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No easy road to outsmart cancer

FATIMA CARDOSO GUEST EDITOR

At the start of every year, we are asked to reflect on the major medical advances in our field over the past 12 months. This year, writing in *Nature Reviews Clinical Oncology,* Elżbieta Senkus and I were forced to conclude that no major breakthroughs had emerged (vol 12, pp 67–68). Despite intense and expensive efforts, 2014 was a year of "failure of surrogates and precocious expectations".

And yet, as a community we continue to raise unjustified expectations on the basis of small trials of short courses of therapy, given between the time of diagnosis and surgery. We know from decades of experience that tumour shrinkage does not correlate with sustained benefit unless it is linked to improved symptoms. We saw it with response rates in advanced cancer, and we now see it with response rates and pCR (pathological complete response) in early breast cancer.

It's astonishing and frightening that new drugs are being approved based on these "failed surrogates" and small phase II trials. We can only hope that these rushed decisions won't do our patients more harm than good.

Reflecting back, the big steps forward in breast cancer came through trials that were simple but large enough to draw definite conclusions, like the ones that showed breast conserving surgery with radiation is as safe as mastectomy, and adjuvant chemotherapy saves lives. These sorts of academic trials simply cannot be run under current regulations, because of time and cost constraints.

And though we are gathering extensive data on many aspects of cancer biology, palpable benefit will remain elusive until we learn how to mine and interpret it. In early breast cancer the standards of care haven't changed in more than two decades; in advanced disease median overall survival is still a dismal two to three years! No predictive factors besides the 'old' hormonal and HER-2 receptors have been discovered, so personalising treatment is still more aspiration than reality.

I am convinced that we can do much better, but only if we reject the temptation to take shortcuts that lead to dead ends. We need to stop wasting time and resources on a myriad of inconclusive trials, and start addressing some of the big strategy questions.

We have learned (albeit slowly) how important collaboration is for success, and today multicentric/multinational trials are the norm. The fragmentation of breast cancer into rarer subtypes makes this ever more important.

In the meantime we can help our patients live longer and better by simply ensuring that each one is treated according to current knowledge and using international guidelines. It is wrong that patients continue to suffer at the hands of physicians who work in isolation and lack sufficient experience. The value of specialised breast units and teams is beyond dispute, but the 2006 European Parliament resolution has yet to be implemented in the vast majority of EU countries. Investment in research must continue, but it must be matched with urgent investment in education and reorganisation of cancer care. ■

Fatima Cardoso is Director of the Breast Unit of the Champalimaud Clinical Center in Lisbon, Portugal

Frédéric Amant

building the evidence base for saving mother and child

MARC BEISHON

Understanding the impact of treating the mother on the long-term health of her unborn child has long been held back by logistical and ethical obstacles to researching this rare patient population. Frédéric Amant took up the challenge.

One of the most astounding pictures to go 'viral' on the Internet recently is of a women breastfeeding her newborn son with her remaining breast after having undergone a mastectomy for breast cancer diagnosed during her pregnancy. Not long ago, the recommended course of action for many invasive cancers detected during pregnancy was an abortion, to then embark on life-saving treatment for the woman.

That's all changed now, in large part thanks to a gynaecological oncologist in Belgium who has made cancer in pregnancy his specialist field. As a result, his group – and those in other centres following his research – are now routinely able to not only save the life of the baby but also avoid compromising the mother's chances of surviving.

Most oncologists work in cancer because of the potential to save lives. Rare is the doctor who gets the chance to save two lives at the same time, as with cancer in pregnancy. That is because it is not common – about 1 in 1,000–2,000 women will be diagnosed while pregnant, although exact figures are not available. "Obstetric and cancer registries are separate, so no one really knows the full pregnancy connection," says Frédéric Amant, head of gynaecological

OLIVIER HOSLET

oncology at Leuven, and the doctor in question. "But with women in western countries having children later in life, there is likely to have been a rising incidence."

Given that there are about 5 million babies born each year in Europe, there could still be some 2,500–5,000 cases of pregnant women with cancer, with each potentially demanding a complex intervention from a wide range of professionals, from obs/gyn, medical oncologists, surgeons and counsellors, to the logistics of managing patients who would prefer to be at home.

All this used to be of purely academic interest, as treating a pregnant woman with chemotherapy has only recently become a standard option. "It was in 2002, after I had completed my PhD, that I started looking at new research options and I was confronted with a patient with cervical cancer who was 15 weeks pregnant. The standard treatment was abandoning the pregnancy and carrying out a hysterectomy. But she had lost a previous baby owing to premature labour, and this was her last chance. We explored the literature in a bid to save both lives."

Amant gave the woman chemotherapy, and she went on to have a healthy baby and both are doing well today. "We knew that others had given chemotherapy for a range of cancers –

It turns out that the placenta is excellent at protecting the foetus from the commonly used breast cancer drugs

breast being the most common in women of childbearing age – and that there was anecdotal evidence that babies were not harmed. But there were so many unanswered questions, and I decided then that this would be an area I could explore systematically and prospectively to really make a big difference personally, rather than playing a minor role in much larger fields such as breast and ovarian cancer research."

In just over ten years, Amant and colleagues have filled in much of the missing information and have paved the way for treating pregnant women with cancer. The most important question is about harm to the foetus, and whether there are later effects as a child grows up, which clearly takes time to answer, and research is ongoing. The results so far show little or no harm. "The reason that is the key question is that, if it is shown that chemotherapy is detrimental to the foetus, then other research becomes unnecessary. But now we have answered basic questions on foetal safety, we have also turned to other important questions such as maternal safety, as there was a belief that women had better chances if they had an abortion before treatment. But again, this is not the case," says Amant.

"Initially, though, it was hard to get grants to do this work, as funders just didn't think it was realistic. Even the powers here at Leuven didn't believe in it at first."

He set about publishing in high-impact journals to raise the profile of the subject, and has now succeeded in establishing an impressive body of work with colleagues, including the world's largest database of pregnant women with cancer, which is maintained at Leuven on behalf of the International Network on Cancer, Infertility and Pregnancy (INCIP).

Consensus guidelines for treating breast and endometrial/cervical cancers are now in existence, with haematological guidelines in preparation. A cohort of children born to women with cancer is being followed up, and a website, cancerinpregnancy.org, details and publicises the work, which also has cross-over into other research on younger women, such as preserving fertility. A key step, says Amant, was recruiting a communications and fundraising officer, Griet Van der Perre, to attract resources, in addition to support from the university.

But not all women, even in western healthcare settings, are yet being offered the chance to undergo treatment without a termination, says Amant. There are organisational obstacles – a smaller hospital may not have the multidisciplinary team needed, or may be unaware of a referral option to a centre such as Leuven. Like many rare cancer conditions, much often depends on a doctor being motivated to read the research and act on it, and there may be a lack of awareness even in larger centres.

"At a meeting last year in Paris I had an oncologist approach me from a large French centre saying he wasn't up to speed on our findings," says Amant. "We've had a young researcher from Italy working with us who would have liked to introduce the work when she returned home, but her boss took it over and then was too busy to do it. I even had a call from a journalist in New York who had cancer when pregnant whose doctors didn't want to treat her until she showed them our research."

Put bluntly, there are women now having unnecessary abortions in many countries – and Amant has a firm ethical stance that where the science shows that treatment is safe he will not perform an abortion if asked. "It does happen that a woman will ask for a termination against our recommendation – but she has to go elsewhere, as is her right. This is not a religious standpoint but an ethical respect for life – in one case a woman with breast cancer and a baby that was almost viable at 23 weeks did ask us to perform an abortion but I said, 'Your

baby has a right to live.' Sadly she went to another hospital to have a termination."

The key is confidence in the robustness of the science. Amant admits that at the start there were doubts. "Our counselling used to be less definite. There are also wider issues to consider, such as the views of the woman's partner, who could be left to bring up a child if the mother dies, and of course there are women who have advanced cancer, where it is often best to have a termination, or decide to go ahead anyway knowing they will die, and there can be heartbreaking meetings."

But now, for women with say early-stage breast cancer, Amant and colleagues are able to lay out the evidence that surgery, and chemotherapy and radiotherapy if needed, can proceed more or less the same as if the woman was not pregnant, alongside the ethical considerations of saving the baby's life.

"I used to spend an hour or so in outpatient meetings to explain the options. Now it takes 15 minutes. I used to also go to the labour ward to check the baby was normal after delivery. Now I don't need to. This is confidence in our work, and of course ensuring that patients trust it." He uses the term 'paradigm shift' to describe the change in practice, a term not to be used lightly, and which won't be proven until it is truly universal across healthcare systems.

The research on chemotherapy and the foetus comes partly from animal studies, in particular on baboons, which have a placenta that behaves in a similar way to a human placenta. Chemotherapy and indeed some targeted agents such as trastuzumab (Herceptin) had been given to pregnant women before the new research, but it was simply not ethical or safe to do this, says Amant.

The first point to note is that chemotherapy is not given in the first trimester, when the foetus is most vulnerable. It turns out, however, that the placenta, which offers little defence against substances such as alcohol, viruses and bacteria, is excellent at protecting the foetus from taxanes and anthracyclines, classes of drugs that are commonly used in breast cancer. "Only 1% and 5% respectively of these drugs are detected in the foetus compared with the blood level in the woman's own circulation," says Amant. "In fact all cytotoxic drugs are found in lower levels in the foetus, and some taxanes are actually undetectable, although other drugs have higher levels, such as carboplatin at 60%."

Antibody drugs are more of a problem, and targeted therapies such as trastuzumab should not be given. Amant says that where trastuzumab has been tried it affects HER2 receptors in the kidneys of the foetus. This can result in potentially life-threatening respiratory problems for the newborn child, because it leads to the foetus producing less urine, which in turn reduces the amniotic fluid which the lungs need to inhale in order to develop. Not giving trastuzumab is, therefore, one of few variations in standard therapy that a woman with early-stage invasive breast cancer can receive when pregnant (although hormone therapies should also be avoided until after birth).

There is time to plan drug treatment in the month after the first trimester, starting at 12–14 weeks

Breast cancer accounts for about 40% of instances of cancer in pregnancy (as with non-pregnant younger women), followed by haematological cancers at about 11%, and then cervical cancer where, although surgery is often not an option, neoadjuvant chemotherapy is.

Amant dispels other beliefs. "It was thought that pregnancy stimulates cancer and makes it more aggressive – but the prognosis is the same as for non-pregnant women with the same grade of tumour," he says, though he adds that breast cancer is often diagnosed at a later stage in pregnant women because changes in the breast can disguise lumps.

He also points out that being diagnosed with breast cancer in pregnancy is not an emergency, and there is time to plan drug treatment in the month after the first trimester, starting at 12–14 weeks (surgery can be carried out earlier).

There is some concern, however, about women who are diagnosed in the first year after giving birth (the incidence is similar to breast cancer in pregnancy), who are generally known to have worse outcomes than the general population of women with breast cancer. The reasons are the subject of current research and part of a spectrum of work that Amant and colleagues are engaged in on younger women.

Allied research includes investigating whether breast cancer raises the risk of a recurrence if a woman becomes pregnant (the evidence so far says not), and exploring the incidence of becoming pregnant during cancer staging or treatment, which seems to be around 3%, prompting calls for oncologists to discuss contraception with their patients, in addition to fertility.

It is the variation in obstetrics and gynaecology that drew Amant in. "I fell in love with it as a student and decided on it after being at my first caesarean section. Just surgery was too narrow – in obs/gyn I realised I could also do everything from endocrinology to fertility to cancer. I became particularly interested in cancer because, while not trivialising all the other complaints that women often have, they really do have major physical and emotional problems with cancer, and I had a lot of empathy with them and felt it would be a field that would have my interest for many years."

Amant, who trained at Leuven, wanted a post in gynaecological oncology there but was told there wasn't one, so went with his family to Pretoria, South Africa to do an oncology fellowship with no promise of a job on his return. "I then got a call from Leuven offering me a post – it was because they saw how motivated I was." For his PhD he started on his goal of selecting research in neglected areas by looking at uterine sarcomas, and went on to qualify as one of Belgium's first gynaecological oncologists, accredited by the European Society of Gynaecological Oncology (ESGO).

Since then he has also established himself as an expert in endometrial cancer, which is the most common gynaecological tumour and has a good prognosis, but again has been neglected. He chairs the EORTC's endometrium committee, and is the current chair of INCIP (International Network on Cancer, Infertility and Pregnancy), but has chosen not to pursue the presidency of ESGO or other larger societies – "I'm not a meetings person and I feel I can have more impact at Leuven," he says.

At Leuven, he has also established a platform for researchers in other cancers, with a new type of mouse model that uses patient-derived tumour xenografts – implanting human biopsies in mice provides an *in vivo* model that is more clinically relevant than using

cultured cell lines. "Essentially, we are cloning the patient's tissue in mice. Once a drug proves effective in mice, the success rate in a patient with the same genetic characteristics is much higher, and my group coordinates a xenograft service for nine tumour types so far at Leuven," he says.

That group is now 18 strong, and is rolling out more research, and also running events such as the recent International Symposium on Cancer in Young Women, held last February in Leuven, which divided into a day on cancer in pregnancy, and a day on topics such as fertility preservation, ovarian damage from treatment, pregnancy after breast cancer and uterus transplantation.

Amant's group is also involved with, or follows closely research on, mainstream breast, ovarian, cervical and others. There is still a lot to do in cervical cancer screening, where only 60% of Belgian women are in the national programme, he notes.

He is optimistic that the early results from the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS), a study of 200,000 women that has recently reported that testing the CA125 blood marker could detect twice as many women with ovarian cancer, will lead to a better outcome for this major killer.

The size of this study in sheer patient numbers highlights the difficulties in assessing outcomes in the far smaller numbers of women and children involved with cancer and pregnancy. That's why, says Amant, the Leuven registry includes a control of non-pregnant younger women who have had breast cancer along with those who had cancer during pregnancy.

This is where the results showing that survival rates are similar in both groups have come from, although there are limitations, as pregnancy data has been retrospectively pooled from hospitals in several countries, but the control is from one hospital, and there is only sparse information on factors such as family history of breast cancer. But Amant says it is much better than previous studies (see *JCO* 2013, 31:2532–40).

He accepts that lack of a control has been a valid criticism of follow-up work on children born to women with cancer, which may explain why some oncologists have so far been reluctant to recommend treatment. The published work is an observational study on the long-term cognitive and cardiac outcome after chemotherapy exposure (see *Lancet Onc* 2012, 13: 256–264).

Importantly, this study identified that children born prematurely do have associated cognitive impairment, so a key message is that there should not be a policy for early delivery, as has been previously recommended. "We have shown that babies suffer more from prematurity than they do from chemotherapy," says Amant.

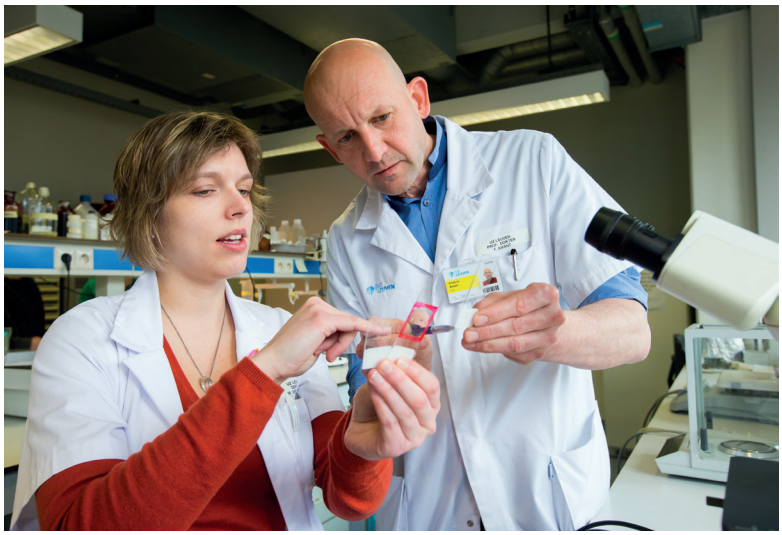
In this multicentre study, 70 children between one and 18 years underwent evaluations, with normal cognitive development seen in the majority. And there was no association with heart abnormalities. "A control group is the best way to improve the research," says Amant, who says that a case control study is underway. Early results were presented at ESMO last year, comparing 38 children with controls, but it needs to be published in a high-impact journal to take hold. His group is also carrying out follow-up work on children whose mothers were exposed to radiotherapy during treatment.

