

## Best Reporter



# *Farewell to chemotherapy?*

With all the good news about precision medicine, it can be difficult to explain why many patients are still being treated with expensive and toxic drugs that do not benefit them. **Pia Heinemann**, science editor for the German newspaper *Die Welt*, won the 2016 Cancer World Best Reporter prize for an article, republished below, that helped readers make sense of the complex reality.

**C**hemotherapy. That's the word Jana Hermann doesn't want to hear under any circumstances. She has breast cancer; she received the diagnosis four weeks ago. She underwent surgery to remove one of her breasts and five lymph nodes. The tissue was sent off to pathology; the 53-year-old was discharged from hospital with pain that was not as bad as she had feared.

Two weeks later, the tumour tissue and the lymph nodes have been examined, the multidisciplinary team has met, and Jana Hermann is sitting in her doctor's office. She looks at him. He is studying his computer screen, running

over her medical records – and he says: “chemotherapy”.

Marion Kiechle encounters this situation 200 times a year – but from the other side of the desk. She is medical director of the Women's Hospital of the Technical University of Munich, and she knows how hard it is for doctors to give bad news to their patients. “Chemotherapy puts an enormous strain on patients,” says Kiechle, “and most of them are very fearful.” She recommends chemotherapy only if it is absolutely necessary – as a last resort in fighting the cancer.

Cytotoxic drugs are designed to destroy rapidly

## “Breast cancer patients can now be tested to determine whether or not chemotherapy is necessary”

proliferating cancer cells – but they are very non-specific and also attack other rapidly multiplying cells. Because of this, patients lose their hair, suffer from nausea, and sometimes their blood count falls. Patients cannot hide the fact that they are having chemotherapy: everyone can see that they have cancer. But most patients want to hide their illness. Jana Hermann is not using her real name. She does not want people who know her to find out that she has cancer. “Chemotherapy,” says Kiechle, “can easily become a stigma.” That is why she talks to her patients about a test that can determine whether chemotherapy is a sensible option for them. Such a test could save many patients from undergoing the harsh treatment.

Every year almost 500,000 people in Germany are diagnosed with cancer. Half of them get away with surgery alone. But of those for whom surgery is not sufficient, many can only hope that their lives will be prolonged if they take the hard chemotherapy route. ‘Chemo’ is the treatment of choice if the cancer is at an advanced stage, if it has spread, or if it is aggressive. But although the cytotoxic drugs that are used have improved significantly in recent years and the side effects have been reduced, many patients still find the treatment worse than the cancer itself.

Scientists have therefore been trying for decades to reduce the side effects of chemotherapy and find entirely new ways of treating tumours. They are also trying to develop tests that indicate whether a cancer patient really needs chemotherapy – or whether a different type of treatment would be preferable.

Breast cancer patients like Jana Hermann can now be tested to determine whether or not chemotherapy is necessary. In Germany alone, about 15,000 breast cancer patients a year could in future be spared chemotherapy. In other areas of oncology, too, diagnosticians are attempting to test the molecular characteristics of different tumours to design tailored treatments for each patient.

Developing the right tests and treatments will be a major challenge for the coming decades. If the researchers fail, the costs to the healthcare system will be enormous.



Sort it out! Heinemann’s article, published in *Welt am Sonntag*, highlighted the growing importance of genomic testing to avoid over-treatment, and flagged up flaws in the way access to tests is being rolled out in Germany

And patients will have to endure unnecessarily harsh treatments.

“In our society, the female breast is incredibly important – it is a key part of our culture,” says Werner Schlake. He is a reticent man, who prefers to talk about the subject face-to-face rather than on the phone. Schlake – who has white hair, a white beard and glasses – is a pathologist in the city of Gelsenkirchen. He is one of around 1,800 pathologists in Germany, and president of the German pathologists’ association, the BVDP. Right now he is furious, because the test that could spare thousands of women chemotherapy is not being offered as standard in Germany.

“Two hundred and fifty years ago, pathologists made their diagnosis with the naked eye,” says Schlake. Then microscopy came along. “We pathologists start off by getting a tissue sample, a piece taken from the tumour.

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It looks like a worm, two or three centimetres long.” This sample is first examined macroscopically by the experts at the pathology institute. Then it is cut into wafer-thin slices, treated with various dyes, and examined under the microscope. The pathologist is looking for specific cell structures. In the pathology lab, each patient’s cancer is classified.

“But now,” says Schlake, tapping the table top, “now we can even examine the molecular level.” In recent years tests have become available that indicate which genes are active in the cancer tissue. Experts call these tests “gene expression tests,” and the ones that have been licensed now include MammaPrint, Oncotype, Endopredict and Prosigna.

