European School of Oncology
Learning to care

September-October 2015

Number 68

cancerworld

STOP THE CUTS!
'Europe must spend more on health', EU Health Commissioner tells *Cancer World*

LIQUID BIOPSIES
Using clues in the blood to guide our clinical decisions

REROUTED NOT DERAILED
Resuming a young life after cancer

Denis Lacombe

Quietly orchestrating the clinical research revolution

Cancerworld

Shaping the future of cancer care

Contents

Printed by
Grafiche Porpora

Cover photograph
Julien Warnand

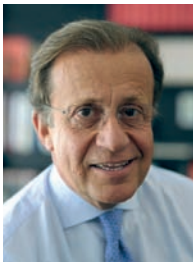
Published by
European School of Oncology

Direttore responsabile
Alberto Costa

Registrazione Tribunale di Roma
Decreto n. 436 del 8.11.2004

All enquiries about Cancer World should be made to:
ESO Editorial Office
Via Turati 29
20121 Milano, Italy
e-mail: magazine@eso.net
Tel: +39 02 8546 4522
Fax: +39 02 8546 4545
All correspondence should be sent to the Editor at editor@eso.net

Cancer World is published six times per year by the European School of Oncology. It is distributed at major conferences, mailed to subscribers and to European opinion leaders, and is available online at www.cancerworld.org



Goodbye or arrivederci?

ALBERTO COSTA EDITOR

Where will European oncology go from here? This is a question many of us will be asking as the ECCO–ESMO congress convenes in Vienna. There's a diffuse sense of uncertainty, coming mainly from the laboratories, where many promising cutting edge innovations still seem to be in the air. Our new vocabulary – gene, genome, molecular, targeted, personalised – has lost its novelty and its shine. What will be the next clinical trial to have us all breathlessly awaiting the results? What innovation will be the next to radically change our clinical practice? A second generation of Da Vinci robots for everybody? Intraoperative radiotherapy? Immuno-oncology? Alopecia preventing devices?

With this in mind, the thoughtful ECCO–ESMO participant will also be worrying about the endless list of cost issues that intrude on clinical decisions. This is not something we were prepared for; we never studied pharmaco-economics (or device-economics) at medical school. How can clinical oncologists take these decisions? Is what we do even still clinical oncology, or is it a highly complex combination of medicine, nursing, ethics, sociology, economics and politics?

On top of this, many of our friends participating in ECCO–ESMO will want to attend sessions that address questions about how and where care should be delivered to their patients. Questions like: should I send all my breast and prostate cancer patients to the nearest certified breast or prostate unit? It's now accepted that all patients with rare cancers must be referred to the nearest centre of excellence, but what about other patients? Can I, a surgical oncologist, continue to practice as I have done for the last 20 years? Is it still OK to 'do' a lung cancer one morning and a liver cancer the next? Can I, a medical oncologist, safely treat a patient with an advanced colorectal cancer, a bone sarcoma and maybe a lymphoma, all within the same outpatient clinic?

These are our common concerns and the things that really matter to all of us who are proud to attend the ECCO–ESMO conference. The Americans have decided to keep well separated the physician researchers (AACR), the cancer doctors (ASCO), the nurses (ONS) and the patient advocates. Here in Europe we have a long tradition of working together, but the will to continue to do so is now in danger.

The details of how ECCO and ESMO should collaborate may be of no great interest to participants at the Vienna conference, but the great majority will undoubtedly feel that staying together is the right thing to do, both for cancer health professionals and patients. Cancer has become all about collaboration, and it's too late for any single specialty to work in isolation.

When we leave Vienna, we want it to be with an *arrivederci* and not goodbye.

Denis Lacombe
quietly orchestrating the clinical research revolution

SIMON CROMPTON

The scientific complexity and economic cost of developing new cancer therapies demand a level of collaboration and sharing that takes both industry and academia well beyond their comfort zones. EORTC head Denis Lacombe believes he has the passion and the vision to help make it happen.

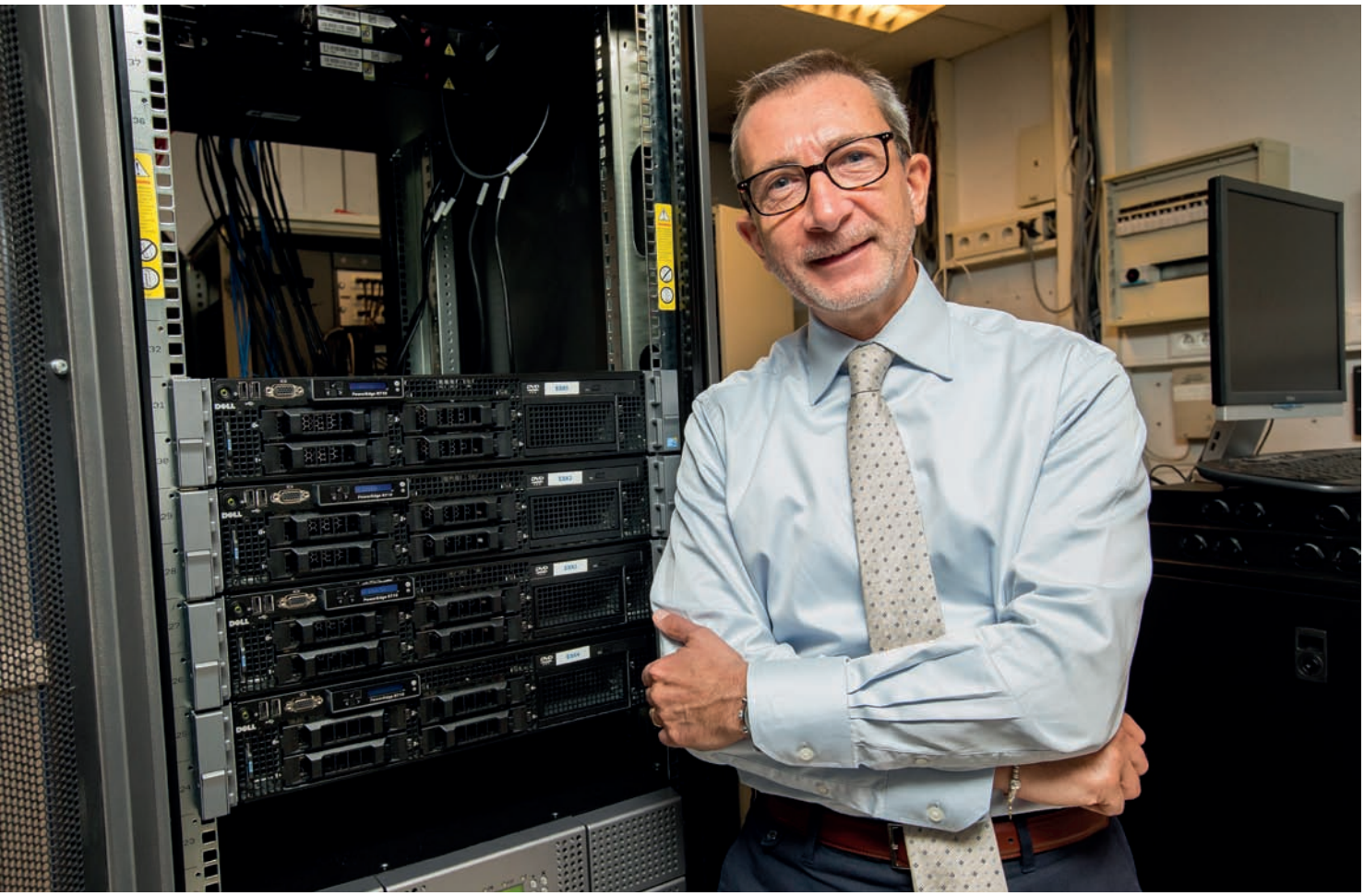
It is 22 years since Denis Lacombe first stepped into the Brussels offices of the European Organisation for Research and Treatment of Cancer (EORTC) on a fellowship. Today, speaking to him two months after his appointment as its Director General, he can still barely believe he has worked his way up to lead the organisation – the only European non-profit body carrying out international multidisciplinary research for all types of cancer.

But though Lacombe, a Frenchman with a research background in pharmacology and pharmacokinetics, clearly has his feet planted in EORTC's history and values, what he really wants to talk about is radical change.

"To be honest, the environment has changed so much, and there is so much potential in the organisation, that I feel that I've just arrived," he says.

Today, says Lacombe, we are witnessing nothing less than a revolution in the way cancer treatments are developed and researched. And he sees EORTC at the vanguard of change in Europe, leading the way against stifling regulations, professional silos and antiquated trials processes, and towards a new era of personalised medicines tested as early as possible on those who need them most.

"The reason I am still here is that I truly believe in our mission," he says. "I believe in the multidisciplinary team, in partnerships, in what



JULIEN WARNAND

The treasure chest. Lacombe with the EORTC servers that store clinical and biological data from many hundreds of thousands of patients, dating back decades

we can do for patients. Most commercial clinical trials are purely drug-orientated, but what we do is independent and genuinely patient-centred, also addressing surgery and radiation oncology. The forms and methods of clinical trials have evolved over the years, but we have always had the capacity to ask the questions that patients want answering, and to follow patients long-term."

As he sets out his credo at the start of our interview, he consults notes he has diligently prepared for our meeting. My questions about the challenges the research world faces – particularly self-interest and insularity in academia and industry – are politely acknowledged as valid, but shifted towards his vision of change and opportunity in Europe, led by EORTC. It rings of genuine enthusiasm rather than corporate PR.

At the centre of his excitement is the concept of a child's toy – the diabolo, an hourglass shaped cylinder, controlled on a string between two sticks. He sketches it on a piece of paper in front of him. This, he explains, is the new shape of clinical research in cancer.

Such is the diversity of disease and drugs now designed to target specific types and people that the classic triangular model of treatment development – with more and more resources being poured in as drugs move from phase I to phase III trials – is no longer fit for purpose, says Lacombe.

"People on trials expect the drug to function for them, but that doesn't work with the classical model"

Historically, EORTC concentrated on large phase II and III clinical trials. But today, he explains, resources are moving "upstream" to early clinical trials involving tissue characterisation, imaging, screening platforms, collection of high-quality data. This should allow for much smaller pivotal trials (trials aimed at changing practice, represented by the narrow centre of the diabolo), which should be done with highly targeted groups, where the benefits are likely to outweigh the risks. Then the diabolo shape opens up again to represent increasing efforts over the longer term to establish the true value of the treatment in real-life settings.

And here new models are emerging for post-marketing studies to answer questions about long-term toxicity and benefits. Adaptive licensing will be key to allowing high-quality real-life prospective cohort studies to gather data on efficacy and safety data throughout recurrences, which can provide benchmarks to guide future decisions on access. EORTC, which has historically put an emphasis on following patients who participated in their studies, is now entering partnerships with European cancer registries to find ways of better exploiting the vast resources of data available on how treatments work over time and in real life.

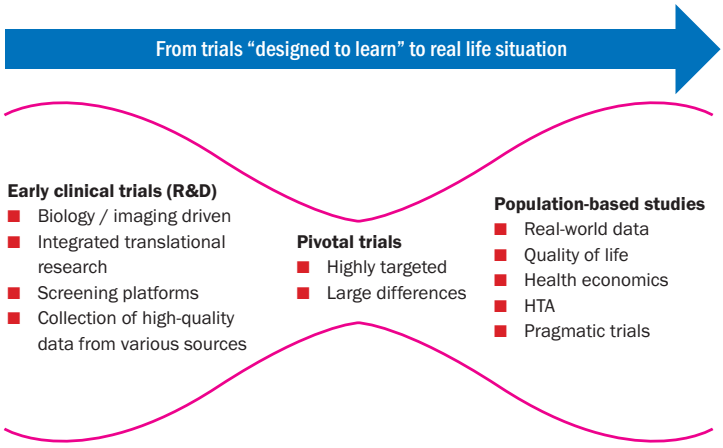
So the days of talking about phase I, II and III trials in cancer drugs are numbered, says Lacombe. "I like to speak instead about clinical trials that are designed to understand and clinical trials that are designed to conclude – we need to change the terminology to change the mindset, because a number of people out there are still thinking about phase I trials in the classical sense, where they were designed to test safety. If we change the mindset, we can change what we achieve."

"The diabolo shape of product development is what the patients want, what the drug regulators want, what the payers want. It's really answering questions for the subset of patients that actually benefit, so that you avoid undue toxicity for those who don't benefit. And the payers, in any case, aren't going to be able to support treatments for small numbers of patients unless we come up with this evidence of clear benefit."

"As for patients, it's like when you buy a car: if you put the key in, you expect it to start. People on trials expect the drug to function for them – but that doesn't work with the classical trial model."

This is why EORTC has completely repositioned itself over the past decade, says Lacombe, who presented the diabolo concept two years ago in a paper with EORTC colleagues published in the *European Journal of Cancer*. Today there is far more emphasis on trials examining biology, developing biomarkers, and bringing together a range of health and scientific dis-

THE CHANGING CLINICAL RESEARCH PATHWAY



The traditionally large and costly phase III trials looking for incremental benefit in largely unselected patient groups must give way to small trials in a subgroup of patients with the greatest chance of deriving benefit. The traditionally small phase I and II trials looking at safety and efficacy must be replaced by a major collaborative effort at an early stage to gain a deep understanding of how the experimental therapy works and in whom, as well as greater efforts, at a later stage, to confirm risks and benefits in the real world

ciplines to work with patients in translational research. "Two things have always characterised EORTC trials," says Lacombe. "They are international and multidisciplinary. So for us, it is an entirely logical evolution."