There is a challenge, though, in convincing older children, especially teenagers, to take an interest in the research "We do send them a

ANN DE WULF

Two lives protected. Lesley Verley is one of a growing number of women who have been treated at Leuven hospital with chemotherapy while pregnant; she is pictured here with husband Andy and newborn baby Marnix – now a healthy 5-year-old

"We have shown that babies suffer more from prematurity than they do from chemotherapy"



birthday card and we also hold a family day to link people in the project."

Another way of refining the research – and dependent on larger numbers and robust follow-up – is determining whether one type of chemotherapy could be responsible for certain harms. The current study pools all chemotherapies and is not large enough to draw conclusions on classes of drug, says Amant. "It may be that some are more toxic. There is a case report, for example, on cisplatin being associated with hearing problems. We also have only small numbers of children whose mothers received carboplatin, which does have higher levels in the foetus." At present, centres in the Czech Republic, Italy and the Netherlands are collaborating on such child follow-up studies with Leuven.

Given the small numbers – Leuven treats just ten women a year but gives advice to other hospitals – it is vital that more national and international collaboration takes place, adds Amant, but as other centres become confident in treating their own patients, more could be lost from Leuven's network of referrals and advice and its database, which is not good for the research. Also a potential confounder is the increasing use of targeted therapies, which could convince more women to terminate pregnancies in favour of new treatments.

That would be a shame, given the evidence that Amant's group continues to build. For example, his colleague Sileny Han has found that a sentinel node biopsy used instead of full lymph node dissection to stage breast cancer is just as applicable to pregnant women. "There are two issues – the foetus is not put at risk by the radioactive tracer used in the sentinel node procedure, and there was a concern that, with changes in a woman's lymphatic system during pregnancy, we might find more false-negatives. But follow-up has shown we don't see any more cancer recurrences, which we would if there were more false-negatives." He adds that Han, together with radiologist Vincent Vandecaveye, has also been looking at the use of whole-body MRI scans to see if they are detailed enough to show cancer sites in pregnant women.

But there are also women who have read about Amant's work and contact Leuven to take part in the research, notably Caroline Swain in the UK who was diagnosed with breast cancer when pregnant with her second son. There is a documentary and articles about her and her family at cancerinpregnancy.org.

More broadly, there is a concern that pregnancy is an understudied part of medicine from the point of view of other treatments, not just for cancer. Amant is on the advisory board of the Pregnancy and Medicine Initiative, which notes that "medical care during pregnancy is lacking proper data and approximately 90% of pregnant women take medicine without knowing the consequences."

Meanwhile a constant stream of media news stories on mothers treated for cancer during pregnancy from around the world show that there is still much to do in embedding this work in practice. A mark of progress may well be when these stories are no longer deemed newsworthy. ■

The vitamin D question: what's the best advice?

EMMA YOUNG

The beta-carotene fiasco warned oncologists off suggesting supplements on the basis of observational studies. But with vitamin D now in the spotlight, how should doctors respond when their patients ask if it could help?

A diagnosis of cancer can prompt a patient to make all kinds of changes. Many adopt a holistic attitude to their health, altering their lifestyle, and especially their diet, in the hope it will help. Some start taking supplements. And one supplement in particular is at the centre of a simmering controversy about whether it might help or harm. That's vitamin D.

In one camp are researchers and clinicians who argue there's no convincing data that vitamin D supplementation can improve cancer prognosis, and who fear it might even be dangerous. In the other, researchers and oncologists who argue that vitamin D deficiency is so widespread, and the preliminary clinical and lab data on cancer is so persuasive, it's high time to ensure that patients at least meet the current recommended levels.

"Although epidemiological and early clinical trials are inconsistent, and randomised clinical trials in humans do not yet exist to conclusively support a beneficial role for vitamin D, accumulating results from preclinical and some clinical studies strongly suggest that vitamin D deficiency increases the risk of developing cancer and that avoiding deficiency and adding vitamin D supplements might be an economical and safe way to reduce cancer incidence and improve cancer prognosis and outcome," wrote David Feldman, emeritus professor of medicine at Stanford University School of Medicine, and colleagues, in *Nature Reviews Cancer* last year (vol 14, pp 342–357).

In the same year, Bernd Richter,

of Heinrich-Heine University Düsseldorf, coordinating editor of the Cochrane Metabolic and Endocrine Disorders Review Group, was prompted to write a cautious editorial in the wake of an equivocal Cochrane Review on the impacts of vitamin D on cancer risk.

"As with other interventions, supplements are a deep interference with people's lives and they have to prove that the benefits as measured by patient-important outcome parameters outweigh the harms," he said, adding that: "Not many interventions in medicine are as much evaluated as vitamin supplementation – and have provided so little good evidence at the same time."

While the debate goes on, one thing is clear: patient interest in vitamin D is growing. While in the UK it's far from routine to check cancer patients' vitamin D status, in the US it's becoming much more common, says Kimmie Ng, assistant professor of medicine at the Dana-Farber Cancer Institute at Harvard Medical School. Ng is studying vitamin D status and colorectal cancer prognosis, for which there is some of the strongest observational data indicating a link. "I believe most US oncologists are aware of the data on vitamin D and colorectal cancer," she says. "Importantly, many patients are also very aware of this data. More and more oncologists whom I have spoken to are routinely checking levels in patients."

So how might vitamin D help cancer patients? And what advice should oncologists give to patients who say they want to start taking supplements?

Vitamin D can be obtained through diet or in supplements as vitamin D3 or vitamin D2. But synthesis in skin exposed to UVB light is an important source for most people. Vitamin D3 (cholecalciferol) made in the skin is converted by the liver into 25-hydroxy vitamin D [25(OH)D3], which is usually measured in blood to determine vitamin D status. Circulating 25(OH)D3 is then converted in the kidneys into calcitriol, a potent steroid hormone, and the biologically active form of vitamin D.

US and UK government guidelines recommend 25(OH)D3 levels of around 20 ng/mL of blood, while the US Endocrine Society recommends 30 ng/mL Yet one study of white Britons found that, in winter and spring, about half have vitamin D levels below the lower recommended figure, and 15% are deficient year-round. People with darker skin living at high latitudes are at an even higher risk of deficiency.

While it has long been known that vitamin D is essential for bone mineralisation, over the past twenty years it has become clear that it plays a role in the health of the immune system. Low levels have been linked to an increased risk of some autoimmune disorders – in particular, multiple sclerosis – and to more frequent upper respiratory tract infections.

The cancer link

The earliest suggestions of a link between vitamin D and cancer risk came from epidemiological studies finding variations in the incidence of certain types of cancer at different latitudes.

In 2008, for example, researchers at the Moores Cancer Center at the University of California, San Diego, looked at data on worldwide cancer

Most studies in cancer patients showed those with higher serum 25 (OH) D3 levels had a decreased risk of mortality

incidence and concluded there was a "clear association" between deficiency in exposure to UVB and breast cancer. Earlier work by the team, again using global cancer incidence data, found a "strong" association between latitude (and so perhaps UVB exposure) and kidney, ovarian and endometrial cancer.

Since then, various teams have taken a closer look at actual vitamin D status and cancer risk. Here, the evidence is inconsistent. A systematic review in Medline of prospective studies published up to February 2012 did find, though, that the majority of studies in cancer patients showed those with higher serum 25 (OH) D3 levels had a decreased risk of mortality. This was particularly clear in patients with colorectal cancer. Another systematic review and meta-analysis of prospective cohort studies of serum 25 (OH) D3 levels and survival in colorectal and breast cancer, specifically, found that higher levels (>30 ng/mL) were associated with "significantly reduced" mortality.

Yet another review of studies, which collectively examined vitamin levels in 17,332 cancer patients, found that overall a 4 ng/mL increase in vitamin D levels was associated with a 4% increase in survival. The strongest associations were between vitamin D levels and breast cancer, lymphoma and colorectal cancer. The association was less strong for lung, gastric, and prostate cancers, leukaemia, melanoma and Merkel cell carcinoma, but it still held. "Considering that vitamin D deficiency is a widespread issue all over the world, it is important to ensure that everyone has sufficient levels," says Hui Wang, professor of the Institute for Nutritional Sciences at the Shanghai Institutes for Biological Sciences, who led the research. "Physicians need to pay close attention to vitamin D levels in people who have been diagnosed with cancer."

Cedric Garland at the University of California, San Diego, who was part of the team that published the analysis of global cancer incidence and latitude, has also been involved in work investigating the vitamin D status of breast cancer patients. This work (*Breast Journal* 2008, 14:255–260) found that those with "high" levels of vitamin D in their blood (with an average of at least 30 ng/mL of 25 (OH) D3) were twice as likely to survive the disease (at a nine-year follow up) than patients with low levels (with an average of 17 ng/mL).

In the wake of these particular results, Garland said: "There is no compelling reason to wait for further studies to incorporate vitamin D supplements into standard care regimens, since a safe dose of vitamin D to achieve high serum levels above 30 nanograms per milliliter has already been established."

There are others who, like Garland, would certainly like to see more randomised clinical trials involving giving supplements to patients, but think the current observational data is compelling. But there are also critics of some of the conclusions drawn from the observational studies.

Correlation or causation?

Kimmie Ng's own work has found improved survival in colorectal cancer patients with higher vitamin D levels. But, as she says, hers and other prospective observational studies "do not prove causality". She adds: "There is still quite a debate, with many scientists on both sides. Most people agree that the epidemiological data has been strongest and most consistent in colorectal and breast cancer. Sceptics point out that higher vitamin D levels may simply be a surrogate for a healthier lifestyle, and thus better outcome. Yet other sceptics argue that higher levels of inflammation in cancer patients – or other poor prognosis factors associated with more aggressive disease – lead to lower vitamin D levels and thus poorer survival."

Like David Feldman at Stanford,

Sceptics point out that higher vitamin D levels may simply be a surrogate for a healthier lifestyle

SOURCES OF VITAMIN D

Most people meet at least some of their vitamin D needs through exposure to sunlight. Season, time of day, length of day, cloud cover, smog, skin melanin content, and sunscreen are among the factors that affect UV radiation exposure and vitamin D synthesis. Some studies suggest that approximately 5–30 minutes of sun exposure between 10 am and 3 pm at least twice a week to the face, arms, legs, or back without sunscreen usually lead to sufficient vitamin D synthesis. Very few foods in nature contain vitamin D. The flesh of fatty fish (such as salmon, tuna, and mackerel) and fish liver oils are among the best sources, while small amounts of vitamin D are found in beef, liver, cheese, and egg yolk. Vitamin D is often added as a supplement to breakfast cereals, orange juice and, in some countries, milk.

Source: US National Institutes of Health http://ods.od.nih.gov/factsheets/VitaminD-HealthProfessional/

* Value for 1 cup of orange juice fortified with vitamin D (check product labels, as amount of added vitamin D varies)

Cedric Garland points to lab research demonstrating that vitamin D has anticancer properties. This work is "abundant", Ng agrees. Vitamin D receptors have been found on a wide range of tumour cells, and Ng says: "We know that vitamin D can decrease cell proliferation, induce cell division and apoptosis, inhibit angiogenesis and metastasis, and has anti-inflammatory properties. Vitamin D can also stimulate host immunity against tumours."

And in January 2015, a team involving researchers at the Dana-Farber Cancer Institute published a paper in *Gut* (doi:10.1136/gutjnl-2014-308852), showing an effect of vitamin D on anti-cancer immune function in actual patients.

Julia Newton Bishop is a professor of dermatology and a clinician, who leads the Melanoma Research Group at the Leeds Institute of Cancer & Pathology, in the UK. She and her colleagues have found that vitamin D can inhibit melanoma cell growth in the lab. Her team has also published work finding that patients with higher levels of vitamin D had thinner tumours at diagnosis. Still, she's cautious about extrapolating lab findings to people. "I don't think there's any doubt that if you put a variety of different cell lines in culture and you add vitamin D you can stop them proliferating. We've reproduced that in our lab, and are just writing the paper up. That is agreed. But of course when you're growing cells in the lab, it's quite artificial. How that translates into man is what we're working on at the moment."

Data from various animal cancer models show that dietary vitamin D3, calcitriol and its analogues cause "a significant reduction in tumour growth and eventual tumour burden," write Feldman and his team in their 2014 review. They write: "The preclinical findings suggest how calcitriol regulation of crucial molecular pathways might inhibit the development and progression of multiple cancers." But, so far, the results of vitamin D intervention trials in people have been, as Newton Bishop puts it, "disappointing".

The 2014 Cochrane Review of randomised trials testing the effect of supplementation (whether with D3, D2 or calcitriol) concluded the results were "contradictory". While there was no increase or decrease in cancer occurrence, there was some evidence for lower cancer mortality following vitamin D3 supplementation, although the overall quality of the evidence was rated as low.

The wrong dose?

With colorectal cancer, the few randomised clinical trials that have been done have either not shown a benefit for vitamin D supplementation on colorectal cancer risk, or have looked at it as a secondary, rather than a primary endpoint, says Ng. One debate centres over the serum levels that may be most beneficial, and so the doses that should be used in trials. One large US Women's Health Initiative

trial, involving calcium and vitamin D supplementation, found no improvement in colorectal cancer risk. But Ng argues there were many limitations to the study. It used what she calls a "very low" dose of vitamin D (400 IUs) and had, she argues, too short a duration of supplementation (the women, aged 50 to 79, were followed for an average of seven years). In addition, she notes, there was poor compliance with the supplementation protocol.

Many cancer patients in the US, after being checked for vitamin D, are being repleted to at least 20 or 30 ng/mL or higher, Ng says. And some patients may be reaching significantly higher levels.

Nithya Ramnath, associate professor of medical oncology at the University of Michigan Health System, has found anti-proliferative effects of calcitriol in lung adenocarcinoma (in *in vitro* studies). "Many of the [lung cancer] patients in the US are already on 1000–2000 IUs per day, prescribed by their primary care doctors," she says.

It's unclear what level of vitamin D might be needed for anti-cancer effects, but the animal work suggests that it's higher than the level recommended for bone health, Feldman and his team point out. The research on multiple sclerosis suggests that blood levels above 40 ng/mL are most beneficial. One large multicentre clinical trial that has been underway at Johns Hopkins University, in Baltimore, Maryland, and elsewhere, for over a year, on patients with multiple sclerosis, uses doses of up to 10,000 IUs of vitamin D per day. So far, there have been no reports of any cases of hypercalcaemia, which is the most likely risk from high doses of vitamin D.

Since the body self-regulates levels of vitamin D synthesised in the skin, some researchers argue that sun exposure may be a safer way for some people to get as much vitamin D as possible. The advice may not be very practical for people who live in a part of the world that provides inadequate UVB year-round. There's also the problem that sun exposure is the biggest major environmental exposure increasing susceptibility to melanoma of the skin.

However, the epidemiological evidence suggests that it's intermittent sun exposure – the sort experienced on sunny holidays, and which is often associated with sunburn – that explains most melanoma in genetically susceptible people (those with pale skin, freckles, a tendency to red hair, lots of moles and a family history), says Newton Bishop. There's evidence that these people are often deficient in vitamin D, and they will probably need supplements to obtain adequate amounts, she says. Other groups of people should be able to spend some time in the sun (without burning) without raising their melanoma risk, she says. NICE, the UK's National Institute for Health and Care Excellence, is currently developing a public health guideline on the health benefits versus risks of sun exposure, she adds.

But some researchers think the debate about the desirable dosage for intervention trials is, at least in the case of some cancers, questionable – because researchers have been using not the wrong dose, per se, but the wrong *type* of vitamin D.

The wrong type?

Ronald Evans, director of the Gene Expression Laboratory at the Salk Institute in La Jolla, California, is involved in human trials of a vitamin D derivative, paricalcitol, in combination with regular chemotherapy in patients with pancreatic cancer. This follows work by his team finding that paricalcitol can collapse the 'living shield' of protective cells that a pancreatic tumour generates around itself, and which can stop therapeutic drugs from getting through.

