom, for a heart complaint, she came under the care of one of the world's leading cancer centres, at Massachusetts General Hospital (MGH), 50 miles away in Boston. There, she has become one of the first patients to benefit from a new approach to cancer, based on science's growing understanding of the human genetic code.

Under this strategy, cancer is no longer considered as a single disease, or even as the 200 or more forms that afflict different organs in distinct ways. Genomic insights are instead defining tumours according to the DNA mutations that drive them.

This new paradigm is providing doctors with the intelligence they need to attack cancer with smart weapons,

THE TIMES

Renee Weaver is a non-smoking, 39-year-old mother with lung cancer. It has spread to her brain, her bones & her liver. Her life expectancy should be eight months, but Renee's doctors are pioneering genetic techniques that promise a revolution in the fight against the deadly disease. Their aim? To contain, & even cure, cancer. Starting with Renee.

A mission to inform. The story of non-smoker Renee, whose advanced lung cancer responded dramatically to treatment with a targeted therapy, brings readers realistic hope tempered with caution

calibrated for individual patients, in place of the blunt instruments of traditional oncology. It has already started to change the landscape of medicine, to transform its capacity to contain – and even sometimes cure – this dreaded disease. And it is coming to Britain.

This year, Cancer Research UK will begin establishing a network of centres that will use similar genetic techniques to guide treatment decisions for British patients. It will be the precursor to treating every NHS [National Health Service] cancer patient this way, perhaps in as little as five years. Renee's experience, though groundbreaking for now, could soon be expected to become routine. You might call it the future of cancer.

There is a tendency to think of cancer as an environmental disease, triggered by exposures such as smoking or ultraviolet light. But at root, it is a disease of the genes. It is the result of DNA defects that cause cells to grow unchecked; carcinogens are dangerous because they inflict this damage. The nucleus of a tumour cell is a place of genetic chaos, with many thousands of mutations. It is these that are the life force of cancer cells, feeding their appetite for proliferation and destruction. But they are also weaknesses that can be attacked.

As scientists have started to identify these mutations – abetted by the work of the Human Genome Project – they have begun to develop drugs that can knock them out. Agents such as erlotinib (Tarceva), trastuzumab (Herceptin) and imatinib (Glivec) neutralise the rogue proteins made by defective genes, killing tumours or weakening them so the body can finish the job. They have proved to be capable assassins, often prolonging life by years, but they cannot be deployed indiscriminately. For the most part, they work only against cancers with the genetic signatures they are designed to target. Doctors must know their enemy when planning attacks.

What this means, according to Daniel Haber, director of the MGH Cancer Centre, is that "you can no longer do cutting-edge oncology without genetic tests". It is not enough to diagnose cancer in a patient according to how a tumour looks under the microscope, and where it is in the body. You

Agents such as erlotinib neutralise the rogue proteins made by defective genes, killing or weakening tumours

have to read the molecular instructions that are driving it, the genes that make it tick.

Some tests that do this have been available for a few years. Indeed, the NHS requires that they be conducted before certain drugs are approved. Trastuzumab is given only to breast cancer patients with a defective HER2 gene, while cetuximab (Erbitux) is prescribed only for colon cancers without mutation in a gene called KRAS.

Provision of testing, however, is still patchy, and those patients who do get it are investigated only for the defect that most commonly afflicts their particular cancer. A bowel cancer patient might get a KRAS test, but nothing else.

The MGH programme is taking such testing to a whole new level. At Renee's first appointment, her doctor, Lecia Sequist, ordered a battery of genetic investigations. A sample of her tumour was screened for about 120 different mutations in 13 genes that are known to affect drug response or prognosis. The hope was that she might be suitable for a targeted therapy – or that if nothing appropriate was available, she might be able to join a clinical trial.

"For someone like Renee, a young, female non-smoker, we had a high index of suspicion that she might have a suitable mutation," Dr Sequist said. "We pushed the lab to go as fast as possible and got the results back in eight days."

They provided a filament of hope. "Dr Sequist had told us that if the test was negative, we shouldn't give up," Renee said. "But when she said, 'We've got your results back,' there was a tone in her voice. We could tell she was happy."