With breast cancer in particular, says Schlake, the correct diagnosis is vital: a lot hinges on it. “The pathologist makes the diagnosis. Cancer or not, aggressive or not.” Only with the correct diagnosis can the doctors select the right therapy – they must decide whether the patient needs radiotherapy or chemotherapy, or whether standard hormone treatment would be sufficient.

The gene expression tests provide the basis for this decision – or rather, this is what they must do in future. At present many breast cancer patients do not get these tests. That is why Schlake is so angry – because there have been great advances in pathology, but patients are not benefiting as they should.

**“There have been great advances in pathology, but patients are not benefiting as they should”**

Germany’s joint federal committee of health insurance providers approved the gene expression tests on August 10<sup>th</sup> 2016 – but only for ‘outpatient specialty medical care’ (Ambulante Spezialfachärztliche Versorgung, or ASV). All patients who want to have the test in ASV can have the cost met through their compulsory health insurance scheme. “That’s great,” says Werner Schlake – he pauses, leans back, leans forward again – “but it is also a scandal,” – because ASV requires certain structures. Established cooperation partners, such as a pathologist and a clinic, must work together and set up a unit to ensure that patients can be cared for outside the hospital system. But these ASV units that would enable every

patient to access the tests don’t yet exist.

The gynaecologist Marion Kiechle says that, even in hospitals, the test could in fact be used for all patients. “But we can’t charge health insurers for them.” The tests, which cost roughly €44 million a year, but would cut the cost of unnecessary chemotherapy by €145 million, have to be cross-financed. The hospital therefore re-allocates unspent money earmarked for other treatments and uses it for the tests.

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It is not only pathologists like Schlake who are infuriated by this. The introduction of the gene expression tests that could spare patients unnecessary suffering, while also cutting the cost to the healthcare system, reveals a fundamental flaw in Germany’s health insurance legislation.

The lawmakers’ aim is to facilitate patients’ transition from hospital to outpatient care. At the same time, the intention is to relieve the financial burden on hospitals – which at present are unable to pay for the tests via their charging system. But because the system has not yet been established, patients can get the tests only at breast centres or specialist hospitals like the one Marion Kiechle manages in Munich.

And yet so many patients could benefit: Schlake picks up a piece of paper on which a map of Germany is printed in red. The number ‘74,500’ is printed on it in bold type. That is the number of new cases of breast cancer in Germany each year. One-third of those diagnosed cannot avoid having chemotherapy, because it is absolutely necessary, Schlake says. Another third definitely do not need chemotherapy. “But until now we have been uncertain about the final third.” The number ‘22,000’ is accompanied by a prominent red question mark. These 22,000 patients are usually recommended by their doctors to have chemotherapy. Over-treatment is unpleasant, but not normally fatal.

However, researchers and physicians now know that two-thirds of these 22,000 patients do not in fact need chemotherapy. Even without it they will not develop metastases. “And it is these 14,500 patients that we can

now identify”, says Schlake. Tissue that until a few years ago was hard to classify can be classified precisely with gene expression tests.

## “Tissue that until a few years ago was hard to classify can be classified precisely with gene expression tests”

Carsten Bokemeyer is another person who believes in the new world of testing. An oncologist, he is director of Medical Clinic no. II at Hamburg University Hospital in Eppendorf, and chairman of the German Society of Haematology and Medical Oncology. “For the ‘right’ patients, the new molecular tests enormously enhance the effectiveness of cancer treatment,” he says.

X-rays of lung cancer patients regularly prove to him what is possible. The cancer cells that show up as light in colour on the X-ray before treatment start to vanish within a few days of therapy. “They just seem to dissolve,” says Bokemeyer.

The new anti-cancer drugs can be divided into several groups. The first group consists of ‘small molecules’. These are so tiny that they can penetrate the cell surface and dock onto certain structures. This interrupts signal transmission in the cancer cell: the cell can no longer divide and tumour growth is halted.

Another group involves tyrosine kinase inhibitors, which have been called a “Lazarus drug” – a treatment that can raise the dead – because of their effect on lung cancer patients who have a specific genetic mutation. They can have a similarly miraculous impact on other types of cancer. Imatinib (Glivec) is one example: for patients with chronic myeloid leukaemia, this is a wonder drug. Before its invention, very few drugs were available to these patients, and many died. The substance can block the modified blood stem cells so effectively that the disease can now be virtually cured.