These initial lab findings were a big surprise, because vitamin D had been tried multiple times as a therapy for pancreatic cancer, and never worked, Evans says. This is partly because it turns out that normal vitamin D is rapidly broken down by the pancreatic stellate cells, which prevents it from binding to the vitamin D receptor on these cells. Paricalcitol, in

VITAMIN D LEVELS AND DOSES

20 ng/mL: guideline serum level of 25(OH)D3 recommended by US and UK governments

30 ng/mL: guideline serum level of 25(OH)D3 recommended by the US Endocrine Society

400 IUs: daily vitamin D supplement for melanoma patients recommended by head of Melanoma Research Group at Leeds Institute of Cancer & Pathology (UK) in patients with 25(OH)D3 levels below 24-34ng/mL range

1000–2000 IUs: daily vitamin D supplement prescribed in US to many lung cancer patients

2000 IUs: daily vitamin D supplement being trialled as a cancer preventive in people with a prior history of cancer (VITAL trial)

Up to 10,000 IUs: daily vitamin D supplement being trialled for people with multiple sclerosis

"We all have to live with probabilities instead of certainties of the results of medical research"

contrast, he says, is very resistant to degradation. So it can successfully inactivate the cells, weakening the wall around a tumour. It's important to note that vitamin D isn't attacking the tumour, he adds – but rather making standard chemotherapy more effective. A study published by the team in September 2014 in *Cell* (vol 159, pp 80–93) found that mice given paricalcitol plus regular chemotherapy lived 50% longer than mice given chemotherapy alone.

Yes, he says, many vitamin D intervention trials have failed to provide positive results. "However, these trials may have been doomed to fail, as our work suggests that the standard vitamin is rapidly degraded by tumours. This is why the use of a modified form is important," he says. Evans hopes it may also be useful for other cancers. "We suspect colon cancer and liver cancer may also benefit from this type of therapy, and we are exploring this possibility," he says.

But while some researchers are clearly excited or at least encouraged about the potential for vitamin D in cancer treatment, others are very cautious.

A major reason for widespread wariness, at least among oncologists in the UK, is because of what happened with beta-carotene, Newton Bishop says. Epidemiologic studies had suggested that vitamin E and beta-carotene were associated with a reduced risk of lung cancer. But a big Finnish study found that men who were given beta-carotene were more likely to die of lung cancer. "That terrified a lot of people," says Newton Bishop. "It gave people the view that you really can't trust observational studies… But if it wasn't for observational studies we wouldn't know that lung cancer is caused by cigarette smoking. These studies are a way of identifying a potentially important thing, which you then have to prove. And then it's difficult to prove. But that's what we're looking at now."

A few randomised controlled trials investigating the impacts of vitamin D on cancer are ongoing. The VITamin D and OmegA-3 (VITAL) trial, for instance, is investigating whether daily dietary supplements of 2000 IUs of vitamin D or 1 gram of fish oil or both reduce the risk of developing cancer (as well as heart disease and stroke) in people without a prior history of these illnesses. But the results will not be available for many years – and the findings may still engender controversy, say David Feldman and his team.

When patients ask...

For now, in the absence of convincing data to the contrary, Newton Bishop says she feels most comfortable aiming for a 25 (OH) D3 serum range of 25–35ng/mL – roughly the level recommended by the US Endocrine Society. A supplement of 400 IUs per day should bring most people into that range, she says. With her own melanoma patients, she says: "in practice, we've measured vitamin D and if it's low, then I've counselled very slow but steady supplementation to that range."

At the moment, patients being treated in Leeds don't tend to ask for vitamin D testing themselves. "It isn't common in Yorkshire to be asked about vitamin D. But I think there's regional variation in interest. Certainly, one gets a lot of email from the US, where they tend to be much more proactive with their health," says Newton Bishop.

Given the abundance of current research, particularly in the US, and the publicity it's attracting, it seems likely that more European cancer patients will start asking for tests. And while many oncologists may be cautious about any potential role for vitamin D, it is something they can expect to be increasingly asked by their patients to advise on.

"The vitamin D story is a… good example of how difficult it is to adequately analyse and critically appraise scientific data," argues Berndt Richter in his editorial. "We all have to live with probabilities instead of certainties of the results of medical research, and this has to be openly and sensitively communicated during any patient–doctor encounter to optimise shared decision making."

On the basis of the existing evidence, Feldman and his team conclude that, while they believe adequate anti-cancer 25 (OH) D3 levels "probably exceed" 30 ng/mL: "The easy availability, economy and safety of this multipurpose pre-hormone indicate to us that the benefits of dietary vitamin D can be recommended, even while we await RCT data." ■

Who should we screen for the BRCA gene?

MARIA DELANEY

Most people carrying harmful BRCA mutations only find out after they are diagnosed with cancer, and often not even then. Population screening is costly and the results can be hard to interpret. But should we do it anyway?

Trish Carlos walks through the door and recognises familiar faces. All looking and wondering. She gives them an inquisitive look… they must be pregnant. Why else would they be in a maternity hospital. But then again, why was she here?

Just a few months previously the dark-haired school teacher from the hilly seaside town of Cobh in Ireland had been standing on the same corridor holding a baby boy. This time excitement is replaced by anxiety. She sits down next to her husband Declan and waits to be called. The genetic service comes down from the Irish capital, Dublin, to the southern city of Cork once a month, and rents a room in the hospital. Trish has been waiting for eight months for today's blood test.

They walk into the rented room. One like any other in the hospital, with a simple desk and examination bed. The geneticist explains that Trish is being tested for a mutation in a gene called *BRCA1* that is linked to breast cancer. She goes through some of the symptoms and says that a mutation can give you a higher risk not only of breast cancer, but ovarian cancer as well.

They leave the room, walk down the corridor without talking and go straight to the car. Trish looks at Declan, dying to say…

Before she gets a chance, he says: "You don't have to say it… I know what you're going to say. You have all of them."

"Yeah!" Trish knows he is talking about the symptoms, the little markers the geneticist had mentioned: early periods, abnormal growth of cells... She'd had a benign tumour removed, aged 13.

"Look it mightn't be. It might be just coincidental."

Trish is one of around 1,500 patients who are seen each year in Ireland for hereditary cancer. Most are related to breast cancer, says Andrew Green, director of Ireland's National Centre for Medical Genetics. "The way people are identified is either because they themselves have had cancer at a young age or they have relatives at young age with breast or ovarian cancer."

The BRCA genes are among the highest profile pieces of DNA that have been linked with cancer. Specific mutations in *BRCA1* and *BRCA2* genes increase the risk of breast and ovarian cancer. These genes produce tumour suppressor proteins, which help repair damaged DNA. If they're not working properly, cells are more likely to develop genetic alterations that can lead to cancer. The harmful mutations are autosomal dominant, which means that you only need one copy of the faulty gene to have a higher cancer risk.

Currently, genetic tests are recommended in most countries when a family history indicates that harmful mutations could be present. Trish's aunt Josephine had been diagnosed with ovarian cancer almost a decade ago, and because her sister had died of breast cancer, Josephine's doctor had suggested BRCA testing. They discovered a *BRCA1* mutation and recommended genetic testing to other members of the family. A few years later, this led Trish and her siblings to the maternity hospital.

Preventative measures can be taken by women with these faulty genes, which include regular breast screening, risk-reducing surgery and the use of cancer-preventing drugs. Actor Angelina Jolie, who has a *BRCA1* mutation, highlighted risk-reducing surgery when she revealed that she had opted for a preventative double mastectomy, and more recently removal of her ovaries and fallopian tubes.

Six weeks later, Trish is back in the same room for her results. The geneticist opens the sealed brown envelope and says: "unfortunately, you have it" – a mutation in the *BRCA1*

"To identify a woman as a carrier only after she develops cancer is a failure of cancer prevention"

gene, leaving Trish at very high risk of both breast and ovarian cancer. The geneticist is surprised that Trish isn't more upset. "We had a feeling that I probably did," she explains.

Her test result means that Trish is registered in the monitoring unit where she will have regular mammograms, ultrasounds, MRIs and blood tests. Abnormalities will be checked immediately in the hope that any cancer will be picked up and dealt with as early as possible. Down the line, preventative surgeries to remove the breasts and ovaries are also an option. "Do you have any questions?" The new mother sits there trying to take the information in. Is she being told that she could lose her ovaries, in of all places, a maternity hospital?

A failure of prevention?

If Trish had no suspicious family history, her mutation would not have been picked up unless she herself was diagnosed with cancer. The same would have been true for two of her sisters and other members of her extended family who were subsequently tested and found to carry the same mutation.

Mary-Claire King who was instrumental in finding the first breast cancer gene, *BRCA1*, in 1990, says "to identify a woman as a carrier only after she develops cancer is a failure of cancer prevention."

Last September, together with two other leading researchers, she called for population screening for harmful BCRA mutations to be introduced. "Based on our 20 years' experience working with families with cancer-predisposing mutations in *BRCA1* and *BRCA2*, it is time to offer genetic screening of these genes to every woman, at about age 30, in the course of routine medical care," they argued (*JAMA* 2014, 312: 1091–92).

Ephrat Levy-Lahad, a co-author of the *JAMA* article, and director of the Medical Genetics Institute at Shaare Zedek Hospital in Jerusalem, says that it wasn't something that just popped into their minds. "It was based on data."

These data came from research on Ashkenazi Jews. Three BRCA mutations are common in this population, present in 1 in 40 people. Among the general population (excluding Ashkenazi Jews), the likelihood of having any BRCA mutation is about 1 in 400.

It was known that having a family history of cancer as well as a BRCA mutation is associated with a high risk of getting cancer. Levy-Lahad wondered if those with no family history had the same high risk.

"We tested 8,000 Ashkenazi men and 10% of them had a mother with breast cancer, which is what you would expect with breast cancer rates," explains Levy-Lahad. The group found 175 BRCA carriers across the study population of 8,000, and "saw that cancer rates for carriers was just as high as it is in other families that are found in cancer genetics clinics." This means that breast and ovarian cancer risks are high in women who carry mutations in *BRCA1* or *BRCA2*, even if these women do not have a family history of cancer. It led Levy-Lahad to strongly feel that "every woman identified as the first in her family, only after she became infected, is a missed opportunity to prevent."

Not everyone agrees with King and Levy-Lahad that BRCA testing should be rolled out to every woman. Karuna Jaggar, executive director of Breast Cancer Action in the US, which played an active role in challenging the Myriad Genetics patent on the BRCA gene, has a number of reservations. "Here in the US, we generally live in a 'more is better, information is knowledge' culture that is pro-screening and fails to discuss its limits and harms," she says.

While she respects King and agrees that more women need access to breast cancer testing, she worries about rolling out population screening without sufficient capacity to provide genetic counselling. "I see people

"Breast and ovarian cancer risks are high in women who carry BRCA mutations even if they have no family history"

who feel they were not informed about the harms and limits of the test before they engaged in it. I see people who talk about the way that family relationships are disrupted and they did not anticipate that. I talk to people who will never know if they lost insurance or their insurance premium went up because they had done BRCA testing, but they're concerned about it."

She feels it's wrong to test people for mutations without full consultations about what the test does and doesn't mean. "You cannot have informed consent without genetic counselling."

A duty to counsel

The current requirement for genetic counselling, when a test is done in a clinical setting, means that waiting lists for BRCA tests are getting longer, because there are too few qualified professionals. In many countries, people with a family history are having to wait more than a year.

Judy Garber, Harvard Medical School professor and director of the Cancer Risk and Prevention Clinic at the Dana-Farber Cancer Institute, points out that most people in the general population will test negative and they probably don't need as much counselling. "But we have a lot of data showing that women who do get genetic counselling and make informed decisions cope very well with the information, even when it's bad."

Ian Jacobs, vice-chancellor of the University of New South Wales in Australia, and a leading researcher in the area of women's health and cancer, conducted a recent cost effectiveness analysis of population screening in the Ashkenazi Jewish population in the north London. He hopes it may be possible to streamline the counselling approach so it's much less time-intensive. "One could have a fairly light-touch counselling probably for most of the population, and a more intense counselling for people who have abnormal results." He believes this would need to be properly evaluated in a trial before rolling out any testing. "You don't [want to] cause more psychological harm than benefit."

An argument for population screening? Trish Carlos found out she carries a harmful BRCA mutation only after one of her aunts died of breast cancer and another developed ovarian cancer

Trish puts a brave face on her diagnosis, but behind closed doors the psychological impact is very real. She feels that her breasts and ovaries are her female identity, and thinks forty is a very young age to be expected to give up all of that. She is scared senseless when she thinks about early menopause or losing her breasts, the one part of her body that she never had a problem with.

She keeps having the same conversations with her husband, who she has loved since they met at school 21 years ago.

"You're not going to find me attractive"... "You won't want to have sex with

She feels her breasts and ovaries are her female identity, and forty is very young to be expected to give up all of that

"ALL WOMEN SHOULD HAVE THE RIGHT TO BE TESTED AT DIAGNOSIS"

DAN TSANTALIS

Florence Wilks, who lives in London, was diagnosed with ovarian cancer five years ago. Following rounds of chemotherapy, surgeries and two subsequent relapses, she is now on maintenance therapy. Though her mother died of cancer of the vulva, Florence had no family history of ovarian or breast cancer. She wasn't offered BRCA testing when she was first diagnosed and only found out about it at a conference last year. After requesting a test she discovered that she had the *BRCA2* mutation.

"It has implications for my future treatment but also for my family and children," she says. Florence believes that all women should have the right to be tested on diagnosis: "The first step is to offer it to women who have been diagnosed with ovarian or breast [cancer], and once that is done it should be offered more generally to the wider population of women," she says.

Routine testing for harmful BRCA mutations is a high priority for Ovarian Cancer Action in the UK. Acting chief executive Katherine Taylor says it is important but currently only happens in a few countries, such as Scotland: "It determines the patient's treatment path," and can help family members "make informed decisions about their healthcare."

"My prognosis is a lot better now," says Florence, who has been told that upcoming treatments work particularly well with women who have her *BRCA2* mutation. "I now believe my future is much brighter. Each day is a gift and nothing is impossible. At one point I could not allow myself to think about my children's weddings or grandchildren, but life is different now!"

Florence's children haven't decided if they want to be tested yet, but she feels that if they also have the mutation, they will have a better outcome than her due to enhanced screening and possibly preventative surgery.

"If we're talking about ultimately sequencing all our genes, well let's start with a couple and see how that goes"

me"... "You're not going to love me."

The constant 'what ifs' and the fear of losing him. Declan keeps saying that she has nothing to worry about, that they'll deal with it together. But it's the unknown implications that frighten her, sometimes to tears. She will have a lower risk of cancer, but how will it affect everything else?

Balancing costs and benefits

The research community are also wondering what the future holds. Jacobs feels that properly designed large-scale population studies are the way to find out whether BRCA screening should be part of it.

One of the factors that need to be considered is whether population screening is cost-effective. The study by Jacobs and his collaborators on screening in the Ashkenazi Jewish population in north London found that, in this population, it is (*JNCI* 2015, 107:dju380).

Evaluating the costs (test and counselling) versus savings (avoidance of cancer and cancer treatment) involved in testing for the three mutations that account for the great majority of harmful BRCA mutations in this population, they found "it works, is successful, there's no psychological harm and is cost effective." Jacobs adds that "there are few things in medicine that you actually save money by making an intervention, but it would seem that this sort of testing in that population saves money as well as saving lives."

When it comes to the general population, however, the cost-effectiveness equation looks very different. The benefit is much lower because you would expect to find a harmful mutation in around 1 of 400 screened in contrast to 1 in 40 among Ashkenazi Jews. The costs will also be higher, because a wide variety of harmful BRCA mutations are found in the general population.

As Jacobs says, general screening would "involve mutation testing for the entire gene, so there is significant expense, though the cost of that is coming down considerably. One would also have to consider the psychological impact of [screening in] the general population where people are not expecting to have a high risk."

Levy-Lahad says there is a lot of research being done on screening of Ashkenazi Jews in Israel, and adds that population screening there is only a few years away. She is not concerned about the lower frequency of BRCA mutations in the general population. "It's going to be rare but it doesn't mean it cannot or shouldn't be done. If we're talking about ultimately sequencing all of our genes, well let's start with a couple and see how that goes. It would be a very interesting test case."