Dr Sequist was happy because the test had revealed that her patient's tumour had a mutation in a gene called EGFR. This is present in about 10–20% of lung cancers, and it is more common still in patients with Renee's age, sex and smoking history. It meant that she could be treated with erlotinib, a drug that inhibits EGFR.

The test greatly improved her prognosis: about 60% of patients with EGFR mutations respond well to erlotinib. It has also spared her the gruelling effects of chemotherapy: instead of intravenous courses of highly toxic drugs in hospital, she can take pills at home.

Renee does not look like a typical cancer patient. The only visible clues to her treatment are a headscarf, to hide hair lost during radiotherapy that shrinks her brain lesions, and a little "teenage acne". She has had some diarrhoea and nausea, and she has lost some weight. But as her husband says: "We'd rather you were alive with a bit of a rash. I just think you're a trooper."

The beauty of MGH's wide-ranging test is that, even had Renee's tumour lacked an EGFR mutation, it could have revealed other genetic guides. A mutation called ALK, for example, present in about 5% of lung cancers, is common in patients with her profile.

"What we're doing is to capture all we can of what's happening genetically in the tumour, to look at everything that might possibly inform a treatment decision," said Leif Ellisen, co-director of MGH's translational research laboratory, which developed the panel of tests, known as Snapshot. "If you really want to have personalised medicine, you have to test a broad spectrum of mutations in every tumour."

"We're testing for all the major mutations we feel can affect therapy, either now or in the near term," Dr Sequist said. "We're looking at the mutations for which there are licensed targeted drugs, as well as for some treatments that are currently in development. That way, when the drugs are ready, we'll be ready too."

Since March, this approach has become the standard at MGH for every patient with advanced lung, breast, gastrointestinal or brain tumours, as well as for malignant melanoma, the most aggressive form of skin cancer. About 900 people with these cancers – the types for which molecular diagnosis is currently most useful – will have the Snapshot test this year.

Many more can expect to benefit in future. New genes are being added all the time – there are now 16 on the panel, three more than when Renee was tested in February. The cancers for which it is indicated will widen further as the International Cancer Genome Consortium, a £600 million [€665 million] project to find all the mutations that drive 50 common tumours, begins to deliver results. The initiative has already borne fruit: in December, the entire genomes of a lung tumour and a melanoma were published, identifying many new defects that could be drivers.

The next challenge is to roll out such programmes, so that they reach patients in small hospitals, and apply them earlier to treat patients whose cancers have yet to spread.

Trastuzumab has already made this second step, slashing recurrence rates after surgery for HER2-positive breast tumours.

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At a cost of about $1000 [€700] and falling, the Snapshot test is well within the affordable range of health providers such as the NHS. And MGH's oncologists are convinced that their methods will soon become commonplace. "For this to become standard in five years is not unrealistic," Dr Sequist said.

It is a position with which Professor Peter Johnson, the chief clinician of Cancer Research UK, concurs. "There's no doubt in my mind that this is the way cancer medicine is going," he said.

So convinced is the charity of the potential of broad-spectrum genetic diagnosis that it is establishing a programme to provide similar services in Britain. In the pilot phase, it plans to set up genetic testing centres at up to six hospitals, with the capacity to scan about 6000 patients a year for a range of mutations. It hopes to extend the scheme to every NHS hospital.

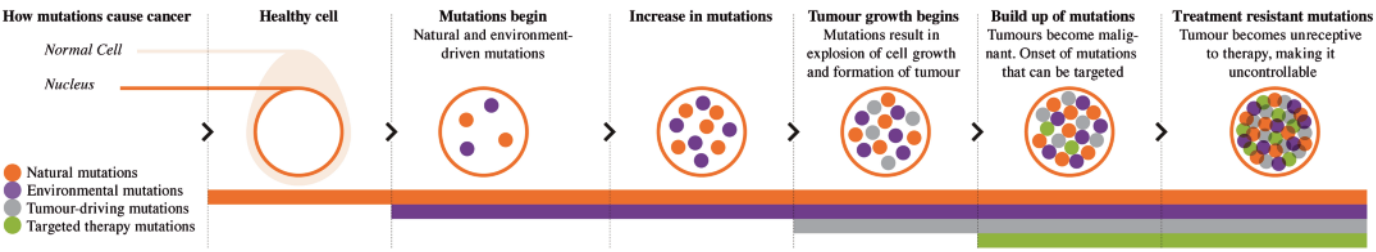
"We think it's clear that this train is already moving," Professor Johnson said. "It's time to take the initiative to apply these insights. Molecular typing of cancer will be in routine practice for many people before long. It's a matter of making sure we're ready."