EORTC was founded on those principles in 1962, building a scientific and operational infrastructure for investigator-driven clinical trials and translational research. It is independently funded through various sources, including national cancer leagues, although some drug studies are conducted in cooperation with pharmaceutical industry partners.

Lacombe gained an early interest in research when he simultaneously trained in medicine and pharmacology in Marseilles in the 1980s. He first arrived at EORTC in 1993, having spent the previous two years working for a small French drug company, and three years before that on a post-doctoral fellowship at the Roswell Park Cancer Institute in the United States. Whereas his time in the United States, where he researched chemotherapy in advanced breast cancer, had opened his eyes to the wide potential of research – "Being in America changed my life" – research within industry felt restrictive and inflexible in comparison. And when his company conducted some research with EORTC, Lacombe was fascinated by the excellence of the European organisation's trial design.

He contacted Françoise Meunier, EORTC Director General from 1991 to 2015, who offered him a fellowship, because she needed someone with experience of industry and pharmacovigilance.

He took up the offer, wanting a new challenge, and has stayed with EORTC ever since, becoming medical supervisor in 1994, and then moving on to head the investigational agent unit, the intergroup office, and the pharmacovigilance and regulatory affairs units (both of which he set up), becoming Assistant Director of Medical Affairs and New Drug Development in 1998, Scientific Director in 2007 and Director of EORTC headquarters in 2010. Today, alongside his strategic role, he has daily responsibility for running the headquarters and managing its staff.

Lacombe may still be shocked that he leads

JULIEN WARNAND

EORTC after all these years, but there can be few who know the organisation or its research environment as thoroughly.

"In the early '90s, the organisation was data managers and statisticians, so I brought my knowledge about how to build the infrastructure you need beyond clinical trials – and it was very important, because by the late '90s, the regulatory frameworks started to change." When Lacombe arrived, EORTC employed 30 people. Today it employs 175.

For all the change, Lacombe insists that the mission remains the same, with the organisation still valuing its long-term capacity to follow patients and update old trials, while repositioning itself to revolve around new trials that understand the mechanism and biology of disease rather than randomising patients to test a hypothesis.

Fundamental to the shift has been addressing a basic question: if new targeted drug development depends on sorting patients according to their molecular features, how do you optimise access to the right kind of patients for trials? And how do you make sure that patients have access to the maximum number of trials that are likely to benefit them?

EORTC's answer has been to establish a molecular screening platform called SPECTA (Screening Patients for Efficient Clinical Trials

"I don't understand why ethics committees approve studies where biological material goes into a commercial silo"

Access). It depends on academics, clinicians and industry working with EORTC to share and contribute to a biobank and database of patient molecular profiles.

"With our access to large territories and a large number of patients, we can set up platforms where patients are molecularly defined and sorted. This is a knowledge development platform, a clinical trial access programme, and it also increases the likelihood of being able to offer to patients the best treatment known so far."

"The concept is to first understand the biology, and then propose a clinical trial, not the other way around."

The first SPECTA platform, in colorectal cancer, started in 2013, and 700 patients in trials across Europe have so far agreed to join the programme. The lung cancer platform opened in June. It is early days, but Lacombe is passionate about SPECTA's significance – and not just because of its practical applications. It may help bring the demise of current research systems which result in a tragic waste of biological data and material.

"Currently, three companies might screen 2,000 patients for the 200 they need for their trial. They store the material of the 2000, but ultimately there are 1,800 they don't care about because they are not the target. For 5,400 people the material is locked away for no purpose. What we're proposing is that instead of the companies screening 6,000 patients, we screen 2,000 and can drive 600 patients to three different kinds of studies."

"I don't understand it when ethics committees approve studies where biological material goes into a commercial silo – it is too scarce to be lost." Lacombe calls such biobanks "butterfly collections": an array of beautiful things left without use, gathering dust.

"It's not the fault of pharma – they must have access. But, as a community – pharma, academia, the patient, the regulator – we must be able to find a better way to access and share in a collegial multidisciplinary way. The patients are telling us that is what they want: they are saying 'Use, re-use, abuse our material, bring knowledge."

It's a fine vision. But I put to him the historic problems of widespread collaboration and sharing – not just because of industry's defence of intellectual property, but a possessiveness of knowledge in academia.

Lacombe points out that a wide range of stakeholders – the European Medicines Agency, industry, government, regulators, payers – have been involved in consultation and planning for the EORTC platform.

"Sharing is certainly a challenge, but it's part of the change of mindset that we need in the new environment, and I want to believe that these programmes will help. Things are now too complex and too expensive to do by yourself."

But how does EORTC manage to sell the added value of collaboration to all these different parties, when tradition, scientific egos – even funding – keep everyone in professional and institutional silos?

Lacombe admits the honest answer is that he does not know. "The only thing I can tell you is that we now have a waiting list of institutions who want to join these programmes. I think you can imagine that Europe is a challenging environment, because there are multiple companies, multiple regulations. But we have so much capacity – and have achieved much more with much less than the United States, and I want to believe that this part of the world is much more innovative. Maybe I'm too naive, a dreamer."

"It's complex, expensive, difficult, but the early signs are good. I believe that things in the future aren't going to be academia, industry, regulator separately. Everything will be much more integrated."

Lacombe's optimism is partly founded on his belief that the partnerships that EORTC has been forging over the past decade and more

will prime a more general process of sharing and collaboration. He refers to partnership 40 times during our two-hour conversation, citing EORTC's partnerships with: the European Society of Pathology, to help establish biobanks and their quality assurance processes; the European Society of Radiology and other imaging societies to help it establish imaging platforms; the European Thoracic Oncology Platform on lung cancer research and establishing SPECTA lung; the European Society of Surgical Oncology on a surgical quality assurance programme. He is keen to emphasise how innovative the latter partnership is, building on EORTC's multidisciplinary agenda to place surgery at the centre of research.

His point is that research needs are so complex now that EORTC cannot do it alone – and neither can anyone else.

"If there is one thing EORTC knows about, it's infrastructure for international multidisciplinary clinical trials. If we can partner with those who have another area of expertise, we can define new questions and make it happen together."

"So yes, maybe individual pathologists might say: 'Why should I send my biological material to EORTC?' But if you are a partner with the Society of Pathology, then you create a certain dynamism around the whole project."

Lacombe believes in Europe's potential for collaboration, despite the EORTC having faced several specifically European problems over the past ten years. Economic pressures on the pharmaceutical industry in Europe affected how the EORTC collaborated with them: "We had to adapt and stipulate that we only wanted to conduct good studies with a good amount of support from them."

And then there have been the problems posed by new regulations on clinical trials, medical devices and data protection, due to be introduced in EU countries in 2016. EORTC has been active in voicing the concerns of academic research. Lacombe believes that one of the major challenges the cancer research community will now face is how to implement the data protection regulations without damaging clinical research. Roger Stupp, EORTC's President, has been vocal in pointing out that time-consuming paperwork is already stifling innovation in research and the ability to share vital data.

JULIEN WARNAND

"The problem is that people who do regulation sometimes don't understand," says Lacombe. "They want a single regulation for data protection, but my banking data is a completely different thing than my biological data. That's a big problem."

Regulators also initially failed to understand that more than 50% of clinical research in the field of cancer was not in drug development –

"So complex are research needs now that EORTC cannot do it alone – and neither can anyone else"

JULIEN WARNAND

with many standards of care based around combinations of drugs, radiotherapy and surgery.

Nevertheless, the new regulations have been improved with the input of EORTC and academic partners. "I think we've helped push forward the simplification of procedures, and helped define low-risk clinical trials – those that are performed without drugs, or are about optimising treatment rather than new treatments – where procedures may need to be less rigorous."

So, he feels the challenges posed by the new regulations are not insurmountable: "We were all concerned 10 years ago when the clinical trials directive came in, but we survived it. I think we will pass this challenge too. It's just a pity that we have to use our energies on this when they would be better placed elsewhere."

Equally, the difficult economic climate, and the expense of traditional means of drug development, will force change in industry and other stakeholders, says Lacombe.

"It's a little bit unfortunate that it has to happen this way, but it's possible that because of the economic pressures we will force people to think differently. I think we should all be anticipating change so that we have capacity to do new kinds of research, but soon, instead of anticipating, people will just be faced with this new situation. Some drug companies are already facing it, and that's why we are getting a lot of enquiries about our SPECTA programme: Can you help with long-term follow-up? Can you help with benchmarking? Can you help us access this population?"

"All stakeholders need to find new ways to interact. Maybe industry takes more time – I understand they have pressures and shareholders to consider – but we all have to accept that we now have to leave our comfort zone. This is not yet happening, so we are doing a lot of communication to try and make it happen."

Lacombe might be the right person to bring this off. He is not a pushy performer – he acknowledges he is shy and is genuinely flattered by the 'personal recognition' that a *Cancer World* interview brings. But he has an infectious enthusiasm about the potential for European cancer research and everything to do with EORTC. This isn't just a job for him.

"Basically, I do only three things in my life because I have no time for anything else: my work, my family and my jogging. That's what I do."

But for all his natural quietness, Lacombe is confident he's the right person for the job. "I think there is a natural selection process of people who have energy and passion," he tells me as we conclude the interview. He knows he may be accused of being a dreamer, but he also knows that following a vision for research in Europe is the only way it can now move forward.

It's a message he has passed on to his children, now aged 12 and 14. "I always say to them, you need a passion to start, and then a vision to continue. You need to want it." ■

What can we learn from liquid biopsies?

MARC BEISHON

Early detection, disease prognosis, a guide to treatment, a key to unlock the secrets of how cancers evolve. Researchers have high hopes for what they can learn from the biological detritus shed by primary tumours and metastases.

With the explosion in knowledge about how genetic abnormalities in cancer change over time, and the corresponding rise in drugs that target them, comes a big challenge. How can these abnormalities be monitored during the course of the disease, so that the right treatments can be started (and stopped) at the right time? And could abnormalities be detected even before there are symptoms of primary disease, such as in pancreatic cancer, where most patients present with advanced tumours?

This is the realm of biomarkers and biopsies, and the good news is that clinicians – traditionally much more cautious than lab scientists – are talking about new non-invasive 'liquid biopsy' techniques that could be widely available in as little as two years' time.

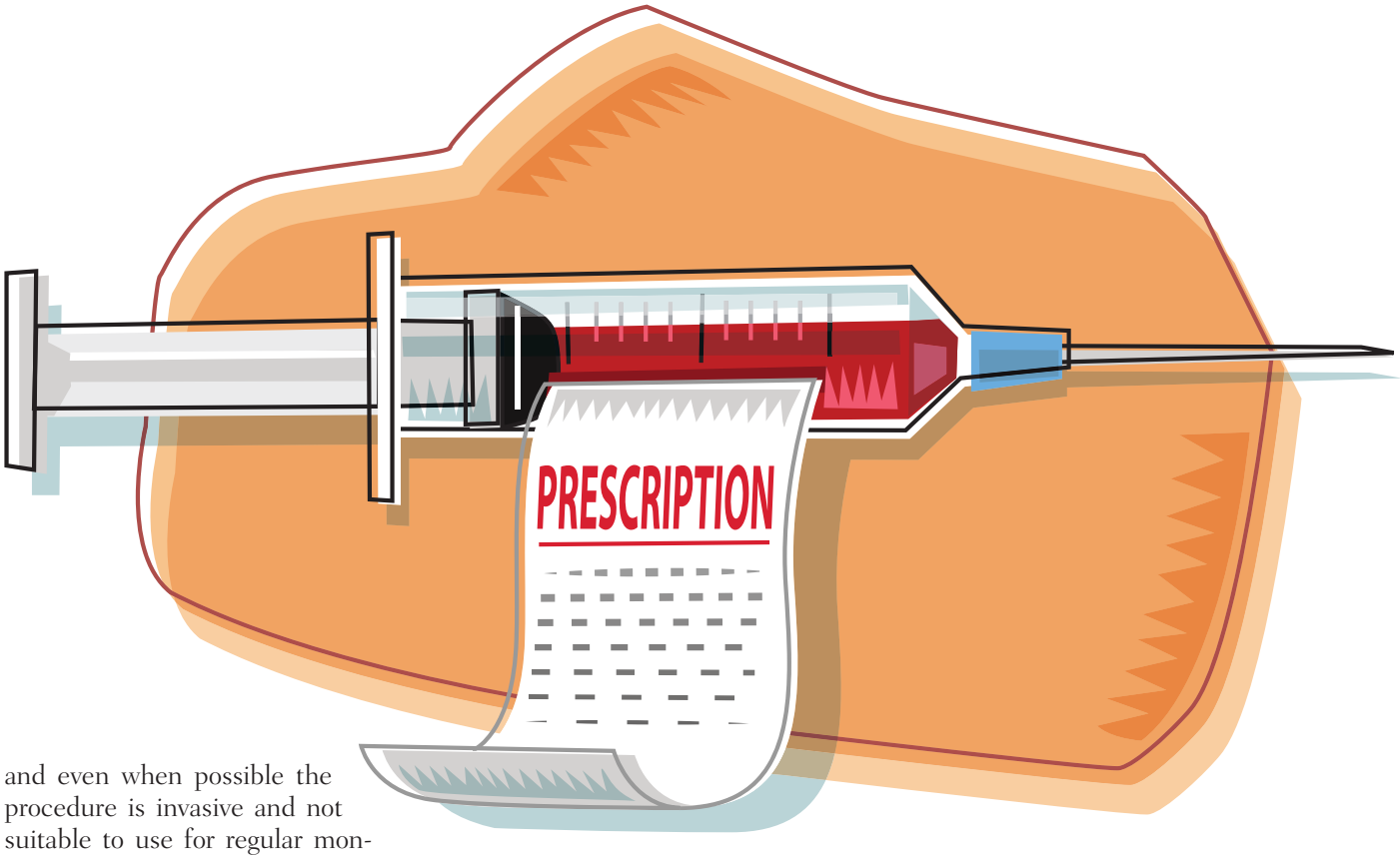
Liquid biopsies are performed on body fluid samples – blood being of most interest but also urine, spinal fluid and others – to look for a wide range of circulating cancer biomarkers, from fragments of DNA and RNA, to 'vesicles' containing tumour material, to whole cancer cells.