An expensive test case, according to Jaggar, who says it will cost $150 billion to test all the women in the United States aged 30 or over. "I took a very conservative price of $1,000 per commercial test. It's easily more than that!" She says that there are many women in the US who currently have cancer who aren't getting the resources they need. "This is in no way to say that women with mutations are less important, it's to say we need to decide how are we going to prioritise our healthcare delivery and our research agenda."

Who benefits?

Another worry for diverse populations is that most genetic research is done on white people of European ancestry. This means that there is currently a lot less known about the genetics of other populations. Aside from Ashkenazi Jews, ethnic and geographic populations known to harbour specific harmful *BRCA1* and *BRCA2* mutations include Norwegians, Dutch, and Icelandics.

This is one of Garber's concerns. "In the US, in the minority populations, not so many people have been tested, so variants would be a problem. That means we would be reassuring some people that they were fine when they were not."

"If they are given information about specific cancer genes, but not others, they may be falsely reassured"

"Something needs to be in place before you do the test, so people can realise what it is and can decline or accept"

Variants of unknown significance (VUS) are a common problem in genetics due to the huge variation in the human genome. Like mutations, they are changes in the DNA that can be found during genetic tests. The meaning of a lot of that variation is not known. In the case of BRCA genes, that means with a VUS result it isn't clear whether you have an increased risk of breast or ovarian cancer. "It's not a yes or no," says Breast Cancer Action's Jaggar. "What are they supposed to do with that?"

These variants are one of Jaggar's main arguments against widespread BRCA screening. "The existence of variants of unknown significance and their relative problems, [demonstrate] how complex genetic testing is. They highlight the necessity for genetic counselling and true informed consent."

Levy-Lahad points out that "you never understand everything," so only mutations that are known to be damaging should be reported back. She suggests there are ways around the unknowns, such as people contacting the testing centre every few years to check for new information.

The Israeli-based doctor says that it doesn't make sense to stop testing because a small minority will find out something that is not yet fully understood. Jaggar thinks this proposal not to tell women is "deeply problematic". She is concerned that this would "further the over-simplification and binary thinking" surrounding genetics. "We need more education for the public about this topic as it's much bigger than BRCA."

Garber also believes education is important and says it is currently unknown how women with little education would react to population screening of BRCA or any other genetic test. If they are given information about specific cancer genes, but not others, "they may misunderstand and may be falsely reassured," says the Harvard professor. They may think "'great... my test is negative. I can't get breast or ovarian cancer' which of course is not true".

'It's inevitable'

Shirley Hodgson, professor of cancer genetics at St George's, University of London, who sits on the Public and Professional Policy Committee of the European Society of Human Genetics, shares many of Garber's concerns.

She argues that, before screening everyone, a proper framework needs to be in place to deal with the consequences of the test, "so that if somebody comes up positive, they have a standard course of action." She is worried about the approach taken by 23andMe, a company that offers health and ancestry genetic testing, direct to consumers, for under €200.

The results include the three most common BRCA mutations, if you take the test in Europe. "They have a blurb that if you have a mutation, you are high risk and you should go and see your doctor," says Hodgson. "I worry that something needs to be in place before you do the test, so people can realise what it is and give them enough information so that they can decline or accept what they're in for."

In the United States, the FDA have currently stopped the company issuing these results. Hodgson feels, however, that genetic population screening is inevitable. "I think that if we go slowly then hopefully people will understand sufficiently and the systems will be in place to deal with it."

This inevitability of genetic screening is the one thing that most experts agree on. Jacobs feels King's comments last year were a "push in the right direction" but further research is needed. Garber says that, in time "we should be able to do this for everyone, not just for their breast cancer genes but for all their genes with one test but we're just not quite there yet." Levy-Lahad, who co-authored the controversial article that spurred on this debate, also says that "it will probably take a couple more years," as studies need to be conducted. "What you always hope for is that you can inspire discussion with scientific data that will ultimately lead to better care for people."

Back in Cobh, Trish now has a second boy and at 35, has another few years before she opts for the preventative surgery that has been recommended by her doctors.

She finds that cancer patients and survivors are the most understanding of her situation. They put her on the same level and know what she might face down the line. "It's a burden. Something you carry with you all the time." ■

Medical tourism: a passport to timely high-quality cancer care?

ANNA WAGSTAFF

For many patients seeking access to treatments unavailable in their home country, the Cross-border Healthcare Directive turned out to be a bit of a disappointment. But a closer look shows it may help raise standards of care in ways that were not widely anticipated.

When Miljana Marković was diagnosed with breast cancer, the news wasn't all bad. The disease had been detected in time to be safely treated with breast conserving therapy, and this was an option she was keen to go for.

But she was worried. Not about the surgery, but about the adjuvant radiotherapy that would be needed afterwards to kill any stray cancer cells that may have been lurking in her breast tissue after the lump had been removed.

Serbia, her home country, has a quarter of the radiotherapy capacity that it needs. Waiting times are long, machines are old, and frequent breakdowns can bring interruptions to a planned sequence of treatment.

Miljana (not her real name) was married to an oncologist, and knew that delays and interruptions could reduce the effectiveness of treatment. After weighing up her options, she decided to travel to Paris for her course of radiotherapy, paying her own costs for the treatment, travel and accommodation.

Miljana was looking for the treatment that would give her the best chance of the outcome she wanted. But by stepping out of her own health system, and finding her own way to healthcare providers in another country, she became a consumer in the "health/medical tourism" market – where a lack of agreed standards and regulation leaves consumers wide open to exploitation.

The health tourism market

In the public perception, particularly in the West, the sector is dominated by services aimed at healthy, relatively wealthy populations – cosmetic surgery, dentistry, IVF and laser eye treatment – often carried out in exotic locations and increasingly in slightly less exotic locations across eastern and central Europe.

The services are frequently marketed by agencies as a package that bundles together travel and accommodation, an introduction to the medical facilities, translation services, help with the paperwork, and even sometimes sightseeing or shopping trips.

The image is not entirely positive. Though many centres have worked hard to establish a good reputation, trust in the sector is undermined by a steady stream of horror stories appearing in the mass media about false promises, hidden charges, and botched

jobs that have to be corrected, often at great expense to the client or their own health services.

Far less visible are the 'medical tourists' who travel in the opposite direction, looking for high-quality treatment rather than a low price. People like Miljana generally head for medical teams with good reputations, but often have to rely on facilitators or agencies if they don't have family connections in the destination country, or language skills, or familiarity with the bureaucratic procedures.

The 'patient touts'

Two years ago, the darker side of some of these services were exposed by two German journalists, in an article in *Die Zeit* titled 'Patient touts' (middlemen that go looking for customers), which won them the 2013 European Health Journalism prize. The article, which was republished in *Cancer World* (May–June 2014), exposed the extortionate payments being demanded by some agents, often well beyond the sum initially agreed, and with no attempt to provide receipts or a breakdown of where the money had gone.

More worryingly, it revealed systematic collusion between some private hospitals and the touts, with fees of up to 22% offered as a bounty for every patient brought in. Rather than providing a service to people who wished to get treatment abroad, these agents effectively act on behalf of the hospital, with a mission to convince patients of the benefits of getting treated at a particular facility.

Far less visible are the 'medical tourists' who travel in the opposite direction, looking for high-quality treatment

The advice amounted to spending €16,500 before consulting a single oncologist – let alone a world specialist!

The result, as was movingly told by one nurse, is that patients can use up their family savings on treatments that are never likely to benefit them, only to end up dying in a hospital bed far from home and all alone.

The increasing complexity of cancer diagnostics and treatment in the era of personalised medicine, and the rapid pace of new knowledge, puts pressure on patients even in more reliable health systems to search out the top international specialist for their particular cancer.

This is creating a market for supposedly "privileged information", often of dubious value at exorbitant fees. One online service, run by a man whose CV shows he has never worked as an oncologist, offers to "act as *the patient's advocate*" (original italics).

"We offer *medical advice* to the patients that come to us and we offer them to find the best possible medical solution …. We take them by their hands and walk with them. From being in the 'cold' you will now feel 'protected'. Our patients feel empowered with their feet on the ground. With our assessment you will become a *wise patient*."

What this meant for one breast cancer patient was a proposal that she should spend €7,500 on a test for a set of genetic mutations that is available online at one-tenth the price, plus a further €6,500 for having the results interpreted – which should be the job of her medical team.

She was warned against using any of the three oncologists she was considering – all leaders in the field of personalised treatment of advanced breast cancer – and was advised instead to use the agency's own "find the top doctors in the world" service, which, for a fee of €2,500, applies a custom-made algorithm with 33 parameters to a literature search for the specific pathology in question. The advice amounted in total to spending €16,500 before even consulting a single oncologist – let alone a world specialist!

Stories like this are fuelling calls for greater regulatory oversight of the health tourism sector, including accreditation for the agencies and rules about what they can and cannot do. The call is backed by many players in the industry, some of whom have long been expecting a boom in business, and blame lack of consumer confidence in part for its failure to materialise.

The industry nonetheless feels in buoyant mood, not least in Europe, where private healthcare providers have gained new access to Europe's massive public healthcare budgets through the EU Cross-border Healthcare Directive, which came into force in October 2013.

Why travel?

A number of factors are set to fuel a rapid increase in the numbers of people seeking to travel abroad for cancer treatment. The spread of "patient power" across Europe means more people are taking the initiative to find out what they need and where they can get it, rather than just settling for what they are offered.

The survival gap between east and west Europe, though not as dramatic as when it was first documented in the early EUROCARE studies, still persists, providing a continued incentive to travel to places that achieve better results.

This gap may well be widening again due to cuts in public spending, which are likely to spell the end of the relatively rapid improvement in survival rates that some of the worst performing countries showed in the 1990s and early 2000s.

This same austerity – public spending cuts and a fall in the number of people who can afford private health insurance – is also creating a "pull factor", as hospitals in many west European countries look to attract patients from other countries to boost their budgets or fill empty beds, the self-same pressures that gave rise to the 'patient touting' reported in the *Die Zeit* article.

This was reflected at a high-profile International Medical Travel Summit in London in April 2015, where delegates from major hospitals in Italy, Spain, Portugal and the UK – including a major NHS hospital – mingled with delegates from facilities in more traditional health tourism destinations such as Dubai, Saudi Arabia, Turkey, the Philippines, Malaysia, Hungary and Poland.

Waiting times have also been increasing in public sector facilities, fuelled in some countries by public hospitals boosting their income with private patients, and in others by a rise in the number of patients relying on public healthcare, in the wake of widespread job losses and wage cuts.

However the real game changer may turn out to be the Cross-border Healthcare Directive – though exactly how, and how far, it will change the game remains unclear.

Cross-border Healthcare Directive

Contrary to the general public perception, this Directive does not in fact break new ground in giving EU citizens rights to treatment in other member states paid for from the public/social healthcare funds in their own country.

This has been possible for many years, not just for unforeseen necessary care – covered via the EHIC card – but also for planned care, via the so-called 'S2 route', which is still available, and is in some ways more generous than the Directive (see box).

One important difference is that the Directive allows people to claim from their public/social health insurance at home to pay for private treatment abroad, so we may expect more US-style advertising (see page 38).

But, as Enrico Brivio, the European Commission Spokesperson for Health and Food Safety, explains, the Directive also contains some important elements that could have a broader impact on health systems across Europe. "Firstly, it establishes, for the first time in EU law, a set of rights that apply to all healthcare delivered anywhere in the EU: a right to a copy of a medical record; a right to make complaints or seek redress; a right to privacy and so on."

Secondly, he adds, there are articles that require a certain level of transparency from health systems, "for instance, on the way they seek to ensure quality and safety," and also from individual providers, "for example, on treatment options and prices".

For some patient groups, it is the potential to use these elements of the Directive to improve access to quality care in their own countries that is of particular interest, says Brivio. "There have been a large number of meetings with patient advocacy groups on the Directive in recent years… Some groups were interested in finding out how they could use the Directive to get better access to care abroad for their members – perhaps because they were facing problems of access in their own country. But there were certainly a large number of patient groups who thought that patient mobility in their particular patient group would probably remain low, but who were very interested in how the provisions in the Directive on transparency could relate to their own agenda for domestic healthcare reform."

Eighteen months after the deadline for implementing the Directive, most governments have now incorporated it into their own national law, says Brivio, but questions remain in some cases over the quality of implementation. "Whilst we think that some member states have implemented the Directive rather well, we believe that we have identified a number of problems with the way that some member states have put the Directive into their national law," he says, adding that the Commission will take legal action against non-compliant member states if needs be.

A cornerstone of the requirements on transparency and patients' rights is the obligation on governments to provide a single National Contact Point where the public can access all the relevant information. A list of where to find contact points for each country can be found at http://ec.europa.eu/health/cross_border_care/docs/cbhc_ncp_en.pdf.

RIGHTS TO CARE IN OTHER EU MEMBER STATES

Citizens of EU countries have had the right to access treatment in other member states for many years under the Social Security regulations, which were first introduced in the 1970s and amended through a series of court cases (the S2 route) together with a number of European court rulings. The Cross-border Healthcare Directive was introduced to try to streamline and clarify this legal area, and introduces an additional route for accessing healthcare in other member states.

S2 ROUTE	CROSS-BORDER HEALTHCARE ROUTE
Entitlement is based on certification from a doctor that the patient needs the treatment and it is not available at home within a medically reasonable time	The patient is entitled to treatments to which they would normally be entitled according to the standard of care in their own health system. Authorisation cannot be refused where there is "undue delay"
Payment is directly between national health insurance funds; covers only treatments in public health service facilities	Patients pay up front and apply for reimbursement; covers treatment in public or private facilities
Payment covers the full cost of treatment excluding co-payments payable in the member state where the treatment takes place	Reimbursement is at the level of what the treatment would have cost at home
Pre-authorisation is always required	Pre-authorisation is required only for very costly or specialist procedures, and treatments requiring an overnight hospital stay

Who is travelling for cancer treatments?

Information about how far cancer patients use their rights to access treatment in other countries is hard to come by and largely anecdotal.

The European Cancer Patient Coalition is tracking use of the Directive, but its president, Francesco De Lorenzo, says it is still too early to tell. His personal perception, however, is that the Cross-border Healthcare Directive "works only in one direction".

"If a particular healthcare service does not exist in my country, I cannot use the Directive to get it in another member state, so it doesn't solve the economic problem behind patient mobility. The result is that it is easier, for instance, for an Italian to seek cheaper, but excellent care in bordering countries, like Slovenia, but it has been very difficult the other way around."

One possible exception may be for patients with rare cancers, says De Lorenzo. The European Commission is committed to establishing European Reference Networks, which will link centres with expertise in specific rare diseases, with a view to catering for the needs of all EU patients, including those in countries too small to develop expertise in diseases that occur infrequently. "Rare cancer patients, therefore, will have the chance to travel abroad to seek care that otherwise would not be available in their own country," says De Lorenzo. He adds, however, that while the Commission is supposed to cover part of the operating costs of the Networks, it does not have a commitment to cover all the costs related to the treatment of patients. It is also unclear how many Networks the Commission will decide to launch.

ECPC is calling for one network for each of the 12 rare cancer families. It is also calling for patients to be relieved of the requirement to pay up front for treatments they access under the Cross-border Healthcare Directive. "We have been advocating very loudly for the creation of a European fund, a pot of money at EU level, where all member states can get their payments back for patients' mobility," says De Lorenzo.

Zorana Maravic, from EuropaColon, says that in her experience, one of the main reason patients travel abroad is for a second opinion. A number of biological therapies have been approved in recent years for treating colon cancer, she says, but many countries do not reimburse them. Getting a second opinion from doctors in a country where these drugs are in routine use can help people decide whether or not it would be worth paying for the treatment from their own pockets. The cost

THE HEALTH TOURISM MARKET

The world health tourism market is worth around €34–48 billion, according to Patients Without Borders, but estimates vary widely. Cosmetic surgery, dentistry and fertility (IVF) treatments tend to be the services most sought after by people in western Europe. Malaysia, Thailand, the Philippines, Turkey and Dubai are among the most high-profile health tourism destinations.

Increasingly patients are also travelling to central and east European countries. Poland is becoming known for cosmetic surgery, and Hungary for dentistry.

People travelling to western European destinations tend to be looking for more high-tech or specialist care for serious health conditions, including cancer. Germany and Austria are key destinations for eastern Europeans. France, UK and Italy also attract patients from abroad. More recently, Spain and Portugal have started marketing themselves as health tourism destinations.