For Renee, the roll-out cannot come too quickly. "If you're just someone who lives in a small town and doesn't have access to MGH, is your life not as important as someone who lives near Boston?" she said. "I'm lucky to be an hour away. This should be standard everywhere."

The pace of advance has also awakened business to the possibilities of a major new market. For example, Foundation Medicine, a Boston-based company that launched in April, aims to develop a one-stop-shop for genomic cancer diagnosis that is accessible to any hospital. Its advisers include Eric Lander, a pioneer of the Human Genome Project.

This enthusiasm for widespread genomic diagnosis of cancer has emerged because of the astonishing progress made by targeted therapies in the past decade. Their potential first became clear in 2001 with the advent of imatinib (Glivec), a drug designed to shut down a mutant gene that causes chronic myeloid leukaemia (CML). It transformed treatment of the disease. Patients who would once have been expected to die within months are still alive today, often living ordinary lives. The team who developed it, Brian Druker, Nicholas Lydon and Charles Sawyers, were awarded the Lasker-DeBakey Clinical Medical Research Award last year for "converting a fatal cancer into a manageable chronic condition". Similar targeted therapies have followed for some solid tumours,

MUTATIONS EXPLAINED



The DNA (deoxyribonucleic acid) in a cell's nucleus makes up genes (bits of code). Genes dictate what a cell does, what proteins it produces (and thus how we are made) and when it reproduces. This replication enables the body to grow and repair itself, but it is also when mutations, i.e., mistakes, occur. These can be inherited or result from environmental factors such as UV light or smoking (called mutagens). Sometimes our cells can fix these mutations, but if they can't they are passed on to future copies of the cells. These cells normally cannot survive but in some cases they keep on dividing until a lump, or tumour, is formed.

They have even begun to crack one of the deadliest and least tractable cancers of all: melanoma

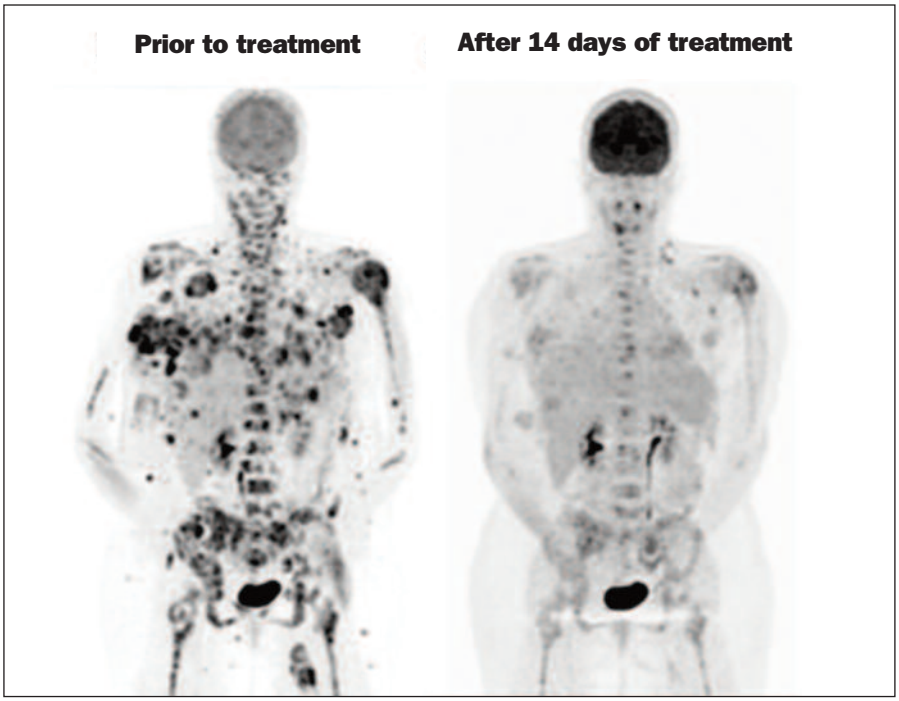
especially those of the lung, bowel and breast. They have even begun to crack one of the deadliest and least tractable cancers of all: melanoma.