Circulating DNA is of particular interest now. Unlike the few other biomarkers in use in cancer, such as prostate specific antigen (PSA), circulating tumour DNA has come directly from a particular cancer – it cannot come from anywhere else – and technology has advanced so that it can be analysed at low cost and with good accuracy and more easily than tumour cells. Analysing DNA in fluids is therefore deserving of the 'biopsy' term.

In Europe, the first application is now approved by the European Medicines Agency (EMA) and on the market, and provides a good example of one of the main benefits of liquid biopsy. It is for the detection of EGFR-activating mutations in non-small-cell lung cancer, which is an indication for treatment with gefitinib (Iressa), which inhibits these mutations.

Whereas previously patients would not be eligible for gefitinib without evidence of EGFR mutation using conventional biopsy, following a trial, the EMA has extended the label of gefitinib so it can now be used if the mutation has been detected in circulating DNA in blood, and it has approved a test kit, made by Qiagen, to do this.

The advantage is straightforward – in advanced or metastatic lung cancer, for which gefitinib is approved, it can be hard to obtain enough or any tissue for testing from some patients,



and even when possible the procedure is invasive and not suitable to use for regular monitoring. The liquid biopsy offers a good alternative, although the study that led to the approval showed that tumour biopsy does give more accurate results.

Coming of age

Fortunato Ciardiello, professor of medical oncology at Naples University, and president-elect of the European Society of Medical Oncology (ESMO), says EMA approval in the case of the EGFR liquid biopsy indicates the approach is coming of age. "There is a lot of evidence now that, especially in large-burden tumours, circulating DNA and other materials can be used as biomarkers, for two main purposes," he notes. "First, after removal of the primary tumour, the presence of circulating tumour DNA or cells could be evidence that cancer is still in the body at micro-metastatic sites. So there could be prognostic value in identifying patients at risk of relapse, although we have achieved complete local control of the cancer.

"Second, and of more interest in the research community in the past few years, is using a liquid biopsy as a way to monitor treatment or follow the evolution of the disease. We know that most cancers are heterogeneous, and that sub-clones and different molecular alterations occur, and that conventional biopsy can miss these as they can be in certain parts of the tissue only.

"Blood biopsy can give us a better picture of the abnormalities from both primary and metastatic sites, and if we identify certain changes such as mutations or gene amplifications, this could be a marker of sensitivity or resistance to therapies, and can help us in 'treat or not-treat' decision-making."

While the lung cancer EGFR test is for a snapshot of the presence of an activating mutation for cancer cell growth, Ciardiello says studies in a number of cancers, such as metastatic colorectal and lung, are now taking blood samples over time to detect changes that can indicate resistance to

ILLUSTRATION: FRED VAN DEELEN, WWW.ORGANISART.CO.UK

Gefitinib can now be used after the EGFR mutation has been detected in circulating DNA in blood

"Sensitivity issues may arguably be counterbalanced by it overcoming tumour heterogeneity"

the initial therapy before other signs of relapse or tumour progression emerge.

"We have to be cautious, as most of the work is experimental, although the evidence is good," he says. "We need standardised methods for exporting DNA and assessing the presence of mutated genes and other alterations. We are moving fast, but liquid biopsies cannot yet substitute for finding abnormalities in tissue. However, with the lung EGFR approval we do have a complementary method, with much more to come."

Howard 'Jack' West, a medical oncologist and director of medical therapeutics in the thoracic oncology programme at the Swedish Cancer Institute in Seattle, US, agrees that liquid biopsies are of particular interest for lung cancer due to challenges of tissue collection, and that addressing molecular variability is now on the agenda. "The more we study and acknowledge tumour heterogeneity, the greater problem we recognise it to be. Before there was an alternative, there was little point in obsessing over this challenge. Even now, serum-based testing isn't necessarily better, but the sensitivity issues may arguably be counterbalanced by it overcoming tumour heterogeneity.

"It may well be that as the technology improves – as it has been and likely will continue to – the sensitivity issues will become less, and serum testing may eventually prove superior to tissue collection even if access to tissue weren't a limiting factor. But this is speculation at this stage."

Nitzan Rosenfeld, who runs a molecular diagnostics group at Cancer Research UK's Cambridge Group, explains why DNA fragments, which are thought to come from dead cancer cells, are of such interest. "Biomarker research is challenging as you can be unsure whether what you are measuring comes from the cancer or from other parts of the body. If it's not completely specific to the cancer, the initial specificity gets diluted by confounding effects from other non-cancer cells," he says. Proteins and RNA, even if mostly specific to the cancer, can often originate from other cells; a marker such as PSA comes from the prostate but not necessarily prostate cancer, which is a reason it is such a controversial test.

"But DNA stands out, as the cancer specific mutations come only from tumour cells, as far as we know, which makes them exquisitely specific – if you know a tumour has a particular mutation, when you find DNA in the blood that has that mutation, even at a distance from the tumour, you know it comes from that cancer."

There is though a lot of other DNA in the blood from non-cancer cells. Rosenfeld notes that 2ml of plasma may contain more than 10,000 copies of DNA from healthy cells, but in some cases only a few dozen copies of a tumour's genome. He adds, however, that obtaining and sequencing circulating tumour DNA to significant sensitivity and specificity has been a great success of new technology in the past few years, which may make it more practical as a source of information about the cancer than circulating whole cancer cells.

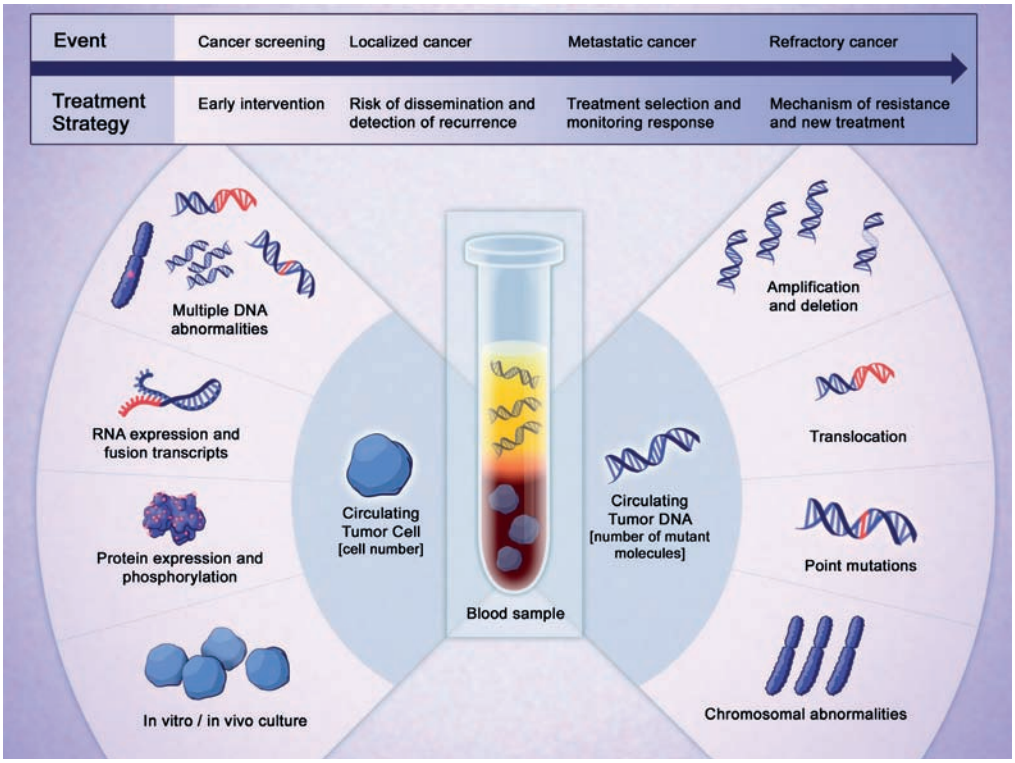
DNA vs whole cancer cells

In blood of people with advanced breast cancer there are around 100 times more copies of the cancer genome present as fragments of DNA than there are intact cancer cells, says Rosenfeld, adding that, "It's harder to analyse cells. They are much more fragile than DNA, which is a robust molecule." Cells first require mechanical methods for isolating them and special detection techniques, and there is currently only one system approved for use in the US (CellSearch).

Circulating tumour cells are, however, also a strong research area, and probably more studied than DNA so far, with new analysis technology being developed. In breast cancer, a certain threshold of circulating cells has been shown to be prognostic for worse outcomes. There is also research similar to that using DNA fragments that is looking at how information from circulating cells can be used to monitor the impact of treatments and the genetic evolution of tumours over time.

Indeed, there is some debate between protagonists of DNA and cells about which is best. West adjudicates: "It remains to be seen whether circulating DNA or cells will emerge as the right platform. So far, more of the recent trials have shown utility of DNA, and what will determine the winner is what actually works – the proof will be in which delivers the sensitivity in larger trials on a reliable basis, as well as turnaround time, which should ideally be under two weeks."

Much impetus for the circulating DNA work has come from Bert Vogel-



Liquid assets. Learning how to isolate and interpret the clues that solid tumours leave in the blood and other fluids could transform the way we detect cancers, select treatments and monitor response

Source: Reprinted from DA Haber and VE Velculescu (2014) Blood-based analyses of cancer: circulating tumor cells and circulating tumor DNA *Cancer Discov* 4:650-661, with permission from AACR

stein's group at Johns Hopkins in the US, Rosenfeld notes. Although knowledge about DNA in the blood dates back to the late 1940s (and circulating tumour cells to the 19th century), other fields such as blood testing for foetal disorders and managing viral infections such as HIV have paved the way for DNA applications in the clinic – cancer has been a late-comer.

In 2008, the team at Johns Hopkins published 'Circulating mutant DNA to assess tumour dynamics', which quantified DNA in a small number of patients and showed how a PCR technique pioneered by the group, known as BEAMing, could sequence such DNA.

A lot of companies are now rushing to produce test kits that raise the bar on accuracy (including Inivata, for which Rosenfeld is chief scientific officer). There is no standard says West. "I've been using the Guardant 360 test [from Guardant Health, a US firm], but I'm just trying to get an early sense of how well it works," he says. "My institution is interested in doing a trial comparing several companies that test serum with the tissue-based next generation sequencing we're doing. There is no default company or test in the US, and I don't think there will be, just as there isn't one company doing next generation sequencing on tissue. But in the next few years we'll likely see many larger institutions identify a test or company of choice for doing serum-based mutation testing."

Ciardiello cautions on the technology, which will be in the hands of often hard-pressed pathology departments coming to terms with rapidly changing molecular pathology techniques, presenting challenges for both quality control and access. Initiatives that have assessed and accredited labs to carry out tissue-based molecular testing, such as for *RAS* in colorectal cancer (see Testing the testers, *Cancer World* Nov–Dec 2012) could be a model for serum testing. But many patients are still not accessing these tissue tests – indeed Ciardiello helped to launch the International Colorectal Cancer Association's 'Get Tested' campaign this year, which aims to raise patients' awareness of the importance of the test.

"It remains to be seen whether circulating DNA or cells will emerge as the right platform"

"We stop prednisone when we see the abnormality emerging, using a blood test to do this"

A diagnostic tool

Rosenfeld agrees with Ciardiello that, while circulating DNA could be a useful prognostic tool indicating the presence of micrometastases after resection of the primary tumour, the greater immediate interest lies in its potential for revealing the evolving genetic profile of the tumour. "What's moving most rapidly is performing cancer genomic analysis on a blood sample with a view to targeting mutations, because the research community wants to use genomics as a diagnostic tool," he says. "Taking a tissue sample and testing it with low-sensitivity genomic analysis is analogous to carrying out high-sensitivity analysis on blood, and there will be particular patients and populations where either method could work better. You are asking the same question from the blood as you would from the tumour tissue."

But if there are no actionable (i.e. targetable) mutations, or if treatment has changed mutations to be non-actionable, DNA can still be used as a highly sensitive monitoring tool, because even a few molecules are specific to the cancer, he adds. "This uses genomic techniques to obtain a quantitative measure, which then functions like a classic (e.g. protein) biomarker. The evidence so far supports the intuition that a higher DNA level is a bad sign, and that you can identify a recurrence earlier by seeing tumour DNA in the blood than by other means."

He notes further work following the Johns Hopkins study, mostly more proof-of-concept studies on quantifying DNA levels and monitoring, including research at his own lab. While there is value in prognostics, he points out that it is more difficult to apply monitoring because there is a need to have pre-defined criteria for tumour progression, which would need randomised trials to establish.

Meanwhile, his lab and others are focusing more now on circulating DNA as a genomic research tool in cancer evolution and emerging mutations, resistance to therapy, and also earlier diagnosis, where adding genomic information from body fluid analysis to other symptoms could prove helpful.

A key paper from Rosenfeld's lab was published in *Nature* in 2013 (vol 497, pp108–112) under the title 'Non-invasive analysis of acquired resistance to cancer therapy by sequencing of plasma DNA'. This proof-of-principle study followed six patients, who had advanced breast, ovarian or lung cancers, for up to two years. The genomic evolution of these tumours included several types of mutations that were identified when treated with drugs such as paclitaxel, cisplatin, trastuzumab and gefitinib. The researchers concluded: "Serial analysis of cancer genomes in plasma constitutes a new paradigm for the study of clonal evolution in human cancers." Other studies have since demonstrated similar results with more patients.