In passive immunotherapy, another new treatment method, antibodies are produced that can recognise structures on the surface of cancer cells. They then block these structures and, through various mechanisms, cause the cells to die or prevent them multiplying further. These “designer antibodies” are now being used to treat breast cancer as well as colon cancer, lymphoma and other malignancies. “For example, in a typical case of lung

cancer caused by smoking, the cancer cells display a lot of changes in their genetic makeup,” explains Bokemeyer. “These tumours behave particularly aggressively. Here the molecularly targeted drugs rarely work, but patients can benefit from active immunotherapy involving what are known as checkpoint inhibitors.”

Carl June of the University of Pennsylvania has helped active immunotherapy achieve a breakthrough. The doctor has spent more than 20 years working on ways of activating the patient’s immune system so that it targets cancer cells in the patient’s body. Normally cancer cells disguise themselves and tell the immune system that they are perfectly normal body cells, thereby protecting themselves from attack. But in pioneering studies, the American doctor was able to show that it is possible to take immune cells from the patient’s blood and modify them genetically in the lab so that when they are returned to the blood they are able to recognise cancer cells and destroy them.

## “In cancer cells displaying a lot of genetic changes, targeted drugs rarely work, but patients can benefit from immunotherapy”

Among the patients he treated was Emily Whitehead, a young girl who was diagnosed with acute lymphatic leukaemia (ALL) on May 28<sup>th</sup> 2010, a few days after her fifth birthday. She had chemotherapy for 26 months. The doctors gave her an 85–90% chance of a cure if the chemotherapy was effective. But eighteen months later the cancer was back. Emily’s chance of recovery dropped to 30%. She received a second course of chemotherapy and was about to undergo a bone marrow transplant when, two weeks before the planned transplant, she suffered another relapse. A third course of chemotherapy failed. Eventually it was suggested to Emily’s parents that Dr June might be



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able to help their daughter, and so the child took part in a highly experimental study. In April 2012 she received genetically modified immune cells. A few months later it was clear that the active immunotherapy was working. The cancer cells were no longer able to hide from Emily's immune system and they were destroyed. Emily left hospital in June 2012. She is now eleven years old – and still well.

### **“We are learning that some substances work very well for certain cancer patients but not for others with the same kind of tumour”**

“We are learning that some substances work very well for certain cancer patients but not for others with the same kind of tumour,” says Carsten Bokemeyer, the oncologist from Hamburg. Active immunotherapy is highly successful for lung and kidney cancer, malignant melanoma and certain types of lymphoma. It is also likely to be approved for bladder, gastric and breast cancer. “But each of the new treatments has advantages and disadvantages. For example, passive immunotherapy is effective for colon and lymphatic cancer, but it requires two to four months to take effect,” says Bokemeyer. For other types of cancer, tests must be performed before treatment starts, to identify which drugs can even be considered.

At present the new treatments that can supplement or replace chemotherapy are being applied only sporadically. “In Germany, between 10,000 and 15,000 people per year could benefit from modern antibody immunotherapy,” says Bokemeyer. That is 15,000 people who doctors have until now often been unable to help.

One of the reasons why more patients are not benefiting from the new therapies is that they are very expensive. Of the €5 billion that are spent on treating compulsorily insured patients each year, more than €1.5 billion is already accounted for by the modern drugs – even though they make up considerably less than a quarter of prescriptions.

Another reason is that the new drugs have not yet been sufficiently tested, and are only approved for special applications.

The new targeted drugs can also have serious side effects such as nausea, vomiting, and blood disorders.

Doctors are therefore only allowed to prescribe them if the patients have been tested to check that the treatment will be effective.

Choosing the right therapy for each patient will be an enormous challenge in the coming years. “If we choose wisely, we will be able to significantly increase the survival of many cancer patients and avoid subjecting others to unnecessary treatment,” says Bokemeyer. “Otherwise, in using the new substances we will simply be burdening patients with side effects – and imposing costs on the healthcare system.”

But it is not only funding that presents problems for modern oncology. Every week, the results of new studies are published, reporting further advances in oncology – basic research is making enormous progress. But nobody yet knows whether this progress will have a lasting effect on patients. There are not enough data. We do not yet have the long-term studies that would show whether a new treatment really prolongs patients' lives.

### **“If we choose therapies wisely, we will be able to significantly increase the survival of many cancer patients and avoid subjecting others to unnecessary treatment”**

There are lots of highly specific drugs, but patients cannot be tested to see whether the drugs are an option for them. The international consulting company IMS Health estimates that, by 2020, tests will only be available for a third of the new drugs that are coming on the market.

The era of precision medicine, in which exactly the right drug can be found for each patient, is only just beginning.

Jana Hermann's tissue samples were analysed in a gene expression test. She didn't discover that until she asked. Her doctor hadn't wanted to raise false hopes. Because for Jana Hermann, there is no alternative to chemotherapy.

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