This skin cancer is readily treatable if caught early, but once it has started to spread it is a reliable killer. Chemotherapy rarely works, and fewer than one in ten patients live for a year. A diagnosis of metastatic melanoma is the proverbial death sentence.

On the wall of Professor Mike Stratton's office, though, hangs a remarkable picture. On the left is a positron emission tomography (PET) scan of a melanoma patient, whose body is riddled with cancer. It is so pockmarked that it resembles a Dalmatian. Next to it is a PET scan of the same body, taken 15 days later. It is almost completely clear: the cancer has melted away.

It is an image of which Professor Stratton, who heads the Cancer Genome Project at the Wellcome Trust Sanger Institute in Cambridge, is justifiably proud. For the drug that caused this extraordinary transformation was developed as a result of a genetic discovery made by his team just eight years ago. "It is an incredible kick for me and my colleagues to look at," he said. "On bad days, I look at that picture and I think things are all right. It gives us huge satisfaction to know that our work can make that sort of difference."

That difference began with the discovery in 2002 that a mutated gene called BRAF is present in about 70% of melanoma tumours. This insight allowed Plexxicon, a biotechnology company, to develop a BRAF inhibitor



A copy of the PET scan images of a melanoma patient that hang on Mike Stratton's office wall. On the left, it shows the patient before treatment with PLX4032, and on the right, 15 days after starting the therapy

called PLX4032. In initial trials, 80% of patients responded so well that tumours often vanished from their scans; the PET images are from one of the trial's participants. Almost two years after starting treatment, about one in five patients who responded remains clear. "The response was far more spectacular than we expected," said Keith Flaherty, of MGH, a leader of the trials. The drug is expected to be licensed next year.

The BRAF experience also highlights another fascinating aspect of cancer genomics that is changing the way the disease is diagnosed and treated. This is because melanoma, caused by exposure to ultraviolet radiation from tanning salons or the Sun, is not the only cancer in which this gene malfunctions. BRAF can also be mutated in colon, lung and thyroid cancer – all organs on which the Sun doesn't shine. The same is true elsewhere: EGFR mutations are found in gastrointestinal and brain cancers, and the ALK mutation that drives some lung tumours was originally identified in lymphoma.

What this suggests is that cancers

that oncologists would never before have grouped together might well benefit from a similar therapeutic approach. The tissue in which a tumour is found may even be less of a guide to the best treatment than its molecular subtype.

While this is still a hypothesis, research is now putting it to the test. Trials are already under way to examine if BRAF and EGFR inhibitors work on cancers no matter where they began.

Dr Sequist said: "We used to think there was one cookbook for colon cancer and another for lung cancer. But there may be general treatment algorithms for colon cancer with BRAF that are the same for lung cancer with BRAF. The paradigm that certain drugs only work for cancers in a certain tissue is just old-fashioned."

For all the improvements that targeted therapy has delivered, however, none tell of unqualified success. In the first place, treatments still exist only for a subset of cancers: there is no agent, for instance, suitable for bowel tumours with mutant KRAS. In the second, though most patients whose tumours match a tailored drug respond for a time, their cancers often return.

PLX4032, the BRAF inhibitor, is a prime example. In trials, its effects generally delivered about ten months of remission, after which tumours started to progress: some patients who initially had results as spectacular as Professor Stratton's scans have since died. "That's still real progress," Dr Flaherty said. "For a metastatic melanoma patient, even ten months is a reprieve you rarely get with chemotherapy. Then you factor in the quality of life. But of course it's not as much as we'd like. We're not calling it quits."

The problem is that cancers, like viruses and bacteria, can evolve resistance to drugs. This can happen in two ways. A tumour can acquire a new mutation that drives it forward even when BRAF or EGFR is knocked out. Or a few cells in a primary tumour may be resistant from the outset. When the larger number of susceptible cells have been killed, the resistant ones can take their place.