Impact on care

The impact is already being felt in clinical practice, at least in some research institutes. A good example comes from Gerhardt Attard's group at the Institute of Cancer Research in London, where liquid biopsies are being used to inform the management of some patients. Research on men with advanced prostate cancer who receive the combination therapy of abiraterone (an enzyme inhibitor that decreases testosterone) and prednisone (a steroid that reduces inflammation), after having become resistant to initial hormone therapy, has shown that about one in five relapse on the combination regimen, because at some point androgen receptor mutations emerge that are activated by the steroid.

"This has a real, immediate impact on care, because we are now conducting trials where we stop prednisone as soon as we see the abnormality emerging, using a blood test do this. Importantly, prednisone is a very effective drug and works, at least initially, for most men, so it's an example where the cancer adapts to turn an excellent drug into a driver of the disease in a small proportion of patients," says Attard.

Beyond the immediate implications for patient care, the research done by Attard's team has revealed important information about the behaviour of advanced prostate cancer and the complex ways in which abnormalities emerge, some of which is outlined in their paper (*Sci Trans Med* 2014, 6:254) on 'Tumour clone dynamics in lethal prostate cancer' (where 'clone' means a group of cells that share common changes).

This work involved looking at different abnormalities in the DNA. "We don't restrict ourselves to mutations,

but have also developed an approach to study changes in copy number, both amplifications and deletions," he says. What his team found was that different groups of clones were circulating, suggesting lethal prostate cancer represents multiple different clones. "The variety and dynamic changes of DNA we detected in circulation were sobering," says Attard. The team also found events that had previously been thought to be early, 'initiating', events in prostate cancer, analogous to mutations of the *APC* (adenomatous polyposis coli) gene in colorectal cancer, actually happened later.

Attard concludes that, critically, the 'actionable' aspect of such genomic work must be its link to treatment: "Clinical practice will be significantly changed for discoveries that show the utility of a test like this for predicting whether a patient will benefit or not from a treatment."

West agrees, and says that newer drugs are likely to be the driver in his field, lung cancer, and that the barriers will come down in the next two to three years. "Currently there is not a pressing need to manage the standard of care with rebiopsy, but that will change with the introduction of the third-generation inhibitors, merelitinib and rociletinib, for EGFR mutation-positive patients with acquired resistance, which will require documentation of T790M positivity [T790M is a secondary mutation that limits the effectiveness of EGFR agents such as gefitinib].

"This will create a market and great need and value for serum-based testing. The other barrier is that there aren't enough large-scale studies proving sensitivity and reliability of the assays, but these are being published now and in the coming year or two."

There are many announcements about liquid biopsies now, and also collaborations starting up, such as Cancer-ID, a public–private consortium supported by Europe's Innovative Medicines Initiative, which aims to validate blood-based cancer biomarkers for DNA, RNA and cells. Its academic leads are Klaus Pantel, based at the University Medical Centre Hamburg-Eppendorf, Germany, and Leon Terstappen, University of Twente, Netherlands (who developed CellSearch). Terstappen says that it will build on the CTC Trap project organised at his centre, which, as its name suggests, has been isolating and studying circulating tumour cells (see www.utwente.nl/tnw/ctctrap and www.cancer-id.eu).

In the US, the National Institutes of Health has recently reported work on the potential of circulating DNA to predict recurrence of the most common type of lymphoma. But it is the potential for early detection of pancreatic cancer that has really caught the attention of the media. Researchers have found a protein associated with circulating cancer exosomes (vesicles containing proteins, and DNA and other nucleic acids), and they were able to detect these exosomes, which carry specific *KRAS* mutations for pancreatic cancer, to "absolute specificity and sensitivity" in both late- and early-stage patients (*Nature* 2015, doi:10.1038/nature14581).

There were only five patients at early stage, however, and questions about whether there could be a screening test for early-stage pancreatic cancer remain unanswered, as there would be false-positives and negatives in the 'real world', which could mean unnecessary high-risk surgery, and pancreatic cancers still have a less than 20% five-year survival rate, even when detected at an early stage.

The research community is nonetheless excited about the potential of liquid biopsies for screening and early diagnosis, particularly in high risk groups. Some say this is where the greatest impact of liquid biopsies will be, despite the rapid progress in blood-based diagnostics to inform drug selection and disease management. Not least, there is potential for increasing our understanding of the way cancer evolves and metastases develop.■

It is the potential for early detection of pancreatic cancer that has really caught the attention of the media

Asking the dumb questions

PETER MCINTYRE

It took ten years of immersion in the world of cancer research to produce the book that won Clifton Leaf a Best Cancer Reporter Lifetime Achievement award. But it started from a simple question: how do claims about winning the war on cancer square with a failure to cut death rates?

When Clifton Leaf was working as the Wall Street editor at *Fortune* magazine in the early years of the new millennium, it seemed there was no shortage of scandals to cover – from the accounting crimes of auditor Arthur Andersen to the house of cards that was Enron. At their heart was a fundamental driver, Leaf said: "Greed. Many of the central figures in these Wall Street scandals were rich already – it was incredible to see that some would do anything to get even richer."

However, when it comes to the world of cancer research and treatment, where Leaf has also spent a decade saying that the numbers do not add up, he has nothing but kind words about the people.

"When I got into the cancer enterprise, I got to talk to lots of people at the beginning, and that now runs into thousands. I did not meet anybody who would not have given their right arm to have cured cancer. There was a different passion and drive and a willingness to engage in the problem that I had never experienced."

Clifton Leaf

This might sound odd, given the storm Leaf stirred up about the failures of cancer research and treatment, and the way the 'war on cancer' has been mishandled. But he has always been clear about the difference between the policies and the people, and he learnt about life's many contradictions early on. At the age of 15 he was diagnosed with advanced Hodgkin disease and experienced a combination of drugs and radiation therapy that almost killed him even as it saved his life.

Now Deputy Editor of *Fortune*, Leaf recently went to Switzerland to receive a Best Cancer Reporter Award for Lifetime Achievement from the European School of Oncology. His work stretches from his 2004 cover story, 'Why we're losing the war on cancer – and how to win it' to his 2013 bestselling book that elaborated on reasons for this failure, *The Truth in Small Doses*. Among

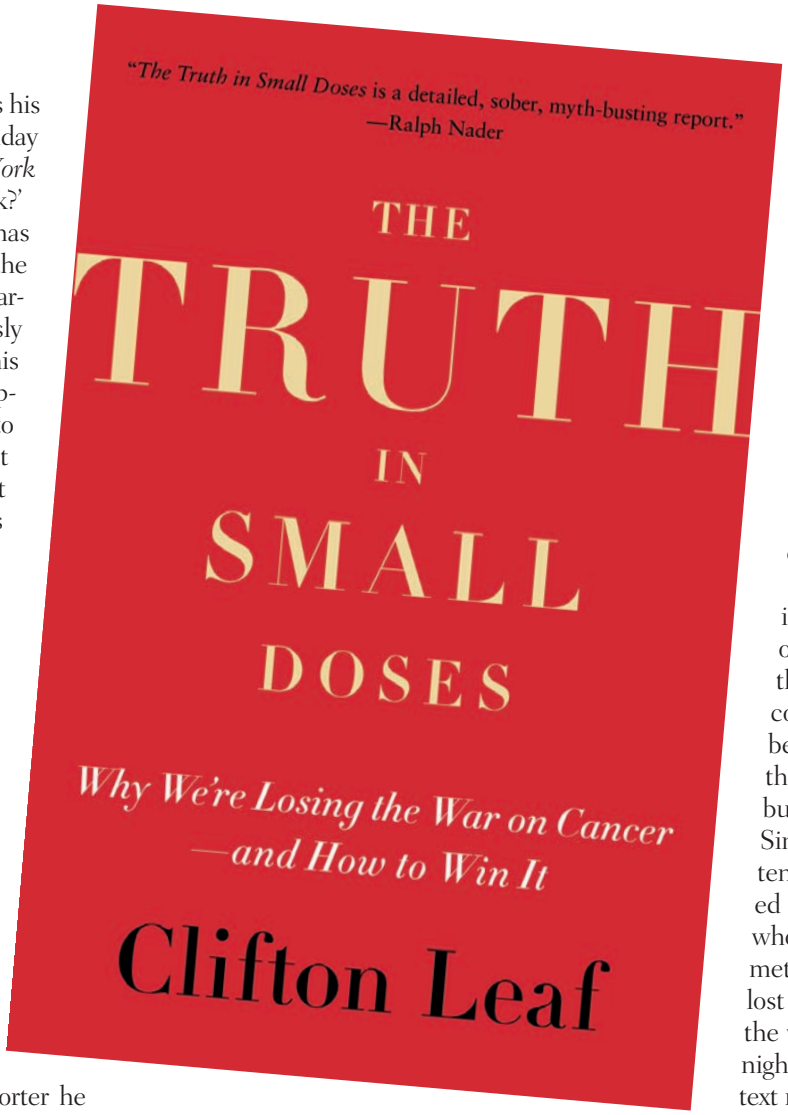
many articles in between was his 2013 cover story for the Sunday Review section of the *New York Times*, 'Do clinical trials work?'

Over this decade Leaf has succeeded in reframing the story of cancer. The usual narrative has science relentlessly unveiling the secrets of this terrible scourge and developing ever more brilliant drugs to treat it. Indeed, when he first came to the topic this is what Leaf believed. "My bias was that of the average American. You only know what you read in the paper. I thought we were getting one breakthrough after another."

He came with no science background, having slept through most of the biology course at high school and never having written about medical science. However, this was a time when Glivec, Avastin and Erbitux were being hailed as wonder drugs, and there was immense interest in the field from investors. As a business reporter he could not ignore it.

"I started thinking about the cancer problem as if it were a corporate enterprise. Instead of a profit and loss statement or a balance sheet, I asked, 'What are the metrics that show how the cancer enterprise is doing? How many people were getting the disease each year, how many were dying and how much were we spending?' The answers were neither clear-cut nor encouraging. Those numbers seemed to be going the way of Enron, and I started to wonder if things were as they should be."

His main conclusion was that you cannot claim a success so long as the cancer burden – the overall number of people developing cancer and dying from the disease – continues to rise. The aging population is a critical factor, Leaf acknowledges. But he says we have to address these population demographics head-on, work to lower the number of people getting cancer and focus on pre-empting the disease process earlier in its progression.



A conversation starter. Leaf wants his award-winning book to stimulate a more critical discussion about how the cancer research enterprise is managed

In the US alone, about 230,000 women will be diagnosed with invasive breast cancer this year and another 60,000 with *in situ* disease. "My question is, how is that winning? We can't say we have a victory because we say we have slightly reduced the age-adjusted death rate.

"Even when they make it through five or six years of treatment many of them still die. They are counted as successes because they exceeded the five-year survival rate but are no longer with us. Since I began this enquiry ten years ago I have collected many people in my life who reached out to me or I met at conferences. I have lost many of them along the way. You hear about it in night-time calls, e-mails or text messages – it is brutal.

"I measure progress by whether the burden of cancer is being reduced or not. I measure the burden by the number of people going through this gruelling awful process."

The dumb questions

The last time *Cancer World* wrote about Clifton Leaf (2007) the headline described him as "asking the difficult questions". He demurs. "I think they are the dumb questions – the really straightforward stuff. Like: at what point does making sure that we have fewer women getting breast cancer become

as paramount as treating it?"

His book focuses on the mismatch between the brilliance of the scientists and what he sees as the minimalist ambitions of the clinical trials enterprise – citing Irv Krakoff on research "aiming to find significant answers to insignificant questions." He describes how the US war chest for cancer goes to the same institutions year after year, how researchers spend 50% of their time applying for grants and filling in paperwork, and how young researchers with bright ideas spend an increasing amount of time doing non-inventive experimental work in large laboratories, gathering an endless amount of 'preliminary data', while their ambitions and inspiration wither.

Opening salvo. Leaf presented his first challenge to the 'official narrative' of a steady stream of breakthroughs in this cover story for *Fortune* magazine, published in 2004

He details the lack of progress on finding cancer markers for early diagnosis and the minimal sums spent on prevention. Meanwhile, as the death toll continues to rise, every step forward is hailed as a breakthrough, especially on the business pages. "Company stocks go soaring on merely the wisp of good news from clinical trials and they fall precipitously when something goes awry."

Part of the problems is the filtration process. "Companies present their data in lofty conferences and the world gathers with bated breath as if a new pope was being chosen. The low expectations that set the context for clinical trials help shape these dramatic responses. If you are used to the fact that nothing works, and something comes along that improves survival by two months, there are hosannas and angels singing and the stock goes through the stratosphere."

There is much more of this in the book, which is fast paced as you might expect from a journalist. He focuses on people who challenge the status quo, and are often marginalised until they turn out to be right.

Undoubtedly his work has had an impact, but Leaf does not consider himself an expert. "I would definitely say expert is the wrong word. I would say I am a hard-working remedial student, well-studied in the way that a remedial student needs to at least be able to communicate with the people I am having a conversation with."

This is one reason that his book includes 81 pages of (often chatty) endnotes and almost 100 pages of references at the back. "I made a real effort to make the sources and references as comprehensive and readable as I could, and used the top-tier journals. I was holding up a mirror and saying, 'this is what you in the medical and scientific community have discovered through your hard work and training'. This is not me saying this. All I am is an aggregator or scribe."

He admits to being a good polemicist. "But what I really wanted to be was a story teller and to have a sense of a shared conversation. I did not think people would listen closely to a long argument any more than they would listen to a bore at a cocktail party."