The European Travel Commission has been asked to do a scoping exercise with the UN World Travel Organization, to define what the "health tourism" sector comprises, and get a realistic idea of the size of the market. They will put forward their findings and proposals this September at a meeting that will include the OECD and World Health Organization.

Early indications are that this definition could be fairly broad – covering everything from proton therapy, through to spa resorts and even guided spiritual walks through a forest. This is something the cancer community might do well to keep an eye on: branding guided spiritual walks as healthcare may not be a problem in itself, but it becomes one if it is promoted as an effective alternative to evidence-based treatments.

SHUTTERSTOCK

of the second opinion itself, will almost always be paid for privately.

For Maravic, the big issue is educating patients about where they can get good quality treatment. "Sometimes the treatment is available even in their own country, but if patients aren't aware of certain options, they don't ask."

EuropaColon's priority is trying to ensure that people with colon cancer know, for instance, that they should ask to be tested for particular biomarkers early on in the course of their treatment to see whether they may be eligible for certain drugs.

Getting access to diagnostic tests – not just for relevant gene mutations, but also high-tech diagnostic imaging – could, in fact, turn out to be one of the most important uses cancer patients find for exercising their rights under the Directive.

This would seem to be supported by figures from the Royal Marsden cancer centre in London, which show that of 293 patients from other European countries seen over the past year, 376 diagnostic tests were carried out, but only half received any treatment.

There are signs that some patients with early breast cancer may be using the Directive to access breast conserving surgery that achieves better cosmetic results – or perhaps more reliable adjuvant radiotherapy. A well-known breast unit in northern Italy, for instance, reports a small but steady flow of Bulgarian patients who opt to pay the difference between the reimbursement they get from their government and the cost of the treatment.

But as the head of the Breast Unit at Lisbon's prestigious Champalimaud Hospital, Fatima Cardoso, points out, it is patients with advanced disease, trying to access clinical trials that could help them, who have the most desperate need to travel. Yet this group is explicitly excluded from cross-border healthcare provisions.

On top of the costs of travel and accommodation, patients travelling abroad to trials have to pay the cost of all the treatment and supportive care other than the experimental therapy itself, which puts this option out of reach for most people, she says. Worse still, it seems that paying your own way for trials abroad may no longer always be an option. Cardoso recently got a young patient of hers accepted onto a trial at Gustave Roussy, only to be told that a condition of participation was that patients should have French insurance that would cover the costs of the "standard of care" treatments.

Cardoso's frustration at the hurdles caused by this confusion and the expense involved in accessing trials in another country is widely shared. Ana-Maria Forsea, a Romanian dermatologist who has tried to help many melanoma patients access trials, comments that: "The procedures to obtain a reimbursement from the authority in one country to be on a trial in another are opaque, long, tortuous, and often the result comes fatally too late if ever."

While the Cross-border Healthcare Directive was never intended to apply to patients being treated within clinical trials, it has been seen as offering particular value to small patient groups, such as those diagnosed with one of the rare cancers collectively known as sarcomas. Even here, however, the Directive does not seem to have made much of an impact so far.

Sarcoma expert Jean-Yves Blay, of the Centre Léon Bérard in Lyon, France, has devoted a lot of time in recent years to helping develop a network within Europe, and people approach him from other countries for second opinions, usually because his team has connections with their medical team, or because they have relatives in France.

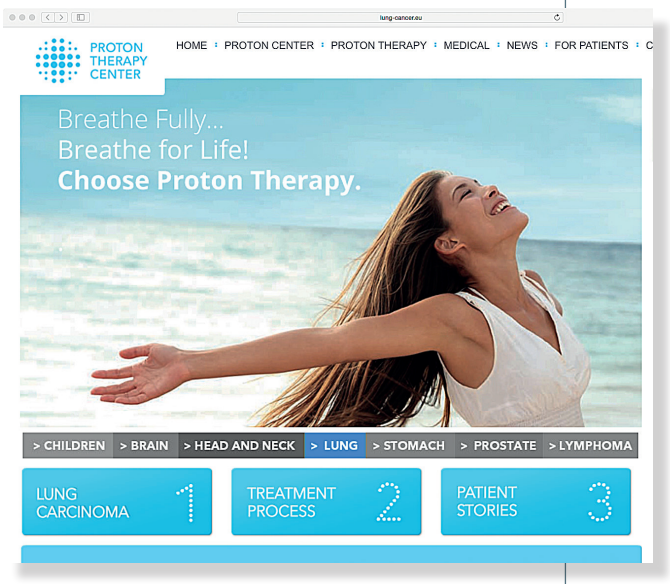
He receives email requests for advice at least once a day, but it is still relatively rare for people to travel for consultations. "I see someone from overseas at my outpatient clinic maybe once or twice a month," he says, "These are mainly people who have private insurance, or who are willing to pay for the travel themselves."

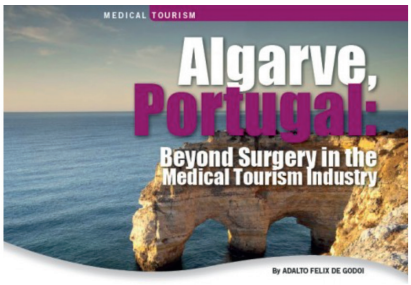
Patients will also travel to his centre to participate in trials, but "only if

Getting access to diagnostic tests could be one of the best uses cancer patients find for the Directive

THE EUROPEAN CANCER TOURISM MARKET

Could the website for this proton centre facility in Prague (www.proton-cancer-treatment.com – accessed 11 June 2015) be a taste of what's to come from Europe's medical tourism market? This bizarrely inappropriate image is aimed at patients with lung cancer – a disease that is still fatal for more than four out of five patients even in countries with the best survival rates. The prostate cancer page (11 June 2015) claims a "97% curability" rate, and says the treatment has "no unwanted side effects"





Portugal, Spain and Greece are among many European countries that have seen strong investment in high-quality healthcare facilities over the past decade, but in the current economic climate, independent facilities are looking to fill spare capacity as more people drop out of private insurance.

With healthcare budgets increasingly stretched across Europe, public hospitals are also under pressure to find additional financing to make up for cuts in public spending. In recent years, NHS hospitals in England have been given the right to devote up to half (49%) of their total capacity to treating private patients – an opportunity some are using more enthusiastically than others. While profits from this private patients unit at the Royal Free London NHS Trust may be reinvested back into the NHS, diverting capacity to private patients adds to the pressure on waiting lists, which is forcing more people to "go private" – or to seek treatment in another European member state, via the Cross-border Healthcare Directive or the S2 route.

they are able to get insurance to pay the costs that are not related to the trial."

Markus Wartenberg, chair of Sarcoma Patients EuroNet (SPAEN), says the problem is not about access to second opinions, "It's what you do with the second opinion in your home country, if top sarcoma surgeons or specific treatments are not available or are not reimbursed. Very often patients may be able to afford the second opinion, but unfortunately not the qualified treatment solutions in the west European countries – on top of all the costs of travelling between the two countries."

SPAEN, he says, does not see travelling for treatment as a good solution. "Our vision would be to establish a Sarcoma European Reference Network that also supports upcoming sarcoma centres in east European countries. If at least one sarcoma expert centre per east European country would be available, this would help. We definitely need to raise the quality of diagnosis, treatment (including access to affordable drugs), and follow up in these countries to improve the situation."

Wartenberg's comment touches on one of the more contentious issues of the whole cross-border healthcare debate. If money is flowing out of weaker health systems to pay for patients to be treated in stronger ones, could that lead to the weak becoming weaker and the strong becoming stronger? If that happens, the Directive could promote a system across Europe that helps those who can afford to travel for treatment abroad at the expense of the majority of patients who need that money to be invested in their own health care systems. ■

Cancer Core Europe

MARC BEISHON

Can deep and close-knit collaboration between a handful of elite centres achieve what broader European research platforms and projects cannot?

There has been talk about setting up a European cancer institute to rival the American National Cancer Institute (NCI) and its network of comprehensive cancer centres for many years. No such large-scale driver of research has ever been established, however, either on the NCI model or any alternative.

Instead, we have seen a plethora of European networking projects that typically have limited lifespans, such as those funded by the European Commission's framework programmes, and several organisations that can lay claim to much good pan-European collaborative work, in particular the European Organisation for the Research and Treatment of Cancer. Founded in the 1960s – more than 20 years after the NCI – the EORTC is the closest Europe has come to an institute model, but it is far smaller in terms of funding and has no laboratories of its own.

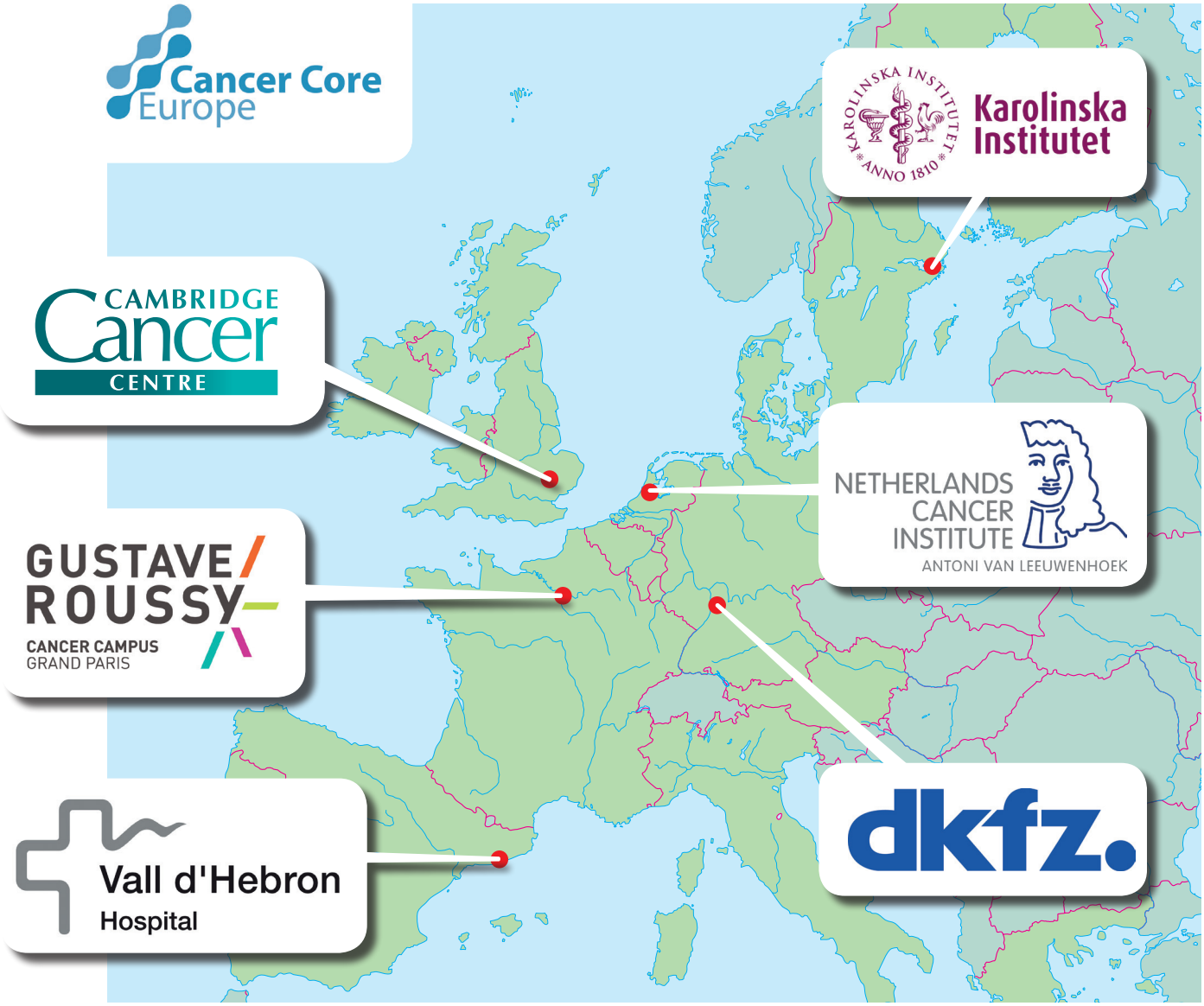
In any case, the vast majority of cancer research funding is spent within countries, and probably the biggest research collaborations are those such as the UK's Experimental Cancer Medicine Centre (ECMC) initiative and Cancer Research UK (CRUK) projects, France's Cancéropôle networks and the German Cancer Consortium (DKTK), which include a wide range of basic and clinical research.

A key characteristic of some of these national initiatives is that they tend to select 'core' centres with the best expertise – CRUK, for example, provides a substantial proportion of its scientific funding to just five research institutes, including Cambridge, Oxford and Manchester. Most collaborative networks involve many centres with interests in certain topics, such as leukaemias and childhood cancers, but 'core' implies a depth of expertise where institutes can contribute fundamental parts of translational cancer research to make a more joined up 'whole'.

Certainly, funders and researchers are recognising that cancer research has long reached a scale and complexity that is beyond any single institute, and many of the most challenging questions now require joint working among partners with equal standing in the depth of their contributions.

About ten years ago EORTC aimed to establish its Network of Core Institutes (NOCI) – around 20 European centres that have the patient numbers and multidisciplinary groups needed to participate in increasingly complex translational research studies. Meanwhile, the EurocanPlatform from the European Commission has also been active in establishing a concept for translational research in Europe, involving more than 20 cancer centres, some of which also committed to the virtual institute idea in 2008 with the Stockholm Declaration, masterminded by Ulrik Ringborg at the Karolinska. Ringborg has also been instrumental in the work of the Organisation of European Cancer Institutes (OECI), which includes research excellence in its accreditation scheme.

It has been hard, however, to establish major trial work at this level.



Martine Piccart, a past EORTC president, reported at the organisation's 50th anniversary conference that it had been much more difficult than anticipated to get NOCI up and running, because it needs a 'horizontal' platform among centres, for information integration, biomarker testing, biopsies, sample logistics and much more.

By 2012, only a few such trials were underway, although the often discussed MINDACT trial, which aimed to validate a gene signature to guide treatment in early breast cancer, has been the vanguard. There was seven years of intensive collaborative work and a struggle to get funding, noted Piccart. A European Union grant of €7 million fell far short of the actual cost of around €45 million to recruit 6,600 women across Europe for the work. But it was a big step in the development of translational research across Europe, and was the first such oncology trial to be supported by an EU grant (from the research framework programme).

It was under Lex Eggermont's presidency of EORTC that the NOCI idea came about. Now he and colleagues at six of the major cancer and research centres in Europe, which are also active in the EurocanPlatform, have set up an elite group of core institutes to try to cut through the many obstacles that have slowed translational research. Eggermont's own centre, Gustave Roussy in

"Precision medicine needs to be one big project and we need to put an end to fragmented data warehouses"

Paris, where he is director, has formed Cancer Core Europe, with the Cambridge Cancer Centre, the Karolinska in Stockholm, the Netherlands Cancer Institute in Amsterdam, Vall d'Hebron in Barcelona, and the National Centre for Tumour Diseases (DKFZ) in Heidelberg, Germany.

There is no doubt these are top centres, and hold a balance between clinical and basic research, and they have worked together anyway in various consortiums. But as Eggermont points out: "The problem with a lot of consortiums is that they are often constructed around a project model, such as the EU framework programmes, and there are just too many partners and work packages – one tries to do everything. It is very difficult to create sustainable activity. We want to create a network built on infrastructure that will last, starting with a few centres that know each other well and are committed to it."

A critical mass

The aim, he adds, is to take advantage of the scale and expertise of the six institutes to establish a critical mass for a prospective dataset that is clinically annotated and is a far better platform for researching precision medicine and personalised treatment. "We have 60,000 newly diagnosed cases each year among the six centres, treat 300,000 patients and follow up a further 1.4 million. We need to unite them in a prospective way, because retrospective databases are like Swiss cheese – they are full of holes that are extremely laborious to fill because oncology is just too complex."

Eggermont and partners in Cancer Core Europe are calling the initiative a virtual 'e-hospital' with the emphasis on data sharing and compatibility for processes such as molecular profiling and standard operating procedures such as tissue processing. "Precision medicine needs to be understood as one big project and we need to put an end to fragmented data warehouses," he says. Five years ago, cancer institutes thought they could "go it alone", he adds, but with the exception of the Sanger Institute, in Cambridge, which has world-class genomic expertise, none have the data to work on the complex questions.