But if resistance remains a significant hurdle, there are grounds for optimism that it will not always be an insuperable one. "We're still losing most of our patients," Dr Sequist said. "But I do think that will improve."

Several trials are under way in which targeted therapies are being given alongside other drugs that, it is hoped, will prevent or delay resistance. Renee is participating in one of them: as well as erlotinib, she is receiving a drug called hydroxychloroquine, originally developed as an antimalarial, which may have an anti-cancer action. The hope is that this cocktail will prolong the effectiveness of her treatment.

The MGH doctors all feel that this multidrug approach to cancer will become increasingly important. Several made the analogy with HIV, which can be controlled with combination therapy, in which different antivirals guard against the development of resistance.

The toxicity of cancer drugs may sometimes prevent them being given all at once, as with HIV agents, but it may be possible to deliver what Dr Sequist calls "pulses" of treatment – a few weeks of erlotinib, followed by a few weeks of something else – to hold a cancer in check. Should tumours regrow, it will also be necessary to retest them for mutations, to pick up any new ones that require fresh therapeutic tactics.

There is another reason why cancer researchers and clinicians speak often about HIV. This is that while there is no HIV vaccine, and no cure, the virus can be suppressed for long periods of time. HIV-positive people, such as Lord Smith of Finsbury, the former Culture Secretary, have taken combination therapies for two decades, remaining well enough to hold down high-powered jobs. A once-fatal infection has become a chronic one that can be managed so effectively it is questionable whether one should think of its carriers as ill.

The advent of genetically targeted therapies, and the molecular diagnostics that underpin them, has brought a similar goal into view for cancer. As Eunice Kwak, another MGH doctor, put it: "If you could cure cancer that would be phenomenal, but if you could make it similar to HIV, so that instead of being a lethal disease it becomes something you can live with and manage, that would be a huge advancement. It is maybe not so far away."

Dr Haber goes farther, noting that for patients whose cancer is caught early, before it has spread, targeted therapy could really change the meaning of the 'C-word' to cure. "We do OK with metastatic cancers, but it's a big challenge to fight a cancer that has got that big," he said. "The key is to get targeted therapies in there early."

Professor Stratton agrees. "I think

If resistance remains a significant hurdle, there are grounds for optimism that it will not be insuperable

The Weaver family, including daughter Emily and son Jacob, pose together at home. Renee said her worst fear when she was diagnosed was the thought of not being able to watch her children grow up. Targeted therapy has, at the very least, bought her more time to spend with them

we will increasingly make cancers chronic," he said. "But we should be aiming for cures – we can aspire to a higher goal." Genomic treatment, he says, will do for many tumours what advances in chemotherapy did for testicular cancer patients such as Lance Armstrong. "We don't think much about testicular cancer now: 40 years ago it was a 100% killer, now 90% of young men are cured," he said. "These therapies will add to that group of patients who can be treated and hopefully cured. Genomic strategies are proving so extraordinary that I would personally voice optimism that ways will be found."

As genomics brings cancer more sharply into focus, these incremental steps forward are starting to become strides. "As I see it, 20, 30, 40 years of genetics are now coming to an application we didn't have before, to new therapies that are smartly designed," Dr Haber said. "I really think it is a revolution."

It is a revolution that reached the Weaver household on May 5, when, just seven weeks after starting erlotinib, Renee returned to MGH for the results of her second scan. She was braced for the worst. Dr Sequist, though, was smiling as she opened the door.

"She told me she had some good news, and showed me the scans," Renee said. "It shocked us all: the primary tumour had shrunk by about 80%, and you couldn't see any other spots at all. I'd hoped she might say there had been a little shrinkage, but I hadn't dared to hope for anything like this."

She is not out of the woods just yet: when erlotinib works, the response typically lasts a year. But, as Dr Sequist said, hardly any patients like Renee who have chemotherapy do so well. There is a chance, too, that she could become one of the growing group of patients in whom erlotinib controls lung cancer for years.

"I'm taking it a day at a time," Renee said. "Whether the results will be this great next time, who knows? But I'm feeling good. I'm trying to go back to a normal life. Thank God for the researchers and doctors who have made this happen. I don't want to think about where I'd be without them."

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