His writing is not just about what has gone wrong. He says that finding good solutions requires good management and good engineering. As deputy editor of *Fortune* magazine, he is responsible for seeing the print edition to press and coordinating the work to gel at the right time. "We get close to missing the deadline every issue but never do. We make it time after time only because it is managed." He says that levels of creativity and innovation and new ways of thinking about story telling are encouraged, not discouraged, by the process.

However, he accepts that many scientists fear it. "There is this idea that if you are being managed there is no way you can have independent thought or creativity or innovation."

Ask Google

He suggests that cancer researchers learn from the business world. "If you look at Apple or Intel or Google or Facebook, so many explosive ideas are possible because of brilliant management. The aim of management is to

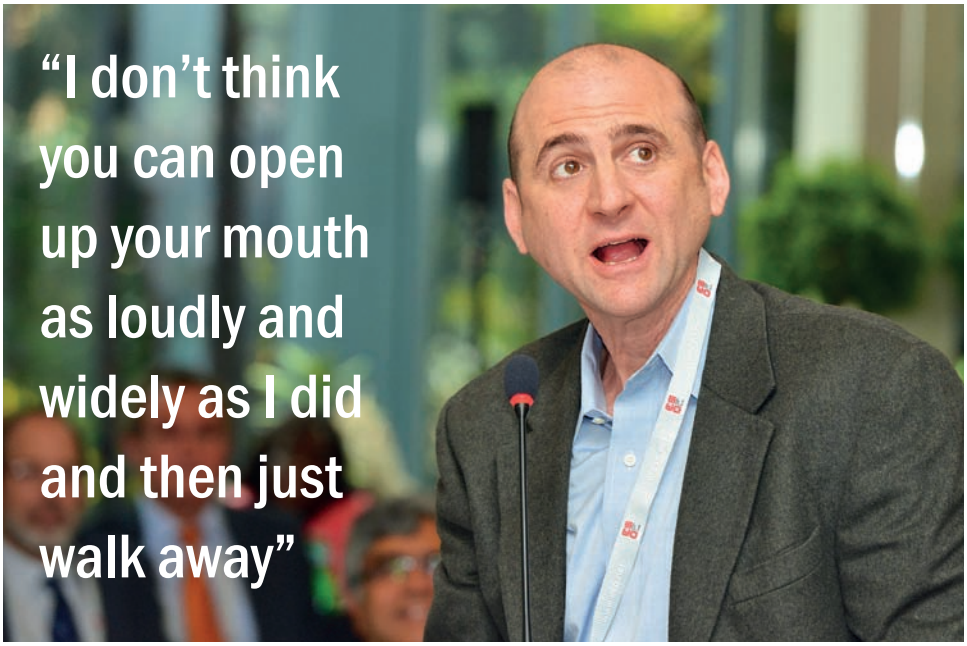
free up the creative idea and to shape and facilitate innovation. What is happening in the cancer world, frankly, is also management – researchers and clinicians are being micromanaged and mismanaged to exhaustion. Sometimes all 'good management' entails is putting an end to the micromanaged systems that don't work and shaking up a culture of deadly caution."

He calls for smaller but longer term grants that free the most creative scientists to get on with their research and a better 'systems approach' to organise trials that we can learn from more quickly and reduce 'me too'-ism. He cites the hopeless coordination in the global hunt for cancer biomarkers and contrasts it with the best business approach. Maybe progress can be made by learning from the likes of Google, a company that encourages hundreds of pieces of innovation in its labs and then throws mass resources at developing those that look most promising.

"There has to be some process to choose what is worth pursuing and what is not and how much effort to put in and where the resources come from and that needs focus. I think of engineering as bridge building, making sure that people and materials are there at the right time."

Leaf does see some progress over the decade he has been beating this drum. There is greater recognition that young scientists need to be given more backing at a time when they are most creative. But he sees little progress in the way that the big grants are doled out in the USA – a bureaucratic and risk-averse process that he believes stifles innovation and enforces conformity.

One big area of change has been the emergence of a new breed of patient advocates. "They are not just here to raise money and wear pink ribbons and march, but to help solve problems. That means helping to recruit for and shape clinical trials; making sure that the questions being asked are the important ones; that the right markers are being used to stratify the right patients; that trials are appropriately controlled. They are engaging more with institutions."



JASON HARRIS

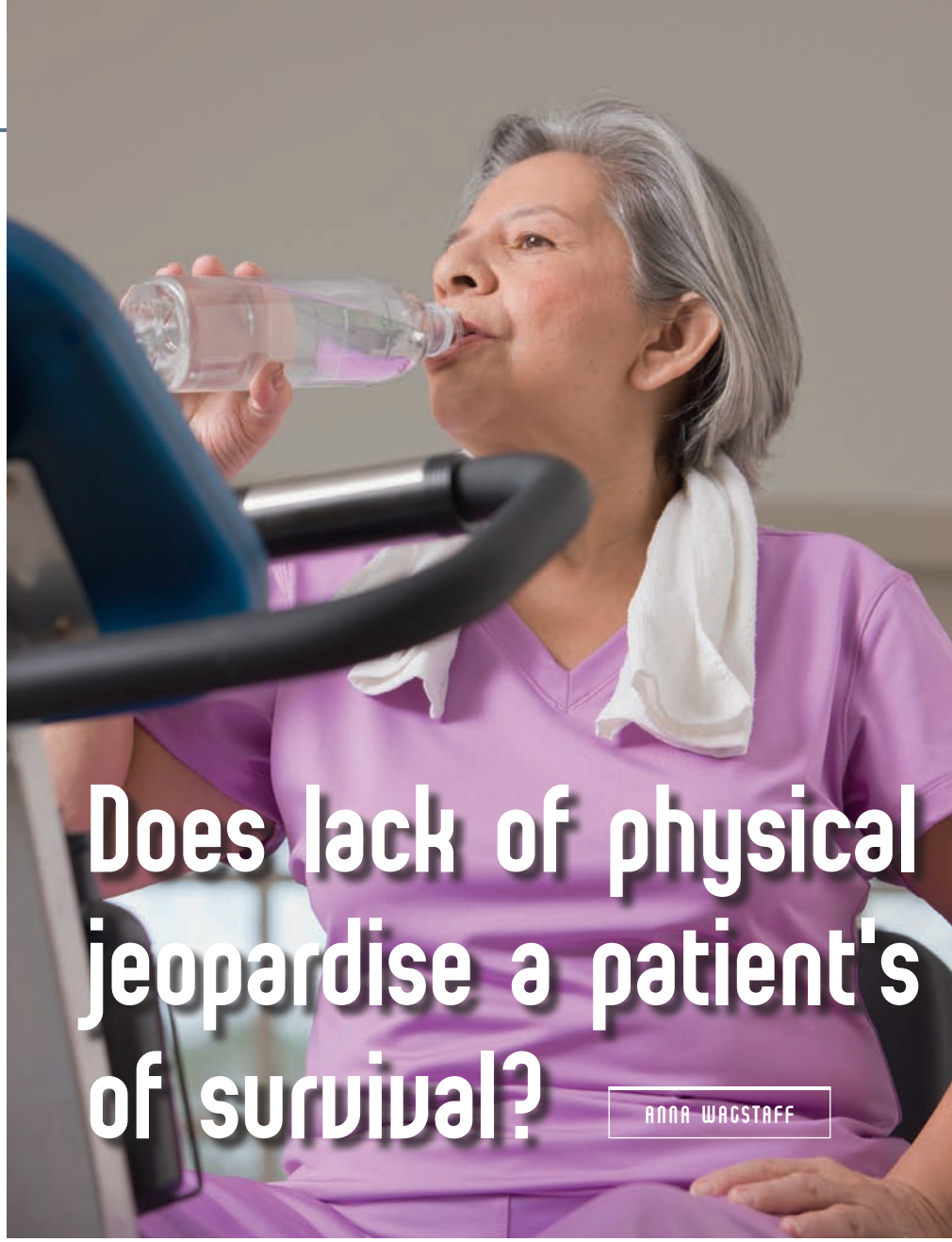
Until the number of people developing cancer and dying from it starts to fall, Leaf does not feel that anyone can claim to be winning a war against cancer. So will he continue to be an active voice?

Leaf has a demanding job and a family for whom he wants to be present and involved. He does not have the time for research and writing in the way that he did, but does not intend to disappear. He is a regular keynote speaker at conferences and is often invited to sit on panels and boards, including three times on the President's Cancer Panel Meeting.

"I don't think you can open up your mouth as loudly and widely as I did and then just walk away. It is kind of cowardly to throw stones and not wait for everyone to come and confront you." In fact he has become friends with many people in cancer research who disagree with him and he sees it as a healthy sign that they seem to enjoy being challenged (as he does).

"I have been lucky enough to have a platform, first with *Fortune* magazine and then through the brilliance of the cancer community at large, then the book with Simon & Schuster. Because I have had that benefit I am going to stick around for a while and see if I can be of help in a collaborative way of keeping the conversation going. I think that is important."

When interviewed for *Cancer World* in 2007 Leaf observed that many of his critics were predicting that the big cancer breakthroughs would come by 2015. A quick look at the calendar would suggest that, unlike his magazine, his critics have missed a deadline. ■



Does lack of physical jeopardise a patient's of survival?

ANNA WAGSTAFF

Exercise reduces the risks of getting some cancers – but what about after diagnosis? What should we be advising our patients?

"Be physically active in everyday life. Limit the time you spend sitting." So says point 4 of the European Code Against Cancer, the 12-point official EU guide to how to lower your risk of getting cancer.

The advice emanates from an impeccable source – the WHO's International Agency for Research on Cancer. It is based in large part on a growing body of evidence showing that a wide range of cancers – but particularly breast and colorectal – are less common in people who are more physically active, keep their weight down and eat a healthy diet.

Adding to this epidemiological evidence is a steady stream of biological studies throwing light on what it is about these healthy behaviours that leads to the lower cancer risk.

As ever, it's not a simple picture. Current evidence indicates that 'energy balance' – the net effect of food (energy intake) and exercise (energy expenditure) – may affect genomic instability, dysregulated growth signalling and cellular energetics, inhibition of apoptosis and of immune surveillance, and angiogenesis. That's five of the ten classic 'hallmarks' of cancer.

But key aspects of the relationship remain unclear. For instance: does physical activity have a direct impact on reducing cancer risk, or does it work mainly through weight loss? How much of the observed correlation between physical exercise and cancer might be explained by the fact that people who exercise more are generally more proactive about their health?

With obesity and more sedentary lifestyles on the rise, the weight of evidence for a cancer link pointing only one way, the proven benefits of exercise on general health, and the lack of associated risks, IARC, the EU and the cancer community are not waiting for more and better evidence: be more active to reduce your cancer risk is the official advice to the general public.

However, when it comes to people who have already been diagnosed with cancer, the question of what to advise – or prescribe – on the basis of current evidence is altogether more controversial.

This January, a report into the role of physical activity and sport in oncology (*Oncol Hematol* 2015, 94:74–86) reviewed the results of eight major studies that looked at how being physically active after having been diagnosed with localised breast cancer impacted on survival. It argued that the data showed "A physical activity higher than

exercise chances

CORBIS

8–9 metabolic equivalent task (MET)-hour per week was associated with a 50% reduction in mortality from both cancer and all causes," and that this translated into a benefit of 4–6% in terms of 5-year and 10-year survival.

As lead author Thierry Bouillet, an oncologist at Avicenne Hospital in Paris, points out, this is "the same benefit as chemotherapy".

While these are observational studies, Bouillet believes they build a credible picture, because they are large – the smallest with just under 1,000 patients, the largest almost 5,000 – and because they account for key confounders such as weight, drinking and smoking habits, and give fairly consistent results.

He also points to stronger evidence from a number of randomised controlled studies on the effect of physical activity in helping patients feel and function better. Bouillet mentions, in particular, the impact on reducing fatigue, which he says is the number one problem reported by breast cancer patients following treatment with chemotherapy, radiotherapy or surgery, and cannot be improved, for instance, by sleep or rest.

Other studies have shown an association between physical activity after breast cancer diagnosis and better mental health, better social and physical function, lower weight, and improved self-esteem. While these are all important in terms of quality of life, as Bouillet points out, they may also feed in to better adherence with therapy, which will have a knock on effect in improving survival.

Bouillet is in no way advocating that physical activity should be prescribed as an alternative to chemotherapy. He does believe, however, that its impact on the course of the disease means that there is now an overwhelming case for prescribing it in addition to chemotherapy for women with early breast cancer.

A 'no' from St Gallen

But when a panel of experts was asked, this March, whether the adjuvant therapy clinical guidelines for treating this group of patients should be updated to include physical activity, the answer was negative.

This was the consensus panel of the St Gallen conference, which every two years meets to deliberate on new evidence and update clinical guidelines on the primary treatment of early breast cancer. And when they came to look at the evidence for an impact of physi-

This translated into a benefit of 4–6% in terms of 5-year and 10-year survival

Exercise as therapy. This karate class uses techniques developed by the French Federation of Sport and Cancer, which are adapted to fit the therapeutic needs, physical abilities and medical risk of patients

CAMI

cal activity on cancer outcomes, they were simply not convinced, although the panel did endorse prescribing both physical activity and weight loss for their general health benefits.

A key voice questioning the quality of evidence for a survival impact was Pam Goodwin, a medical oncologist at the University of Toronto's Mount Sinai Hospital, who has spent much of her career researching lifestyle factors associated with breast cancer.

She argues that the evidence for an impact of greater physical activity on cancer outcomes in early breast cancer is simply not strong enough to tell patients their breast cancer outcomes will be improved if they become more active or lose weight. "The St Gallen adjuvant therapy guidelines focus on breast cancer specific survival and reduction in risk of recurrence. It wasn't that I or anybody else was opposed to having breast cancer patients who are interested in being physically active be active – there's no problem with that. The issue is that we don't have the evidence to tell them that it will improve their breast cancer outcomes."