He places great emphasis on what he calls "harmonising readout understanding", meaning say the outputs from biomarker assays and gene profiling, so that close-knit groups of researchers across the institutes are working to the same rules. Simply scaling up data without harmonisation will just amplify lack of quality, and make it far more difficult to reach the goal of more rapid and reliable outcome research, he says.

Cancer Core Europe has appointed a scientific officer to develop its work programme. Fabien Calvo is a pharmacology professor, a past deputy at France's National Cancer Institute (INCa) and has been part of numerous research networks, including co-launching the International Cancer Genome Consortium in 2008. "I can see from travelling among the six sites that there is outstanding research at each but also some weaknesses, but they are really good representatives of what can be done at national level," says Calvo. The institutes are genuinely also world leaders, he adds, but have particular strengths, such as proteomics at the Karolinska and early-phase trials at Gustave Roussy.

He confirms that establishing data sharing infrastructure is the first step – and also probably the most complicated. "Then we want to coordinate clinical trials, especially for targeted medicines, and we are working with pharma to share information and we need them to provide drugs." Also on the work programme is molecular analysis of tumours and the development of biomarkers.

That some of the institutes were collaborating before the official Cancer Core Europe announcement was confirmed by Carlos Caldas, professor of cancer medicine at Cambridge, speaking at the launch last year. He noted that a breast cancer trial was about to be started by Cambridge, Vall d'Hebron and the Netherlands Cancer Institute, with drug firm Genentech. "I don't think this trial would have been possible at any of the institutions individually," he said. It is a "very demanding" trial using the latest imaging and profiling of circulating tumour DNA and will also involve Gustave Roussy and maybe the other Cancer Core Europe institutes. It's a true investigator- and science-led trial, rather than a typical pharma-led trial, where a company spreads its own protocol among a wide number of centres, he added.

But funding from pharma is clearly important, and Eggermont says that Cancer Core Europe will also look for grants from various sources. He notes

that the EU's EIT Health/InnoLife initiative on healthy living and active aging has selected Cancer Core Europe to represent oncology in current bid preparation. "They like the infrastructure we are building," he says.

World leading collaboration

That infrastructure could also be world leading, given that, despite the dollars flowing into US research, the American cancer centres are not actually networked in this way, although some are very large. "The main institutes in the US are all islands," says Eggermont. The US is good at joint genomic research, adds Calvo, but not so good at clinical trials, where collaboration matters for translational research, and the cancer community is not as well funded as might be thought.

President Barack Obama has recently called for a drive for precision medicine, but Harold Varmus, the Nobel laureate who has recently stepped down as director of the NCI, has spoken out about a "shocking" drop in the institute's budget. He said that basic research is the fuel for innovation – advances such as immunotherapies are testimony to this – but there is so much more to be done, and he stressed that Americans should not become "slackers" in "funding the most fundamental things".

Eggermont agrees about the importance of basic research but adds that the Cancer Core Europe concept is also fundamental to organising the "chaos" that bringing discoveries out of the lab to the clinic can bring.

Chaos could also be a good word to apply to the state of European cancer research, a topic that Richard Sullivan, director of the Institute of Cancer Policy at King's Health Partners Integrated Cancer Centre in London, knows only too well. Writing back in 2008 on the possibilities for a European institute, he was prescient in saying that the big cancer centres were likely to take the lead on their own, given the lack of direction and funding from national and European organisations.

He points out though that it may be premature to launch Cancer Core Europe, as the EurocanPlatform is still under analysis as a model, and that the six institutes are by no means the only major research institutes in Europe. "It does raise the question about how we get the best out of the best researchers," he says. "Of course they are powerful centres with lots of great technology, but what really is going to happen that wouldn't happen otherwise, because there are lots of other collaborations in this crowded translational space, such as the WIN Consortium, also led by Gustave Roussy, the EORTC, and the Breast International Group, to name but a few."

Undoubtedly there are strong national networks too – the UK's Experimental Cancer Medicine Centre initiative, for example, looks similar to Cancer Core Europe, as it reports that over the last seven years it has supported more than 1,000 early-phase trials and 700 biomarker studies, and aims to harmonise trials. Other European projects include Cancer-ID, a public–private consortium supported by Europe's Innovative Medicines Initiative that is validating blood-based biomarkers. Eggermont's response is again about sustainability, level of expertise and whether the goals really are similar.

It's also the case, says Sullivan, that cancer research is much bigger than the translational platform that Cancer Core Europe is pursuing. "What benefits patients is also research into surgery, radiotherapy and palliative care to name but a few areas."

"We also need a view on whether there is a strategic plan and how we can measure success in say five years' time," he adds, "and I also have a question about how inclusive or exclusive this initiative will be. Will it truly capture the best Europe has to offer?"

Sullivan says that the EU's Horizon 2020 research programme should spread its net wide to capture innovation across the continent. "There are smaller institutes doing niche work in areas such as imaging, and countries like Poland are producing some excellent work. Because cancer has become such an important area of biomedical research, a lot of governments and charities are now investing heavily in it. We tend to think that Europe is smaller than North America but really it isn't in terms of impact in cancer research."

Eggermont stresses that Cancer Core Europe will open the door to other centres in Europe, although the bar to join will be set "very high". Soon there will be a website and work programme to view, and the cancer community can start to decide whether there is a new powerhouse that will take everyone forward. ■

"It's a very demanding, science-led trial that would not have been possible at any of the institutions individually"

Recognising and reducing the risk of chemotherapy extravasation

When chemotherapy drugs leak from the veins it can cause serious injury to the patient, greatly heighten their fears of undergoing future treatment cycles, and undermine their trust in their medical team. Knowing how to assess and reduce the risks, and what to do when things go wrong, is essential.

Extravasation occurs when medicines leak from the compartment where they are intended to be, such as a vein or muscle, into the surrounding tissues. The impact of this accidental administration depends on the pH and metabolic effects of the drug on the tissue. Some drugs cause no harm while others can cause serious injury such as loss of function or tissue damage requiring grafting or, in extreme cases, amputation.

Key factors to consider in recognising and reducing the risk of extravasation are:

- the patient to whom you are giving the drug
- the drug that you are giving and its potential for causing harm if extravasation occurs
- the device you are using for administering the drug
- any risks that may be associated, and how to mitigate them
- observation of the patient while they are having the infusion and after an extravasation injury.

European School of Oncology e-grandround

The European School of Oncology presents weekly e-grandrounds which offer participants the chance to discuss a range of cutting-edge issues with leading European experts. One of these is selected for publication in each issue of *Cancer World*. In this e-grandround, Cheryl Vidall, Head of Nursing and Governance with Alcura, Alton, UK, reviews how to recognise and reduce the risk of extravasation with chemotherapy. Anita Margulies, who is co-chair of the European Oncology Nursing Society (EONS) Education Working Group, and from Zurich, Switzerland, poses questions asked by the audience during the live e-grandround, which was held in collaboration with EONS.
Edited by Susan Mayor.

The recorded version of this and other e-grandrounds is available at www.e-eso.net

CURRENT CLASSIFICATION FOR CYTOTOXICS

NEUTRALS: GROUP 1	INFLAMMITANTS: GROUP 2	IRRITANTS: GROUP 3	EXFOLIANTS: GROUP 4	VESICANTS: GROUP 5
Asparaginase	Etoposide phosphate	Carboplatin	Aclarubicin	Amsacrine
Bleomycin	Fluorouracil	Etoposide	Cisplatin	Carmustine
Cladribine	Methotrexate	Irinotecan	Daunorubicin liposomal	Dacarbazine
Cyclophosphamide	Raltitrexed	Teniposide	Docetaxel	Dactinomycin
Cytarabine			Doxorubicin liposomal	Daunorubicin
Fludarabine			Floxuridine	Doxorubicin
Gemcitabine			Mitozantrone	Oxaliplatin
Ifosfamide			Topotecan	Epirubicin
Melphalan				Idarubicin
Pentostatin				Mitomycin
Rituximab				Mustine
Thiotepa				Paclitaxel
ß-Interferons				Streptozocin
Aldesleukin (IL-2)				Treosulfan
Trastuzumab				Vinblastine
Bortezomib (Velcade)				Vincristine
				Vinorelbine

Patient factors

When we consider the patient, we need to think about the patient's previous experiences, including use of parenteral therapies, which will impact on their preconceptions and also their vein access. Medical history must be considered, because patients with peripheral vascular disease, neuropathy, stroke and diabetes have specific requirements, and these conditions can increase the permeability of the veins and increase the risk of extravasation. Patients who have neuropathy or have had a stroke may not sense any changes, so if you cannulate an area of numbness they may not be aware or able to tell you there is something wrong until the injury is quite extensive.

We also need to consider how well a patient can communicate. Children may not have the vocabulary to tell you that something's wrong, and patients with impairments affecting communication may not be able to tell you that things aren't right, so you need to observe them carefully and recognise changes in their condition.

It's important to empower patients to be partners in their care and encourage them to communicate any concerns that they have. My experience has been that there are patients who tell me if the area around where their chemotherapy is being given hurts, or is sore, or numb or painful. However, some will not mention these symptoms. It is helpful to ask patients whether the area feels different, which may give you more objective feedback.

Patients should be made aware of the risk of extravasation. Before we start treatment we tell patients the basic facts, without going into unnecessary detail. This includes explaining that, on occasion, the cannula or lines may leak and this may require urgent intervention depending on the drug being infused.

Drug factors

In the UK we use the five-point grading system for drugs in terms of the tissue damage they cause:

- Vesicant – blistering and necrosis
- Exfoliant – inflammation and skin shedding
- Irritant – sclerosis, burning, local warmth, hyper-pigmentation, discomfort, erythema or tenderness
- Inflammitant – flare, inflammatory reaction
- Neutral – no inflammation or tissue damage on extravasation.

Across Europe, the categories of vesicant and exfoliant are often put together.

The table opposite classifies commonly used cytotoxics into the five categories. The vinca alkaloids and the anthracyclines are groups of agents that are frequently used, and we need to be aware that they can cause significant tissue injury should they extravasate.

We tend to associate extravasation with cytotoxic agents, but other drugs and agents, such as sodium bicarbonate, hypertonic saline, and diazepam, can also act as vesicants.

Question: *Who should be responsible for assessing patients for extravasation risk before their therapy starts?*
Answer: *This varies in different countries. Doctors give infusions in some countries, but in the UK most chemotherapy infusions are administered by nurses. My personal view is that the person who is going to administer the chemotherapy should assess the patient. This should include assessing the quality of the patient's veins, considering the risk of extravasation at different infusion sites, as well as medical history and conditions such as diabetes or stroke.*
Question: *We know how busy everyone is, but how much time do you consider necessary for a basic assessment of a patient?*
Answer: *Everybody is pushed for time, but there is a risk of overlooking something important if you have not fully assessed the patient and relevant risk factors before treatment, which increases the risk of problems. Assessing the patient's medical history, including any conditions they have and treatments they are on, and other factors influencing the patient, takes a few minutes, plus a couple of minutes observing them in the clinic. Vein assessment takes a little longer, probably 15–20 minutes.*

Choice of device

The choice of device is very important. I am mindful of the fact that in the UK we have access to virtually any device we want to use to gain intravenous (IV) access, but some countries do not have the opportunity of using an implanted port or a peripherally inserted central catheter (PICC) line, and so they have to use an alternative option. However, where you know you are using high-risk drugs that could potentially cause harm, the use of a central line allows large volumes to be infused into a large vein, achieving rapid dilution of the drug (see figure below). Another advantage is that a central line can be buried deep under the skin. The devices that tend to be used for central access are Hickman lines and PICC lines, or you can use an implanted port (Portacath).

Peripheral cannulas are more commonly used than central lines, partly based on cost. They are used in superficial veins, which tend to be smaller, so it is necessary to consider the size of the device that is going into the vein. In the past, a large device might be used to give a large volume, but a very small device can still deliver a large amount of fluid. The small yellow 24-gauge cannula is often called a paediatric or neonatal cannula. Despite having a very narrow lumen, they can infuse 22 mL per minute, which amounts to 220 mL in 10 minutes, and it is unlikely that a faster rate would be required.

Small cannulas leave only a small puncture hole when removed, reducing the risk of extravasation. In addition, you can draw blood from one of these small lines, although drawing too quickly through such a narrow lumen can haemolyse the sample.

Most people are skilled in the use of a peripheral cannula, while a higher level of skill is required for using a central line. But inserting a peripheral cannula in the correct location is very important. If a cannula is inserted near the wrist or another joint where there is going to be a lot of movement, this can cause friction within the vessel, which can lead to inflammation in the vessel wall (mechanical phlebitis). In a permeable vein this movement can encourage infiltration through the vessel wall and transport the drug into the surrounding tissue. Ensuring a good flow of blood around a small cannula will allow the drug to be diluted quicker and also minimise the risk of

CHOICE OF DEVICE

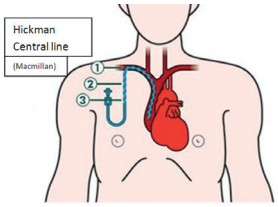
CENTRAL LINE

Deep under the skin

Large vein

Good, rapid dilution of the drug

Requires higher level skill (?)



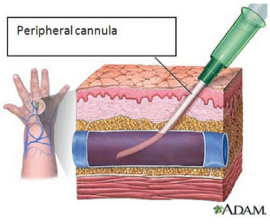
PERIPHERAL CANNULA

Superficial, smaller veins

Size of device

Movement from limbs / joints

Risk of mechanical or chemical phlebitis



direct chemical contact with the vessel wall, so reducing the risk of chemical phlebitis.

Assessing the patient's veins is also essential in selecting the correct device. This should include consideration of the duration of therapy and the total number of vein accesses required to complete treatment and the frequency of infusions. Device choice should also take into account the drug to be infused and the patient's preference. A central line may be more appropriate where the veins are not very good, but this also depends on the number of cycles that are going to be infused and infusion time.

The drugs that are going to be infused are important to consider, because extravasation from a peripheral cannula may lead to a significant impact on the function of the affected limb. For this reason we avoid the back of the hand and the anticubital fossa, because of the major impact of tissue damage on functioning.

We also have to consider patient choice. Some patients say that they don't want a central line and we should honour their choice, but let them know that, if the veins become impossible to access peripherally, they may need a central line. The cost of using a central line versus the benefits to the patient has to be considered as well. Some lines cost hundreds of euros to place, whereas peripheral cannulas may be a few euros. The benefit to the patient of having a peripheral cannula is that it comes out after treatment, and they can get on with their life without any equipment requiring further care. A central line is the easiest option for healthcare professionals to access, provided that there are no problems with the line, and each treatment may be quicker.

BENEFITS AND DISADVANTAGES OF DIFFERENT TYPES OF CENTRAL LINE

IMPLANTABLE PORT	HICKMAN/GROSCHONG	PICC
Benefits	**Benefits**	**Benefits**
Large vein access – rapid drug dilution	Large vein access – rapid drug dilution	Ease of placement
No visible external parts (body image)	Durable for course of treatment (1–2 years)	No risk of insertion pneumothorax
Lower infection risk		Cost
Longevity (can be for many years)		
Normal sports		
Disadvantages	**Disadvantages**	**Disadvantages**
Cost	External parts can be easily damaged	Line fractures
Requires expert line placement and training to access	Body image impact	Limitations on activity
	Lifestyle limitations	Cardiac arrhythmias
	Cost	Line migration
	Expert line placement	Infection
		Higher thrombosis risk
		Limited durability (may need replacing)

The table above summarises the benefits and disadvantages of different types of central lines. Implantable ports are placed in large veins, achieving rapid dilution of the drug. They don't usually have any external visible parts, which reduces risk of infection, and it has good longevity, lasting up to 10 years. Patients like this option because they don't have external parts to deal with, body image may be more positive and they can play sports. However, it is the most expensive form of central line and requires expert line placement and training to access. The Hickman or Groschong line also accesses large veins and achieves rapid drug dilution with good longevity. However, there are external parts that can be damaged and also affect body image. They are more costly than peripheral cannulas but less expensive than implantable ports. The PICC line is easy to place, with no risk of insertion pneumothorax and is cheaper than the other two options. Disadvantages include line fracture, limitations on activity and limited durability.