Goodwin points out that large series of observational studies don't have a particularly good track record, "It's like the old story of HRT and breast cancer risk. For years the studies said the benefits outweighed the risk, but when the randomised studies were done, we found that the breast cancer risk was increased with the commonly used combination therapy, and a lot of the added benefits we thought existed didn't."

Observational studies, she argues are wide open to bias and confounding, "and in these types of studies, the obvious bias to be concerned about is a healthy person bias."

"If you take a thousand breast cancer patients, and show that those who are more physically active have better outcomes, better overall mortality, and some evidence of lower breast cancer mortality, what we don't know is whether those women in general are healthier. The way that could impact the results is that healthier women could be in general more compliant with screening programmes, more likely to have their breast cancers diagnosed at an earlier stage, and more compliant with their breast cancer treatment. And you can try to adjust for all of that, but the reality is that you can't fully adjust, in the absence of data from randomised trials."

Goodwin raises the possibility that the causal link may also work the other way around, that women who are generally less healthy may get more aggressive cancers, and that the biology of that cancer may be "built in" at the time of diagnosis and therefore not amenable to change by increased physical activity (or weight loss) post diagnosis.

It was because of these uncertainties that the panel took the decision it did. "We felt we should apply the same standards in evaluating evidence on physical activity and obesity as we use for drug treatments," says Goodwin. "In other words we want clear data relating to efficacy before we say to breast cancer patients: 'If you do this, your outcomes will be better.'"

If there was no way to generate that data, she adds, then maybe the panel would have taken a different approach. However, randomised controlled trials are ongoing or about to start looking at the impact of physical activity and weight loss on cancer prognosis. CHALLENGE, led by the National

"We don't have the evidence to tell them that it will improve their breast cancer outcomes"

Cancer Institute of Canada, is a randomised trial generating evidence on the impact of exercise on recurrence in colon cancer, while Jennifer Ligibel's team at the Dana Farber in Boston is set to launch a randomised controlled trial to get data on the impact of weight loss on breast cancer outcomes. Like all survival studies, they will take time, but the answers they give should be reliable.

Bouillet finds this reasoning highly frustrating. A founding member of CAMI, the French National Federation of Sport and Cancer (sportetcancer.com), and himself a karate blackbelt, he's spent 15 years building evidence, changing attitudes and developing practice around the role of physical activity and sport in cancer. He doesn't see the need to wait a further 10 years.

"We started in 1998. In the beginning nobody believed in us. In those days, the main thing for physicians was to say: you have cancer, you must rest. No movement, no sports, nothing. It took a long time to change people's minds."

Today the CAMI federation has almost 60 partner institutions across France that run courses in karate, modern dance, yoga and Täi chi, specially adapted for people with different types of chronic medical conditions. Most courses are run at local gyms and leisure centres, but Bouillet says that hospitals are increasingly getting involved. The Institut Gustave Roussy, for instance, is a CAMI affiliate, and hosts dance and karate classes every Monday and Thursday.

Each course, explains Bouillet, is designed to give the right type of exercise as well as the right intensity: "Enough to break sweat, regularly, three times a week, for six months is needed for biological and clinical modification," he says.

Risk assessment is done by the patient's doctor, who must sign a form for them to participate, and the courses are led by qualified instructors with a one-year university diploma in Sport and Cancer.

French health policy

The CAMI project received a major boost in April, when the principle of prescribing physical activity adapted to the patient's "pathology, physical abilities and medical risk" was introduced as an amendment into a new piece of health legislation – Loi de la Santé – as it passed through the French National Assembly. The amendment sets the framework for such a service, spelling out the governance of the organisations and instructors responsible for delivering the courses, and the responsibilities for training physicians in prescribing "adequate physical activity". It paves the way for this sort of exercise to be reimbursed as a medical treatment through health insurance.

A summary statement published in association with the amendment refers specifically to breast cancer treatment, spelling out the benefit of physical activity for counteracting fatigue, but more controversially mentioning its impact in reducing recurrences and increasing survival chances by more than 50% – a figure that also appears on the CAMI website.

Oreste Gentilini, a breast surgeon at the European Institute of Oncology in Milan, is not yet convinced about the numbers on survival, but believes Bouillet has certainly got one thing right: physical activity can do a lot of good for people who have been treated for breast cancer, and the medical profession is letting its patients down by not taking time to explain its benefits. He argues for a culture change.

"For too long we've been forgetting the importance of having a healthy lifestyle. In order to convince our patients, we first have to be convinced ourselves. This is not easy because physicians tend to highlight research on what is achieved by direct medical interventions, either surgery or drugs or whatever. But the data available at the moment are solid enough, and basically they all go in the same direction, supporting lifestyle as a preventive and also therapeutic measure. So we should take time to explain to patients the results."

He points out that after the shock of being diagnosed and treated for early breast cancer, people often look for advice about what they can do for themselves to improve their survival chances. Many doctors do talk about the importance of taking time to be physically active and exercise on a regular basis, says Gentilini, but they often fail to clearly explain why, and how much patients could benefit.

Gentilini is himself involved in research on the impact of physical activity on patients' quality of life, and acknowledges that it is difficult to get

hard evidence on the impact on recurrence and survival. He is currently recruiting to a randomised controlled trial looking at the benefits of a moderate increase in exercise for women with a sedentary lifestyle who have had breast cancer, but this will look at the impact on quality of life, and some biological parameters, not at survival.

He argues, however, that on the basis of the current evidence, doctors should be advising their patients of the survival benefit conferred by physical exercise. "I'm not sure if it provides a 50% or 40% or 30% reduction, but all the studies which were conducted showed a reduction in mortality or risk of recurrence, and we cannot ignore this any more."

Pamela Goodwin, in contrast, has no doubt that the guidelines consensus panel was right to insist on better evidence before advising patients that physical activity or weight loss confers any survival benefit. She points to research being undertaken at the Fred Hutchinson, led by Anne McTiernan, about diet, physical activity and obesity, which indicates that all three impact on physiologic mediators of the link between lifestyle and cancer – such as oestrogens, insulin and inflammatory markers – but these impacts are greatest with weight loss and diet, and occur to a much lesser extent with physical activity alone.

A situation of 'equipoise'

"We're in a situation of equipoise in relation to breast cancer outcomes," says Goodwin. "We have enough evidence to start a trial. We're all hoping that the observational evidence will be confirmed. But we have to be careful with our patients. I talk to all my patients about this, and recommend lifestyle change. We have a wellness programme at our centre, where we introduce women to physical activity, we give them individualised programmes, individualised diets after a diet assessment, and weight loss goals if they are overweight. And there's a group who really enjoy that."

But as she points out, there are also many women who do not enjoy it. "Part of it is that they don't want to feel guilty that they contributed to their cancer, or the recurrence of their cancer if they do not adopt a healthier lifestyle. But part of it is that these are women who have not been very active and many of them are overweight. And some resist the lifestyle change. In the absence of evidence that it will improve their outcomes, all I can say to them is that we are studying this, we hope future research will show it can improve survival, but we don't know for sure."

So what about the French National Cancer Institute INCa? Do they back the St Gallen position, and if so, what do they think of the amendment to the Loi de la Santé?

Julie Gaillot, INCa's lead on tertiary prevention, is clear that there is still uncertainty about the impact on survival: "We can say that even though observational studies seem to show an effect, for the moment it has not been confirmed through randomised controlled trials."

As for the amendment to the Loi de la Santé, Gaillot explains that INCa was not consulted. She agrees that, on the basis of current knowledge, it would be wrong to suggest that physical activity can lead to a 50% reduction in mortality risk. However, she expects that this wording is likely to change when the proposed legislation is scrutinised by the upper house, the French Senate, later this year.

On a broader note, Gaillot certainly backs the general principle that doctors should be encouraging patients to be more active, and she agrees that a change of mentality is needed. "It's hard for doctors to introduce physical activity, because they are not trained and educated about the benefits of exercise for people who are ill, whether it's cancer or other chronic illnesses, or in the general population."

Widespread coverage in the mass media, she says, is sparking interest among patients and health professionals, many of whom are looking for good advice. INCa has the responsibility to provide that advice, which it will do, she says, but only based on validated evidence.

For Gaillot, this means primarily the evidence from randomised controlled trials regarding benefits on fatigue, quality of life, body composition and fitness – and not just about participation in sports but more generally adopting a less sedentary lifestyle. These recommendations will need to be specific about the type, the amount and the intensity of exercise needed to achieve specific benefits, she says.

And they will not endorse any specific benefit on survival: "We would first need more solid evidence," she confirms. ■

"For too long we've been forgetting the importance of having a healthy lifestyle"

Championing cancer care in an age of austerity:

an interview with the European Health Commissioner

Vytenis Andriukaitis talks to *Cancer World's* Anna Wagstaff about what Europe needs to do to safeguard and extend access to high-quality cancer care in challenging times.

How can European countries provide a rapidly rising number of patients and survivors with the treatment and care they need when governments are cutting health spending? They can't, says European Health Commissioner Vytenis Andriukaitis.

A surgeon by profession, and former Lithuanian Health Minister, he says he is unhappy that, in response to the financial crisis, some governments raided their health budgets as part of their efforts to cut public spending, and argues that such a policy is counterproductive.

"The message is clear: The healthcare system creates conditions for jobs and the economy to recover, and spending on health must be seen as an investment… Investment, investment, and once again investment is the way to fight against cancer," he told *Cancer World*.

It's an important message to get across, particularly as these healthcare cuts are often perceived as a response to pressure from Europe, which in the wake of the financial crash is taking a tougher line on policing the size of the budget deficits run by Member States.

Less widely known is that the Commission now also makes an annual review of how governments' economic plans align with the EU 2020 strategy for "a smart, sustainable and inclusive economy" – and since 2012, this review has included health spending. This means that the Commission can, and does, now make explicit recommendations in relation to national health systems, which gives added weight to the strong message from the Health Commissioner about increasing investment.

The Vilnius Declaration

Though Andriukaitis only joined the Commission in 2014, he nonetheless played a key role in discussions about what type of health services recommendations from the Commission should be aiming for.

In his capacity as Health Minister, he hosted a European conference in Vilnius during the 2013 Lithuanian EU presidency, which issued a call for European leaders to work with governments and civic society to "help ensure that European health systems are people-centred, sustainable and inclusive and deliver good health for all".

The Vilnius Declaration called for: increased investment in health promotion and disease prevention; universal access to high-quality, people-centred health services; and healthcare policies that are based on evidence and focus on cost-effectiveness, sustainability and good governance.

Having now become one of those European leaders to which the Vilnius Declaration was directed, Andriukaitis says that the Commission did respond to the call for action and took up many of the Vilnius recommendations in its 2014 'Communication on effective, accessible and resilient health systems'. For him personally, the declaration, he says, served as a source of inspiration when framing his own priorities as Health Commissioner – particularly his focus on "Prevention, promotion and protection."

Equal access

For people with cancer, however, particularly in countries with the poorest outcomes, it's the Vilnius call for "universal access to high-quality, people-centred health services" that is of real interest. What can Andriukaitis do for them?

"That part of the Declaration

Taking on the challenge. Andriukaitis answering questions from MEPs last September, during the parliamentary hearing to confirm his appointment as Commissioner for Health and Food Safety

EUROPEAN COMMISSION

"The health system creates conditions for the economy to recover; spending on health is an investment"

"The high costs of personalised medicine pose a serious challenge to the principle of equal access"

was primarily addressed to Member States," says the Commissioner, "because access to healthcare falls mainly under their competence." There are, however, ways in which the Commission can help, he adds. "Inequalities between social groups both within and between Member States, lie behind a lot of the gaps in outcomes. From our side, the Commission is ready to be more active in cooperating with Member States in raising issues, especially relating to social determinants, advising them to pay more attention to disadvantaged groups, to evaluate needs and properly implement their national cancer programme."

There are funds available to help with this, he adds. "You can use European social and investment funds for activities that reduce health inequality between regions and social economic groups, including the development of healthcare infrastructure, health promotion, e-health solutions and better training for the health workforce."

He mentions also the proposal for European Reference Networks, which should improve access to expert care for people with more rare cancers.

Andriukaitis recognises, however, that the high costs of 'personalised medicine' pose a serious challenge to the principle of equal access, and stresses the need to find a way of dealing with this "without discrimination against patient access to healthcare or undermining the cost-effectiveness, resilience and sustainability of Member States' health systems".

The Commission, he says, is backing efforts to generate reliable, timely, transparent and transferable information that Member States can use to evaluate the cost-effectiveness of new therapies. It will shortly be introducing a permanent mechanism to oversee this work, which, since 2006, has been led by EUnetHTA on a project-by-project basis.

Affordability

Better health technology evaluation, however, cannot by itself resolve the problem that the prices of many new therapies are simply unaffordable for many European healthcare systems – what can the Commission do about that?

"Negotiating prices of medicines and their inclusion in health insurance systems is the responsibility of Member States," Andriukaitis responds, and "any action on this front will be done voluntarily and without prejudicing international competencies." He adds, however, that he is "keen to foster discussions and support cooperation between Member States in these areas, so as to make medicine more accessible to patients."

He mentions, in particular, moves by Belgium and The Netherlands to start exchanging information about the prices they pay for drugs. Luxembourg is now interested in joining the initiative, says Andriukaitis, and the government has indicated that it is keen to address the cost issue within the wider discussions it is promoting on personalised medicine during its EU presidency, which will continue until the end of 2015.

Andriukaitis mentions also discussions between Romania and Bulgaria about cooperating to address the cost of drug prices, and says he is optimistic about making progress. "When I started in debates with Member States in 2012 and 2013, there was a lot of resistance from many, many countries [about cooperating over negotiating drug prices]. But after 2013, I see the hesitation is rapidly changing, especially relating to new medicines, which are attractive but very costly… I would like to propose an open method of cooperation in this field, and to encourage Member States to be more active."

Reducing the burden

Important though all these measures are, Andriukaitis argues that the biggest contribution to improving access to high-quality care will have to come from effective action on prevention, which will free up resources by reducing the overall burden of ill health.

He suggests that it is in the preventive setting that the personalised approach to medicine could have the greatest impact, by improving targeting of actions. "Personalisation will change prevention programmes for obesity and cancer," he says, and mentions, in this respect, the work being done by

EUROPEAN COMMISSION

the current Joint Action on Cancer Control, which includes looking at public health genomics and the use of genetic testing in population screening.

He also stresses the importance of including health considerations in every aspect of government policy: education departments should be investing in PE teachers, transport departments in improving bike lanes – while departments of industry should include the health costs of alcohol, tobacco and unhealthy foods when calculating the overall economic contribution from these industries.

"We are ready to discuss with Member States our ideas on a comprehensive approach to managing alcohol, tobacco, nutrition, overweight, obesity, and other risk factors within some framework of actions, and encourage Member States to cooperate on this between themselves and with the Commission," he says.

He is aware, he adds, of the concerns that have been expressed by some health NGOs, including the European Public Health Alliance and the Standing Committee of European Doctors, that the current Commission is prioritising the interests of economic growth over health – concerns that came to a head in June when the NGOs walked away from the EU Alcohol and Health Forum, calling it "a free PR front for the industry".

Steps have since been taken to improve the way the Forum functions, says Andriukaitis, and the Commission fully backs the work of the Committee on National Alcohol Policy and Action, and the Joint Action to Reduce Alcohol-related Harm. He mentions, too, the EU Health Policy Forum, which he is in the process of relaunching, and which will provide a valuable platform for

"Effective action on prevention will free up resources to improve access to high-quality care"

"Labour mobility is a fundamental principle in the EU, but solutions need to be found at national level"

all health-related NGOs, he says, including those working on alcohol-related harm.

Staff shortages: a test for European solidarity

Giving added urgency to the goal of reducing the burden of ill-health are projections from the Commission of a shortfall of two million healthcare professionals and ancillary workers by 2020.

Coming as he does from Lithuania, Andriukaitis is only too aware of what this could mean for poorer Member States, many of which are already struggling to retain staff that have trained within their system, but choose to work abroad.

Can the Commission help find solutions that will work for all Member States?

"Sustainability of health systems is of course impossible without sufficient and adequately trained health workers," Andriukaitis replies, and he refers to a 2012 action plan drawn up by the Commission, which focuses on encouraging Member States to cooperate by developing effective recruitment and retention strategies; increasing evidence-based policy making in workforce planning; recruiting according to the WHO code of practice on international recruitment; and anticipating the skills needed for the future.

"We understand there is a huge challenge for all of us to cooperate in those fields," he says. "Labour mobility is a fundamental principle in the European Union, but solutions need to be found at national level, with the possible support of bilateral agreements."

Does he worry about whether there is a sufficient sense of solidarity within today's EU, particularly given the cracks over the Greek bail-out talks, for governments to make the effort to abide by the WHO code of practice, which requires richer countries to take into consideration the needs of poorer Member States vulnerable to health workforce shortages?

"I don't believe in any crisis and Brexit and Grexit and so on," says Andriukaitis. "It creates problems in public opinion, but I see most of the European Union as more integrated, more strong, and more efficient, and my belief stems from my practice," he says.

Europe's record in collaborating on fighting cancer, he believes, speaks for itself. "In September we will celebrate 30 years of EU action on cancer. Can you imagine? In 1985 Europe Against Cancer was launched, and today it's good that we still see possibilities to cooperate.

"You can see the huge progress that has been made, and can you imagine how we could keep moving forward without a more integrated approach, without seeing better conditions for partnership at a European level, better options for opening doors, using the open method of coordination to encourage prevention actions across the European Union as a whole?"

"The lead shown by the cancer community," he adds, "is an example I would like to see followed by others.

"I want to help Member States better identify areas of improvement in public health, a better analysis of public health data. We need more targeted approaches and easier identification of tools, Joint Actions, best practice exchange, targeted interventions, to improve the areas where the burden is highest.

"An example is a more focused approach to chronic diseases, which we hope to launch later this year. I also want to promote a more intensive discussion with stakeholders on public health issues, and I intend to relaunch the EU Health Policy Forum in the coming months, which should give easy access to information for civil society and personal and professional groups across the EU, and encourage their input into our efforts to improve citizens' health."

To the uninitiated, this may sound like a list of talking shops. But if Europe is going to find solutions that work for all its Member States to providing high-quality care to a rapidly growing number of patients, when economies are sluggish and the cost of healthcare is escalating, these are the forums where those solutions will need to be mapped out, and where the case championed by Andriukaitis for investing more in healthcare, will need to be made. ■

Are progression-free and disease-free survival the new gold standard for cancer trials?

Showing that a new drug can keep advanced cancers from progressing, or stop early cancers from returning, is quicker, cheaper and easier than showing that it helps patients live longer. But how can we judge in which instances these surrogates will accurately predict overall survival?

Overall survival is the gold standard and primary outcome of interest for cancer clinical trials. It is an 'appropriate measure' for evaluating cancer drugs and therapies, based on recommendations from regulatory bodies who have declared that a primary outcome in clinical trials should demonstrate that a new treatment has some sort of clinical benefit (FDA, 2007).

In performing a clinical trial, there is an idea that all researchers need to show is an improvement in overall survival for a drug to be approved. It is of course not that simple. There are issues in following patients over longer follow-up periods, when there may be potential confounding with secondary or tertiary treatments making it hard to show which treatment contributed what to the overall survival.

In terms of clinical trials, the good news in cancer is that patients are

European School of Oncology e-oncoreview

The European School of Oncology webcasts monthly e-oncoreviews, in addition to its fortnightly e-grandrounds. These offer comprehensive overviews of specific topics, giving participants the chance to pose questions during the live webcast.
In this issue of *Cancer World* we publish an e-oncoreview presented by Gregory Pond, associate professor at the Department of Oncology, McMaster University, Hamilton, Ontario, who reviews the statistical validation of progression-free and disease-free survival as surrogates for overall survival in oncology clinical trials.
Edited by Susan Mayor.

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

living longer with therapies that are much more effective than 20 or 30 years ago. However, in terms of clinical trial design, there is increased risk of confounding factors with this longer life span. Patients will go on to get further line treatments than they would previously have been given. Additionally, because the patients are on-study for longer, trials also have to go on for longer, which increases costs for trials.

Early biomarkers

One of the questions for trial designers is whether we can identify some sort of early biomarker to use instead of overall survival that will give us an indication that a treatment is potentially effective. We ideally want a marker that requires a short period of time until the event occurs. A successful early biomarker will, most of the time, show a larger treatment effect than what we might see if we use overall survival (OS), and there should be less confounding, as patients receive fewer second- and third-line treatments. All of this will reduce the sample size required, reduce the length of time required for the clinical trial and, ultimately, reduce the cost of performing a clinical trial.

An example of a trial that used an early biomarker is the National Cancer Institute of Cancer MA.17 phase III randomised, controlled trial of letrozole in postmenopausal women with breast cancer who had previously completed five years of tamoxifen. The primary endpoint was disease-free survival (DFS). More than 5000 women were enrolled and at the first interim analysis, which occurred 2.4 years after the start of the trial, there were 207 DFS events (i.e. 207 women were no longer disease free).

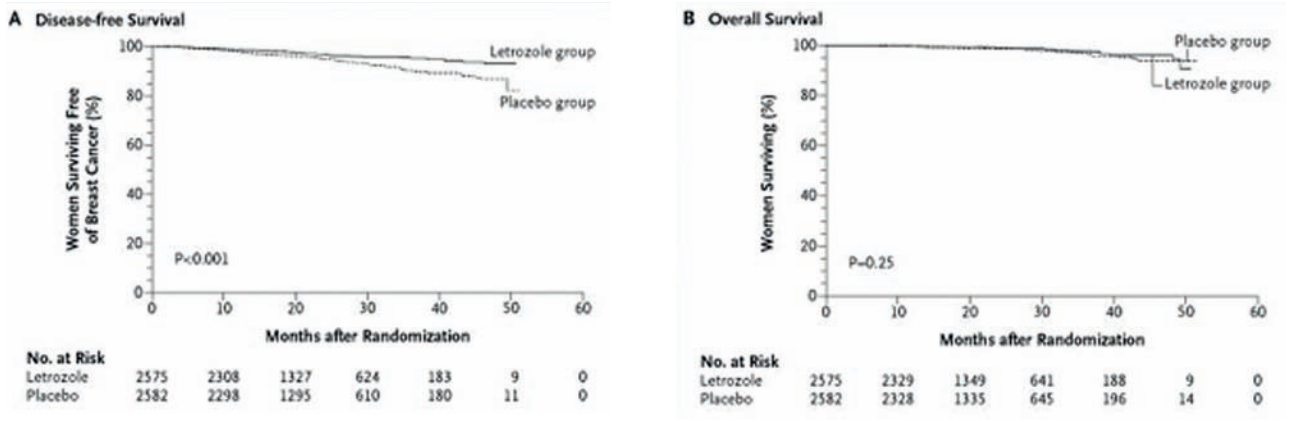
The DFS plot (see left-hand graph, below) shows there is a separation of the curves between the letrozole group and the placebo group. The OS plot (right-hand graph) shows no separation between the two groups (*NEJM* 2003, 349:1793–1802). However, because of the difference in the DFS curves, the Data and Safety Monitoring Committee recommended stopping the trial on the grounds that letrozole had been shown to be superior to placebo.

Long-term follow-up demonstrated improved overall survival with letrozole in this patient population. However, using OS rather than DFS to achieve the same level of significance (alpha=0.05) would require follow-up of about 10 years. Using the early biomarker of DFS meant that publication occurred about eight years earlier than it otherwise would have done. This is a good example of where using an earlier biomarker showed a great advantage over OS, enabling earlier publication showing the same statistically significant results.

There are two ways we can find early biomarkers to improve clinical trial efficiency:

- Find a marker that shows clinical benefit
- Find some sort of surrogate marker for overall survival.

RCT OF LETROZOLE IN POST-MENOPAUSAL BREAST CANCER



The significant benefit from letrozole could be seen in the disease-free survival curves about eight years before it became evident in overall survival

Source: PE Goss et al (2003) *NEJM* 349: 1793–1802, © (2015) Massachusetts Medical Society, reprinted with permission

Finding an early biomarker that is a surrogate for overall survival

One definition of a surrogate marker is: "any laboratory measurement or physical sign that is used in therapeutic trials as a substitute for a clinically meaningful endpoint that is a direct measure of how a patient feels, functions or survives and is expected to *predict the effect of therapy*." It's not just related, but it has to predict the effect of therapy as well.

Correlation by itself does not imply surrogacy; the figure (*right*) shows an example. The horizontal axis is the outcome in terms of the surrogate marker and the vertical axis is the true endpoint. There are two values, one for the control group (group C) and one for the experimental group (group E). In this example there's a perfect correlation, so once you know what the outcome is in terms of the control group and the surrogate marker, you can tell exactly what the true endpoint value will be. The same thing applies for the experimental group: if you were given the outcome in terms of the surrogate marker for the experimental group you would know exactly what the true endpoint value would be, for example with median progression-free survival and median overall survival.

There is a perfect correlation in this example, but the problem is that this is not a good surrogate. This is shown by the dotted lines, which illustrate a larger value for the median surrogate endpoint in terms of the control group, giving a lower value for the true endpoint, if you compare between the control and the experimental group. What this illustrates is that, even though there is a perfect correlation between the surrogate and the endpoint for each particular value, it's not a good surrogate endpoint.

From a statistical point of view we have to use specific criteria to define a surrogate. The most commonly used and gold standard criteria are the Prentice criteria defined in 1989 (RL Prentice, *Stat in Med* 1989, 8:431). This is defined as: "A test of the null hypothesis (H0) of no effect on the surrogate is equivalent to a test of H0 of no effect of treatment on the true endpoint."

What does that mean? Essentially what we're saying is that a marker can be used as a surrogate if it meets two conditions:

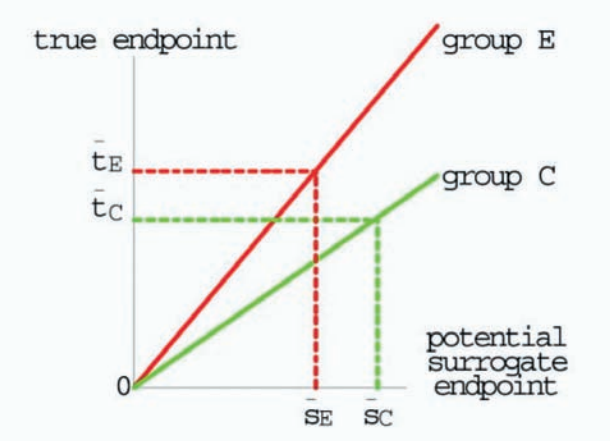
1. It predicts the final true endpoint
2. It fully captures the effect of the treatment upon the final endpoint.

This means we are looking at two different things, not just that the surrogate is related to the endpoint itself, but that it also captures the treatment effect.