Peripheral cannulation requires good veins that will last the duration of the patient's treatment course. A cannula is suitable for short courses of treatment in patients with healthy veins. It

can be quite cost-effective, is quick and easy to place and is removed after use. There is a good range of size available, with the 24-gauge (yellow, with colours being universal) being excellent for giving peripheral IV drugs. In my experience it's very rare that you need to use a bigger cannula for routine infusion. The choice of device is very important, selecting the smallest to deliver the drug over the time required. This also gives faster dilution of the drug, as the blood flows past the cannula and allows dilution along the way. Minimising the chemical contact with the vessel wall reduces the risk of extravasation injury occurring.

Disadvantages of peripheral cannulation include the fact that the wrong device is often chosen. Staff are often unaware that a smaller device is better. It also requires expertise to place and choose the insertion site correctly, and is not suitable for long courses of treatment if patients have poor veins.

Selecting the vein, I tend to start with the patient's non-dominant arm, using the most distal site suitable for initial cannulation wherever possible, but avoiding the back of the hand, moving higher up the arm with any subsequent attempts to avoid leakage and extravasation. Subsequent cannulation attempts should be at a site proximal to the initial insertion. Cannulation attempts should be avoided on skin with altered sensation or on skin that is bruised, painful or infected.

The figure *right* shows examples of common complications with cannulas, which can include:

- Mechanical phlebitis due to the device rubbing on the vessel wall
- Chemical phlebitis caused by the drug making contact with the vessel wall
- Thrombophlebitis
- Extravasation or 'tissuing'
- Infection introduced through poor cannulation technique, contamination of drugs or skin contact
- Infusion reaction
- Embolism, from the drug, glass or thrombus formation
- Migration, mislocation, fracture, or the cannula falls out.

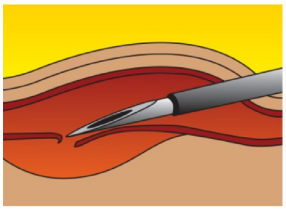
Preventing complications after the cannula insertion

Asepsis is essential, using non-touch technique throughout. It is important to monitor the site throughout the infusion and avoid over-manipulation of the cannula. All connections should be secure to avoid drugs leaking out, and it is essential to ensure the drip does not run dry. A good IV dressing should be used to hold the cannula stable and minimise the risk of movement while the cannula is in the vein. The infusion rate and the dilution of the drug are very important in preventing complications. The drug concentration can cause irritation to the vessel and the pH can be affected by the amount of diluent. What you want is fast dilution of the drug to minimise the risk of chemical injury.

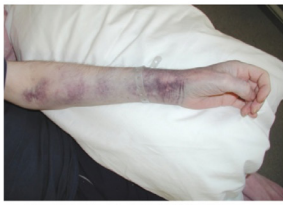
The risks of extravasation

Extravasation causes pain, injury and loss of function to the patient. It can also mean delays in treatment for cancer, which can reduce efficacy and may

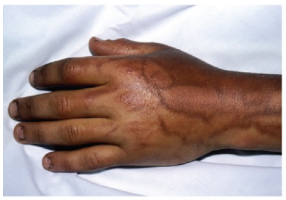
COMMON COMPLICATIONS WITH CANNULAS



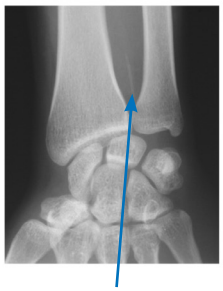
Transfixation



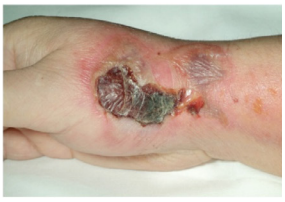
Haematoma



Phlebitis



Cannula fracture and migration



Vesicant extravasation

Transfixation occurs when the back wall of the vein gets slightly damaged when the cannula is put in, so extravasation occurs even though the cannula insertion appears to be fine. Although the cannula can be guided into the vein, there is a small leak area that can cause localised extravasation. Phlebitis can occur if there is infection within the vein. The arrow in the X-ray in the above figure points to a tiny white line which shows where the cannula fractured. Haematoma is common and underlines the need for staff being well trained in cannula use. The final image shows a vesicant extravasation in the wrist caused by a cannula being placed in a cephalic vein on the wrist joint, where there is a lot of movement.

Source: Images courtesy of Cheryl Vidall, Alcura, Alton

lead to fear of having further cycles. It may also mean having to rebuild confidence in the clinical team. Nurses often feel responsible for the injury having occurred, and it may reduce their confidence in giving chemotherapy. The problem can also lead to loss of reputation from an organisational perspective, and may result in compensation claims.

PROGRESSION AND TREATMENT OF EXTRAVASATION: DOXORUBICIN

This series of images tracks the progression and treatment of extravasation in a patient treated with doxorubicin. On day 1 there is very little to see, but significant blistering emerges on day 8 and day 10. The large area of tissue damage resulted in prolonged loss of function and residual scarring to the patient at six months, and required surgery

Source: Images courtesy of Helen Roe, UKONS Chemotherapy Forum and Consultant Cancer Nurse, North Cumbria University Hospitals NHS Trust

Measures to reduce the risk of extravasation

It is essential to observe patients and monitor what is going on during treatment. Ask patients to report any change in sensation without delay. If using a pump or monitor, make sure the pressure sensors are set very low, because a change in pressure could suggest that something is going on either within the device or the vein. Observe the flow rate and take any resistance seriously.

The position, size and age of the venepuncture site are the most important factors to consider in the prevention of extravasation. The risk can be significantly reduced by the following measures:

- Use a central line or peripherally inserted central catheter (PICC) for slow infusion of high-risk drugs
- Never leave a butterfly if administering cytotoxic drugs; stay with the patient throughout (or avoid butterflies altogether)
- Avoid small and fragile veins
- Use a recently sited cannula
- Site the cannula so it cannot be dislodged
- Use the forearm and avoid sites near joints.

Managing extravasation

Immediate action is essential when extravasation occurs. Aspirate the cannula and then remove it and document the amount drawn back from the aspiration, even if this is zero. Palliate the patient's immediate symptoms with cold or warm analgesia (depending on the drug). Mark the affected area, take a photo and make sure the clinical team is aware of what has happened. Treat the patient with Savene for anthracycline injuries (or dimethyl sulfoxide [DMSO] 99% if no Savene), and check the protocol for other injuries.

The ESMO–EONS guidelines on the 'Management of Chemotherapy Extravasation' (*Ann Oncol* 2012, 23 suppl 7:vii167-vii173) provide a lot of information and the best management practice.

Summary

Extravasation is a risk with chemotherapy and other drugs given intravenously. It is essential to consider the patient, what drug is being given, and which device is being used in order to assess and minimise the risk of extravasation. Patients should be observed and monitored carefully during administration of chemotherapy, being alert to any change in sensation. We need to document care and observations together with actions and follow-up when extravasation occurs, and involve the patient in their treatment plan. ■

newsround

Selected reports edited by Janet Fricker

Personalised therapy for carcinoma of unknown primary site

JAMA Oncology

Almost all carcinomas of unknown primary site (CUPs) harbour at least one clinically relevant genomic alteration with the potential for personalising therapy, a retrospective US study has found.

Between 2% and 9% of all cancer diagnoses present as CUP, with diagnostic workups often failing to locate the primary tumour site despite use of multiple imaging modalities, invasive procedures (endoscopy and colonoscopy), serum biomarker tests, immunohistochemistry staining and mRNA expression profiling. Such investigations can cost over $10,000.

Recent evidence for diseases such as primary non-small-cell lung cancer suggest that use of targeted therapy selected by information acquired from gene sequencing can significantly improve outcomes. Such factors have led oncologists to question whether upfront tests guiding therapy selection for all patients with CUP would prove of greater value for clinical management than the 'potentially futile and expensive' search for primary lesions currently undertaken.

In the current study, Jeffrey Ross and colleagues, from Albany Medical College, New York, undertook comprehensive genomic profiling assays based on next-generation sequencing of 200 consecutive CUP formalin-fixed paraffin-embedded specimens taken from metastatic sites to discover opportunities for targeted therapies. Altogether there were 125 adenocarcinomas (ACUPs) and 75 non-adenocarcinomas (non-ACUPs), all of unknown primary site, obtained from metastatic sites including liver (25%), lymph node (19%), peritoneum (7%), soft tissue (6%), bone (5%), brain (5%), skin (4%), and pleura (3%).

Results show at least one genomic alteration was found in 96% of CUP specimens (n=192), with a mean of 4.2 genomic alterations per tumour. Furthermore, one or more potentially targetable genomic alterations was identified in 85% of CUP specimens (n=169). The most frequent genomic alterations were in TP53 (found in 110 samples, 55%), KRAS (found in 40 samples, 20%), CDKN2A (found in 37 samples, 19%), and MYC (found in 23, 12%). Strikingly, alterations in the RTK/Ras signalling pathway (including ALK, BRAF, KIT, and KRAS) were found in 72% of ACUPs (n=90), but only 39% of non-ACUPs (n=29) ($P<0.001$).

"Given the poor prognosis of CUP treated by nontargeted conventional therapies, comprehensive genomic profiling shows promise to identify targeted therapeutic approaches to improve outcomes for this disease while potentially reducing the often costly and time-consuming search for the tumor's anatomic site of origin," write the authors. ACUP tumours, they add, were more frequently driven by genomic alterations in the highly druggable RTK/Ras signalling pathway than non-ACUP tumours.

In an accompanying commentary, Gauri Varadhachary, from MD Anderson Cancer Center, in Houston, Texas, envisions using algorithms integrating immunohistochemistry profiles, tissue-of-origin profiling and comprehensive genomic profiling to maximise clinically meaningful benefit. "An algorithm such as this would then continue to evolve as additional experience is gained with matching the right patient to the right drug and as the trade-off in costs, accuracy, and benefits became clearer."

- J Ross, K Wang, L Gay et al. Comprehensive genomic profiling of carcinoma of unknown primary site: new routes to targeted therapies. *JAMA Oncol*, April 2015, 1:40–49
- G Varadhachary. Carcinoma of unknown primary site: the poster child for personalized medicine. *ibid* pp 19–21

Timing of adjuvant chemotherapy influences breast cancer survival

Journal of Clinical Oncology

Time to initiation of adjuvant chemotherapy (TTC) after surgery influences survival outcomes in breast cancer, a large retrospective cohort study has found. The US investigators found effects for patients with stage III breast cancer, triple-negative breast cancer, and trastuzumab-treated HER2-positive tumours.

Randomised clinical trials have shown survival benefits associated with adjuvant chemotherapy in early stage breast cancer. However, since breast cancer is known to be a heterogeneous disease, different subtypes may influence the benefit of adjuvant chemotherapy. Little information exists about the impact that TTC has according to breast cancer subtype.

In the current study Mariana Chavez-MacGregor and colleagues, from MD Anderson Cancer Center, set out to evaluate the association between TTC and survival according to breast cancer subtypes and stages at diagnosis. The investigators identified 6,827 women with stage I to III invasive primary breast cancer diagnosed between 1997 and 2011 who had received adjuvant chemotherapy at MD Anderson. Patients were categorised according to time from definitive surgery to adjuvant chemotherapy into one of three groups <30 days; 31 to 60 days; and >61 days. Cox proportional hazard regression models were used to determine associations between TTC and survival outcomes for each of the subtypes.

Results showed that initiation of chemotherapy 61 days after surgery was associated with adverse outcomes for distant relapse free survival for patients with stage II disease (HR=1.20; 95%CI 1.02–1.43). For patients with stage III disease, delays of more than 61 days had an adverse effect on overall survival (HR=1.76; 95%CI 1.26–2.46); relapse free survival (HR=1.34, 95%CI 1.01–1.76) and distant relapse free survival (HR=1.36, 95%CI 1.02–1.80).

For patients with triple-negative breast cancer, starting chemotherapy more than 61 days after definitive surgery had an adverse effect on survival in comparison with initiating treatment in the first 30 days (HR=1.54; 95%CI 1.09–2.18). The same held for patients with HER2-positive tumours treated with trastuzumab who started chemotherapy more than 61 days after surgery (HR=3.09; 95%CI1.49–6.39).

"Among patients with stage II and IIIBC [breast cancer], TNBC [triple negative breast cancer], and HER2-positive tumors, every effort should be made to avoid postponing the initiation of adjuvant chemotherapy. This may lead to an improvement in outcomes for these subsets of patients," write the authors.

In an accompanying commentary, Marco Colleoni, from the European Institute of Oncology, Milan, writes, "The results can only be regarded as hypothesis generating and new data are required before widespread modification of current clinical practice. The influence of the play of chance on the observed results cannot be overlooked given the multiple subgroup analyses and end points considered, and the inconsistency in trends for the three chemotherapy initiation time intervals."

■ D de Melo Gagliato, A Gonzalez-Angulo, X Lei et al. Clinical impact of delaying initiation of adjuvant chemotherapy in patients with breast cancer. *JCO* 10 March 2014, 32:735–744

■ M Colleoni. Time to initiation of adjuvant chemotherapy for early breast cancer and outcome: the earlier, the better? *ibid* pp 717–719

Intensive follow-up improves survival in colorectal cancer

■ Annals of Oncology

For patients with colorectal cancer, intensive follow-up strategies improve overall survival, increase detection of asymptomatic recurrences, and are associated with a shorter time in detecting recurrences, a Spanish meta-analysis of 11 studies has found.

Once colorectal cancer is detected, curative surgery is the treatment of choice for non-metastatic disease. However, even though patients are considered to be free from the illness and cured after surgery and adjuvant treatment, 30% who present with stage II or III disease experience disease recurrence. Around 90% of these recurrences will present in the first five years after 'curative' surgery. Over the last few decades, there has been a significant variability in follow-up strategies used after the curative resection of colorectal cancer.

In the current study, Salvador Pita-Fernández and colleagues, from the Galician Agency for Health Technology Assessment, Santiago de Compostela, set out to review the evidence of the impact of different follow-up strategies for patients with non-metastatic colorectal cancer after curative surgery in relation to overall survival and other outcomes. In total 11 studies were examined including 4,055 patients, of whom 67% had undergone curative surgery for primary colon cancer and 33% had undergone curative surgery for primary rectal cancer.

In nine studies (*n*=3,611), patients who had undergone intensive follow-up were compared with another group of patients who had undergone less intensive follow-up; while a further two studies compared patients undergoing intensive follow-up with another group who did not undergo any follow-up. The follow-up strategies, which included colonoscopies, proctoscopic explorations, serum carcinoembryonic antigen (CEA) levels, imaging tests and liver function tests, were defined according to frequency of monitoring.

The meta-analysis showed that overall survival rates improved significantly for patients having a more intensive follow-up (HR=0.7; 95%CI 0.7–0.9). In comparison with less-intensive follow-up, patients who were followed up intensively showed a higher probability of detection of asymptomatic recurrences (RR=2.59; 95%CI 1.66–4.06); attempts at curative surgery at recurrence (RR=1.98; 95%CI 1.51–2.60); and survival after recurrence (RR=2.13; 95%CI 1.24–3.69); and a shorter time to detection of recurrence (mean difference = –5.23 months; 95%CI –9.58 to –0.88). More-intensive follow-up of patients operated for colorectal cancer is not associated with a greater detection of total recurrences, or a decrease

in mortality related to disease, even though there was a trend towards a protective effect.

"The results of this meta-analysis indicate an improvement in the overall survival of patients who have undergone more intensive follow-up after curative surgery for CRC," write the authors. The study, they add, provides data on the survival of patients once recurrences are detected, which has not been explored in any previous meta-analyses.

■ S Pita-Fernández, M Alhayek-Aí, C González-Martín et al. Intensive follow-up strategies improve outcomes in nonmetastatic colorectal cancer patients after curative surgery: a systematic review and meta-analysis. *Ann Oncol* April 2015, 26:644–656

Adherence to diabetic treatment declines with cancer diagnosis

■ Diabetologia

Following a cancer diagnosis there is a decline in adherence to glucose-lowering drug (GLD) treatments, a Dutch population study has found.

Cancer patients with diabetes are known to have significantly higher overall mortality than those without diabetes. Overall, only 65–85% of users of glucose-lowering drugs are regarded as adherent, and there have been concerns adherence may decrease further following a diagnosis of cancer. If a diagnosis of cancer influences adherence among users of glucose-lowering drugs, this could also affect HbA1c levels, leading to poor metabolic control, higher risks of complications and worse overall mortality.

In the current study, Marjolein Zanders, from the Netherlands Comprehensive Cancer Organisation, and colleagues, explored the impact that a cancer diagnosis has on adherence to glucose-lowering drug regimens. For the study, the community pharmacy (outpatient) database was used to identify all new users of glucose-lowering drugs between 1998 and 2011, and the Eindhoven Cancer Registry was used to identify individuals who also had a diagnosis of cancer (with the exception of non-melanoma skin cancer).

The investigators then matched 3,281 patients diagnosed with cancer to four control patients each (total 12,891) for age, sex, duration of follow-up, type of glucose-lowering drug used and year of first dispensing of drug. The team used the medication possession ratio (MPR), which divides the cumulative days of drug exposure by the total number of days in that time window, as a proxy for adherence.

Results showed that, before cancer diagnosis, the MPR increased by 0.10% per month (95%CI 0.10–0.10), and that besides a significant drop in MPR at the time of cancer diagnosis of –6.3% (95%CI –6.5 to –6.0), there was an ongoing, monthly decline in MPR of –0.20% (95%CI –0.21 to –0.20) after cancer diagnosis.

The largest drops in MPR at the time of cancer diagnosis (in the range 11–15%) were seen among patients with stage IV disease and gastrointestinal or pulmonary cancers. The drop in MPR was –8.3 for colorectal cancer, and –12.5 for oesophageal, stomach, pancreas or liver cancers, –15.2 for pulmonary cancers, and –0.8 for urinary cancers.

In contrast, a diagnosis of prostate or breast cancer seemed to have little influence, with prostate cancer having an MPR of +2.1 and breast cancer having an MPR of –0.5.

"This study revealed that the medication adherence among users of GLDs [glucose-lowering drugs] was influenced by cancer diagnosis. Although the impact of cancer was more pronounced among cancers with a worse prognosis and among those with more advanced TNM stages, the difference in prognosis associated with these cancers seemed to only partly explain the impact of cancer on medication adherence," write the authors.

In future studies, they add, the reason for the decline in MPR needs to be further elucidated among different cancer types, with more information required about whether it is the patient who prioritises the fight against cancer (over glucose-lowering drug treatment) or whether it is the advice of the physician to stop treatment.

■ M Zanders, H Haak, M van Herk-Sukel et al. Impact of cancer on adherence to glucose-lowering drug treatment in individuals with diabetes. *Diabetologia* May 2015, 58:951–960

Cognitive impairment in breast cancer attributed to post-traumatic stress

■ JNCI

Prior to treatment, breast cancer patients may show limited cognitive impairment that is largely caused by cancer-related post-traumatic stress disorder (PTSD), the prospective Cognicares study has found.

When neuropsychological studies first demonstrated cognitive impairment in subgroups of cancer patients, the deficits were attributed to the neurotoxic effects of chemotherapy. An increasing number of studies, however, have found evidence of pre-treatment cognitive impairment. Hypotheses regarding cancer-associated cognitive deficits have included shared vulnerability for cancer and cognitive impairment and the biological effects of the cancer itself.

In the Cognition in Breast Cancer Patients: the Impact of Cancer-Related Stress (Cognicares) study, Kerstin Hermelink and colleagues, from Munich University Hospital, tested the hypothesis that pre-treatment cognitive impairment may be attributable to cancer-related PTSD.

Between January 2011 and August 2013, at six breast centres in Munich, 166 women who were newly diagnosed with stage 0 to IIIc breast cancer (case patients) were compared with 60 women who had undergone negative

routine breast imaging (controls). The women all underwent traditional and computerised neuropsychological testing, clinician-administered diagnostic assessment of stress disorders, and self-report assessments of cognitive function and depression, with assessments undertaken prior to local or systemic interventions for case patients and one week after negative mammograms for controls.

Results showed that prior to the first course of treatment, the patients and healthy controls exhibited similar levels of performance on standard cognitive tests. However, in one test of attention (index phasic alertness), case patients demonstrated significantly higher error rates than controls (P=0.02).

"Consistent with the hypothesis of the study PTSD symptoms predicted performance on these indices while the effect of case patients vs control patient status was not statistically significant when PTSD symptoms were accounted for," write the authors.

"The Cognicares study indicates that limited cognitive impairment that may occur in breast cancer patients already before treatment is most probably largely caused by traumatic stress in the wake of a cancer diagnosis," they conclude.

In the study, less substantial pre-treatment cognitive impairment was found than that reported in many previous well-controlled and methodologically sound studies. "This discrepancy may be because of elimination of additional confounding factors, especially effects of surgery, in the present study," write the authors.

The authors add that their results apply to patients who have access to excellent medical care and who enjoy relatively high standards of social security. "Under different circumstances, cancer patients may show more cognitive impairment," they write.

■ K Hermelink, V Voigt, J Kaste et al. Elucidating pretreatment cognitive impairment in breast cancer patients: the impact of cancer-related posttraumatic stress. *JNCI* published online 16 April 2015, doi:10.1093/jnci/djv099

Survey reveals low use of decision aids in prostate cancer

■ JAMA Internal Medicine

More than one-third of clinicians treating patients with prostate cancer use decision aids a US survey has found.

Men diagnosed with clinically localised prostate cancer have multiple options for disease management, including active surveillance, surgery, and radiotherapy. Since each treatment carries adverse effects on health-related quality of life, treatment decisions need to incorporate patient preferences and personal values, and therefore require adequate patient knowledge about prostate cancer and relevant treatments.

In an effort to facilitate shared decision making in clinical practice, decision aids have been developed and evaluated for a variety of malignant neoplasms, including prostate cancer. Decision aids have been shown to increase patient knowledge and involvement in decision making, and lower patient anxiety and uncertainty.

Simon Kim and colleagues, from Case Western Reserve University School of Medicine, Cleveland, Ohio, undertook a national survey to evaluate physician familiarity and use of decision aids in prostate cancer. Between November 2011 and April 2012, a nine-item survey exploring use of decision aids in clinical practice, familiarity and usefulness of decision aids, perceptions of possible barriers towards using decision aids, and trust in other organisations in promoting decision aids for prostate cancer was mailed to a random sample of 711 radiation oncologists and 711 urologists.

Results showed that 642 respondents completed the survey, giving an overall response rate of 45.1%. In total, 35.5% of respondents (37.4% of radiation oncologists and 33.7% of urologists) stated they currently used a decision aid in their clinical practice, with 21.5% saying that they were 'very familiar' with decision aids, 58.5% 'somewhat familiar', and 20% 'not familiar'. Only 16.5% viewed decision aids as 'very useful' and only 9.2% were 'very confident' decision aids improved treatment decisions.

Overall, 45.6% of physicians who used decision aids strongly agreed that they were applicable to their patients in comparison to 7.8% of those who did not use them. Furthermore, 45.6% of physicians who reported not using decision aids strongly or moderately agreed that their patients could not process information from decision aids compared to 25.1% who used them.

"Although respondents from both specialties tended to view DAs [decision aids] positively in general, the lack of strong familiarity with DAs may partly explain their low use in the clinical setting," write the authors, adding that efforts to address barriers to clinical implementation of decision aids might facilitate greater shared decision making.

"By engaging physicians in developing DAs that are user friendly, creating incentives for their use, and facilitating collaborations across specialty organizations, SDM [shared decision making] may become a more integral part of treatment decision making for clinically localized prostate cancer," they write.

In an invited commentary considering the paradox of why decision aids have a low rate of usage in clinical practice, Michael Barry writes, "One key issue is that decision aids do not fit easily into the workflow of clinical care. Decision aids are best initially deployed outside a physician visit so patients can get up to speed about their condition and the treatment options."

■ E Wang, C Gross, J Tilburt et al. Shared decision making and use of decision aids for localised prostate cancer: perceptions from radiation oncologists and urologists. *JAMA Intern Med* May 2015, 175:792–799

■ M Barry. Resolving the decision aid paradox. *ibid*, pp 799–800

How long do I have?

Story of a myeloma patient

The patient rejects the 'standard of care'. The oncologist cannot answer his question "How long do I have?" Is the treatment course they agree on 'second best', or 'best'?

WISHWDEEP DHILLON

We met almost three years ago. I was in the first year of haematology and oncology fellowship training. He was in his early 60s and had recently retired. His primary care physician had referred him for evaluation of incidentally detected monoclonal proteins.

Over the next few days, the workup unfolded. His skeletal radiographs showed lytic lesions, and his bone marrow biopsy showed sheets of plasma cells inundating the marrow space. It was multiple myeloma, a malignancy of plasma cells. I explained to him how these cells, which manufacture antibodies under normal circumstances, had mutated into bone-eating parasites and that his bones had become susceptible to fracture and collapse, like a fort attacked from within.

A prognostic panel showed that he had one of the most aggressive types of multiple myeloma, defined by deletion of chromosome 17p. Patients with this subtype often need aggressive treatment, respond poorly to treatment, and have worse outcomes. Once the diagnosis sank in, he asked me, "How long do I have?"

Given his disease burden, it was clear (to me) that he needed to be treated. The unfavourable genetic profile of his disease conveyed a sense of impending crisis. However, there was a catch. He had few symptoms, if any, and was in a wonderful overall state of health. His only complaint was mild lower back pain. Most

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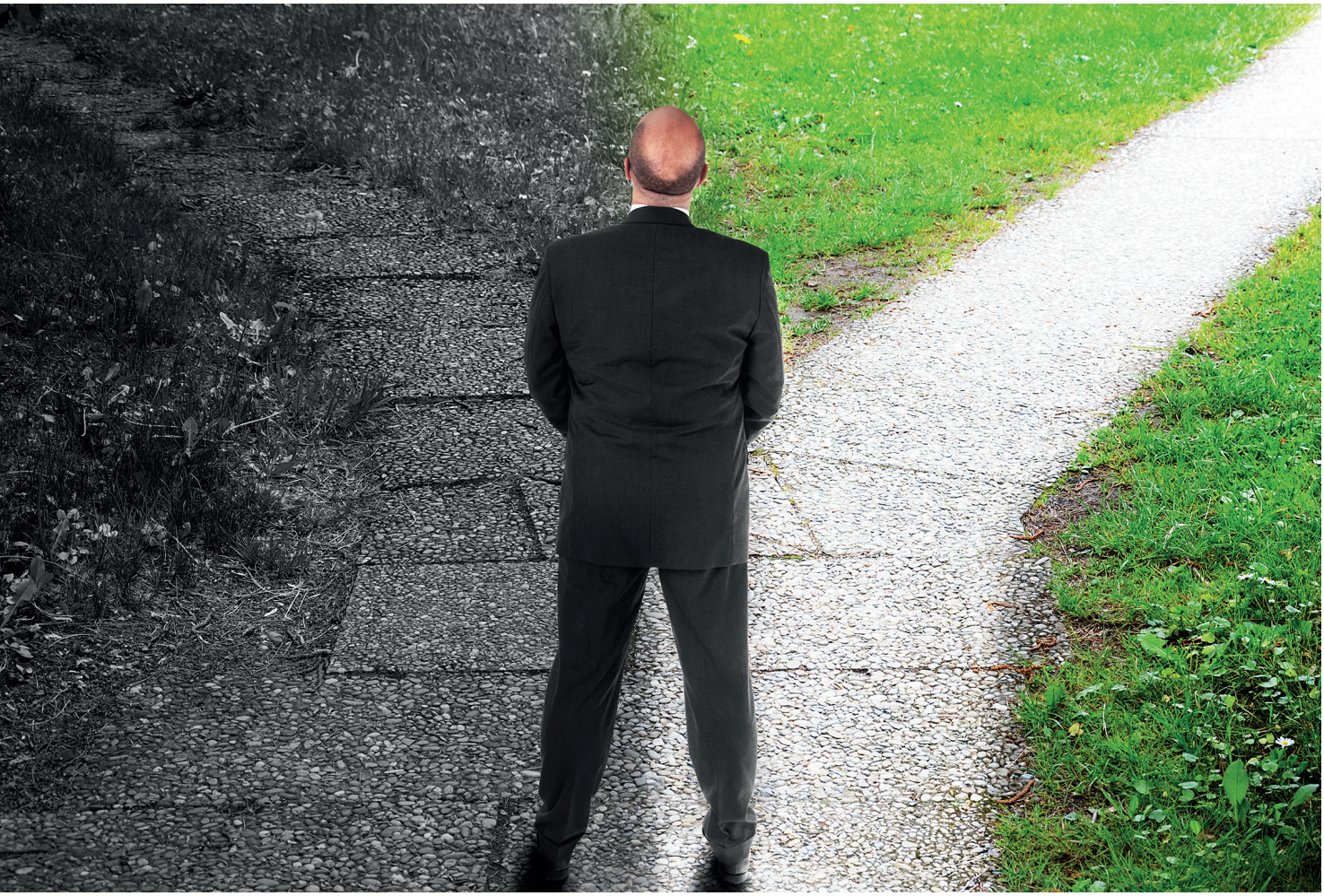

important, he did not want any treatment that would affect his quality of life.

Whereas I sought to protect his excellent health through treatment, he did not think he needed to be treated. We had hit a philosophical roadblock. Optimal treatment consisted of multidrug therapy followed by autologous stem cell transplant. As we discussed treatment-related side effects, his anxiety became palpable. It was clear that although we viewed this treatment as a "standard" approach, he viewed it – especially the transplant part – as extremely toxic.

He was truly concerned about being hospitalised or missing out on a cruise with his wife or skipping a weekend with his grandchildren. What mattered to him were "not the years in his life, but the life in his years." I sensed his reluctance to proceed, but without treatment, he was at significant risk for disease-related complica-

Whereas I sought to protect his excellent health through treatment, he did not think he needed to be treated

Each conversation about transplantation seemed to further strengthen his resolve not to have it

tions like kidney damage, spontaneous fracture of his bones, or paralysis. I felt that some treatment was probably better than none.

We negotiated, and he agreed to be treated, but only with two drugs, and refused the transplant. As expected, this milder treatment programme did little to reduce his monoclonal protein level. Unexpectedly, for him at least, it caused no significant side effects, and given how well he tolerated it, he agreed to try our originally recommended regimen, which consisted of three agents.

Once on the triple-drug regimen, his disease burden plummeted and then plateaued at a low level, which I viewed as particularly concerning, especially in light of the aggressive nature of his disease. It was at this point that we reintroduced the recommendation for a stem cell transplant; however, as before, each conversation about transplantation seemed to further strengthen his resolve not to have it. After another round of negotiation, we were able to collect his stem cells and freeze them for possible future transplant. He opted to continue the triple-drug regimen and tolerated it without any appreciable side effects.

Once we got over the 'hump' of transplant, he seemed more at peace at subsequent visits, probably because he had avoided it. I was also more at peace because, even though he refused a transplant, at least we had access to his stem cells, deep frozen. I continued to see him in the clinic until I finished my fellowship in the summer of 2014. We have kept in touch since then, and he continues to do well.

It has been almost three years since he was first diagnosed, and although his myeloma has not been eradicated, his disease burden and the extent of bone damage have remained stable. Although I am still unsure whether his decision to forgo transplantation was the 'right' one, it made me appreciate the questions that come up quite often in the life of an oncologist: How do you define the 'best' treatment? What should drive cancer care: the years in a patient's life or the life in those years? Did I treat him, or did he teach me?

In the story of my patient, I see the amazing story of multiple myeloma. Once a death sentence, myeloma patients are living much longer now. Over the past few years, myeloma research has reached an unprecedented level of advancement. The number of approved therapies for treatment of myeloma is expanding, and drugs like bortezomib and lenalidomide have transformed the landscape of survival. In addition, two more promising drugs, pomalidomide and carfilzomib, were recently approved for refractory myeloma.

Despite our progress, stem cell transplantation is still one of the best available tools for treating multiple myeloma; however, with the advent of targeted and less toxic therapies, it is likely that we will continuously re-evaluate its role in myeloma. Even after his disease stabilised, my patient often asked me, "How long do I have?" Every time, I would tell him I honestly did not know. I loved that answer. ■

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How do you define the 'best' treatment? Did I treat him, or did he teach me?