Statistically, there are a couple of problems with the Prentice criteria. First, and most problematic, it is impossible to prove this condition, because it is saying that we have to prove a null hypothesis is true, and from a statistical point of view you can never prove that a null hypothesis is true. This means that we can't follow the Prentice criteria strictly, though we can use them as a framework and relax the criteria slightly, and that's what people have done in terms of trying to validate a statistical marker.

How do we do that from a statistical point of view? We have to demonstrate that there is a good correlation between the surrogate and the true marker. We also have to demonstrate that a good correlation exists between the treatment effects, so whatever

CORRELATION BY ITSELF DOES NOT IMPLY SURROGACY



The true endpoint shows a higher median value for the experimental arm than for the control arm, while the reverse is true for the potential surrogate endpoint

Source: SG Baker and BS Kramer (2003) *BMC Med Res Methods* 3:16, reprinted with permission

THE PRENTICE CRITERIA

H0: $\alpha = 0 \Leftrightarrow$ H'0: $\beta = 0$
"A test of H0 of no effect of treatment on the surrogate is equivalent to a test of H0 of no effect of treatment on the true endpoint"

Source: RL Prentice (1989) *Stat in Med* 8:431

the treatment effect is for the surrogate this has to be related to the overall treatment effect or indeed the true point of interest. We have to repeatedly demonstrate this both at the individual patient trial level and the individual trial level.

Validating a surrogate marker

An example of the statistical validation of a biomarker is a study of 5-fluorouracil-based therapy in colorectal cancer published in 2005 (*JCO* 2005; 23:8064–70). The research group used three-year DFS as a surrogate for the true endpoint of five-year OS. It required nearly 21,000 patients and 18 trials for the group to carry out this validation. There are three key plots in the results:

- The first plot (*top left*) looks at the relationship between three-year DFS and five-year OS. It shows the correlation is quite strong, with an R^2 value of 0.85. This means the three-year DFS is highly correlated with the five-year OS.
- The treatment effect plot (*top right*) looks at the hazard ratio between treatment arms in terms of DFS and OS. Again, there is a high correlation value of R^2, at 0.90. This means that if you know the hazard ratio for DFS – the effect of treatment on the surrogate marker – you have a strong correlation with the hazard ratio for OS, i.e. the effect of treatment on OS.
- The third is a calibration plot (*bottom graph*) – if you have a hazard ratio for DFS, how well can you predict what the OS value would be? The graph shows that the OS hazard ratio is within about 95% of the predicted confidence intervals, as would be expected. As a result, we can conclude that the DFS hazard ratio can predict the OS hazard ratio reasonably well.

The group showed excellent correlation between the estimates of the surrogate marker and the true marker, or true OS. There was an excellent correlation between the treatment effects in terms of the hazard ratios and they showed an excellent calibration plot. There is also biological plausibility, in terms of DFS being related to OS. Finally, multiple formal analytical approaches were used to validate this, proving a validated surrogate marker. To quote Daniel Sargent, "These results suggest that DFS after 3 years of median follow-up is an appropriate endpoint *for adjuvant colon cancer clinical trials of fluorouracil-based (5FU) regimens*, although marginally significant DFS improvements may not translate into significant OS benefits."

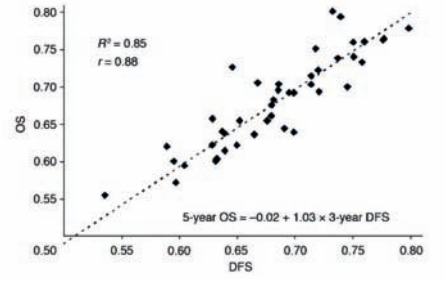
Do we need a surrogate in this context?

One question raised is whether we need a surrogate in this particular context: adjuvant colon cancer clinical trials of 5-fluorouracil-based (5FU) regimens? The use of 5-FU-based chemotherapy is going to be reduced as we move into a new era of molecularly targeted therapy.

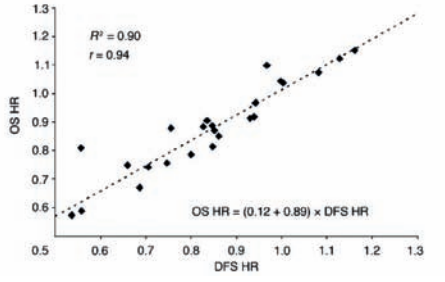
This highlights one of the problems in statistical validations of a biomarker. What we have to

VALIDATING A SURROGATE MARKER

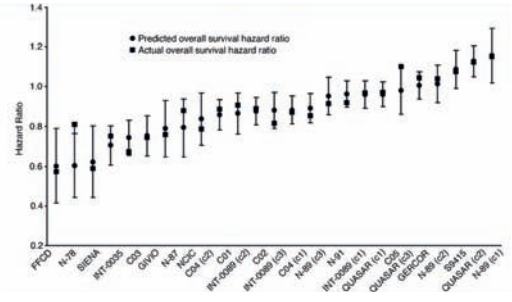
Correlation between OS and DFS



Correlation between OS and DFS hazard ratios



DFS hazard ratio as a predictor of OS hazard ratio



Daniel Sargent and colleagues used these three data plots to validate DFS as a surrogate for overall survival for 5-fluorouracil-based therapy in colorectal cancer

OS – overall survival, DFS – disease-free survival, HR – hazard ratio

Source: DJ Sargent, HS Wieand, DG Haller et al. (2005) *JCO* 23:8664–70, republished with permission, © (2005) American Society of Clinical Oncology

do in clinical trials is to gather data to validate whether a surrogate is valid or not. But once we have those results, the surrogate may or may not be needed, as we already know the answers for that particular trial. This raises a bit of a difficulty with the validation of any particular marker.

Can DFS or PFS be used as surrogates for all clinical trials?

The next question is: can we use DFS, or in some cases PFS, globally for all clinical trials? Unfortunately, we cannot. In some settings DFS has become accepted as a surrogate, but it is not universal for every treatment in every single cancer.

What are the settings in which we can use these surrogates? There has been a lot of work into whether we can use DFS in particular settings, but we haven't looked at every setting, because there are a lot of issues when trying to validate a surrogate. Generally, it has been recommended that we need 10 or more clinical trials to assess whether a marker is a valid surrogate, and it has to be validated every time for a specific treatment in a specific setting at a specific time point.

For example, in later work, Sargent et al note, "It is unlikely that the surrogacy of PFS for OS would have been demonstrated in the current context … with current salvage therapies." What might prove to be a validated surrogate at one point may no longer be once there are more advanced second-, third- and fourth-line treatments.

Pragmatic validation

As researchers we are not really interested in what's happened previously. We want a validated surrogate to use in future clinical trials. So how do we go about deciding whether or not we can use PFS or DFS as a surrogate marker for OS in future clinical trials? We have to settle for pragmatic validation, which means a biomarker has to:

- Have biological plausibility
- Have clinical utility demonstrated in clinical trials, for example having been validated in previous settings similar to the clinical trial being planned
- Satisfy clinicians, regulators, statisticians, and other researchers.

Early markers have the greatest potential benefit but are also the most difficult to validate because they are furthest away from when the true OS outcome occurs.

An ideal marker for a future clinical trial must be reliable, consistent, unbiased and clinically relevant. So is PFS/DFS an ideal marker? A study published several years ago (*JCO* 2009, 27:5965) looked at all the definitions used for different outcomes in clinical trials. Depending on the particular trial, DFS was defined in many different ways statistically, but the way the same definitions were used was not consistent from trial to trial.

Another issue that comes up when using PFS is when the timing of the evaluation of an event is not consistent between different treatment arms. This can make it seem as if progression is happening earlier in one arm than another, when in reality it is simply being recorded earlier.

A third issue is differential censoring. Patients do not necessarily leave a clinical trial just because of progression. Some stop the trial when they have adverse events and others may just decide to withdraw. These patients will generally be censored for the outcome of progression or PFS. But problems arise when the censoring itself is related to the outcome. For example, if a patient with grade 2 fatigue on a trial treatment believes it is working and if they have shown a small reduction or stabilisation of their disease they might be willing to tolerate the treatment a little bit longer. In contrast, a patient with the same grade 2 fatigue as an adverse event who does not believe the treatment is working may see a slight increase in their scan and come off treatment a little bit early. In this case, censoring is definitely related to the outcome. The problem is that this informative censoring may have a large effect on the outcomes, particularly if there is a different rate of informal censoring between treatments.

Summing up

In summary, PFS and DFS may often be poor surrogates for OS. It is very difficult to validate surrogate markers, although there is a lot of research trying to validate PFS and DFS in specific contexts. Unfortunately, validation often occurs too late to benefit particular clinical research, but it can be used as a basis for suggesting PFS and DFS may be useful for future studies.

The clinical relevance of PFS is unclear. As an independent outcome, PFS/DFS is most clinically relevant when there is the smallest benefit in clinical trials in terms of gain as a potential surrogate (that is, when PFS/DFS is most strongly related to OS, and the time from PFS/DFS to OS is small). Conversely, PFS/DFS would be most beneficial in clinical trials as a surrogate when in fact it has least clinical utility.

The use of PFS/DFS as a primary outcome in clinical trials is likely to increase, but it should be used with caution and understanding of all of the issues that affects its validity as a surrogate marker for overall survival. ■

Rerouted, not derailed: resuming a young life after cancer

PRUNE ANTOINE

Paediatric oncologists are highly focused on how to minimise and manage the long-term damage their treatments can inflict on a young patient's health. But for survivors, the most immediate challenge is how to get an interrupted life back on track.

Today is the last day for 18-year-old Alexander Mangels. Standing with his mother in the pastel-toned *Kinderonkologie* unit of the University Hospital of Münster, he bids a warm farewell to his paediatric cancer team. His walk is strong, but his grip trembles. "Cancer has stolen a year of my life," he says, between gritted teeth. The awkward teenager with his bald head takes a last look at the nurses who have accompanied him for more than a year. The dates of his chemotherapy treatment are engraved on his memory: 17 November 2013 to 1 February 2015.

When the diagnosis of leukaemia is first pronounced, Alexander is only 16 years old, and his adolescence is brought to an abrupt end. Goodbye to college, first flirtations, parties. Alexander wanted to rebel or fall in love. Instead, he has fallen ill; it is his body that revolts against him.

In place of turning into a man, he becomes a child again: fragile, submissive, over-protected by his relatives, sustained by doctors. A room on the 7th floor of an octagonal concrete tower defines his horizon – it looks like a space shuttle when he is in a good mood, he says. The walls are plastered with children's drawings and joyful teddy bears hiding intensive care plugs. He spends his days in bed or walking the hospital corridors attached to a drip. His new friends are cancer patients like him. "Some were young but still died," he says. There is

GETTYIMAGES

not a tear or a sob; his gaze is fixed and his lips tightly pursed.

During his treatment, he says, he was not afraid. It was more a sense of fury. "Why me, why that? You accuse God, the world, the others... And then you save your energy and go to war." But he never thinks about the future, his focus is on the present, his daily life summed up by the results of his blood tests. "If the values collapsed, I collapsed too," he remembers.

At first, he believes chemotherapy is 'only' supposed to make his hair fall out. As he methodically swallows his pills during the eleven treatment cycles, spending one week at home, then one week in the hospital, he discovers the side effects: headaches, nausea, extreme tiredness and weakness. "There were days I didn't even have the strength to speak. I could only eat prechewed stuff." He refuses to talk to a psychologist, saying: "There is nothing to talk about. Cancer is just there."

His cancer remission feels like freedom. Alexander will return home and start an apprenticeship as a sales assistant in September. As for the transition to normal life, "Well, we'll see once it is there," he retorts. The only thing Alexander will remember from the 7th floor of "*Kinderonko*" is patience. "You learn to accept the illness. At least you'll have quite a story to tell to your kids one day."

Alexander survived childhood cancer and thanks to medical progress, he is not the only one. An estimated 65,500 people in Germany alone have survived cancer in childhood. Across Europe, the number is closer to 600,000, and growing, which amounts to 1 in every 500 adults. While some of these former patients will go on to lead lives untroubled by what they have been through, others may suffer long-term problems, particularly as a result of having been treated with radiotherapy or chemotherapy. "The increase in the childhood cancer cure rate has been dramatic over the past twenty years," says Gabriele Calaminus, a paediatrician at the University Hospital Münster, with soft blue eyes and scruffy blond hair. Most of the doctors and nurses at the paediatric cancer unit are women: "Probably the maternal instinct", she smiles.

Having just said goodbye to Alexander, she sighs and looks out at the horizon: the windows of her office give a view over the peaceful Nordrhein-Westphalia countryside that surrounds the city. "From a 20% cure rate in the 60s, we went to nearly 78% today – the proportion varies depending on the type of cancer. We owe this success to the proliferation of clinical trials and rapid progress in chemotherapy cures, which usually work better in kids than in adults," she says. "We now have more children who survive than who die. But what happens

"What happens to them when they walk out the door? The price of their recovery is very high"

to them when they walk out the doors of the '*Kinderonko*', when they're finished with their treatments? The price of their recovery remains very high."

Like the sword of Damocles, while the likelihood of a cancer relapse fades with time, former childhood cancer patients are always at increased risk of various health problems arising from side effects of their treatment. Going through chemotherapy or radiation therapy during childhood has consequences. Chemotherapy with anthracyclines can lead to heart problems. Some treatments may deteriorate ovarian function, impairing fertility. Radiation may stunt growth and enhance the risk of cerebral stroke or secondary cancers. As for the psychological consequences, these can be similar to post-traumatic distress syndrome, and increase the risk of suffering depression or finding it hard to integrate socially in later life.

Monitoring and prevention

The likelihood of suffering these late effects will vary according to the treatment protocol, the dose levels and the young person's age and medical condition. A US study estimated that more than eight in ten people treated for cancer in childhood in the past suffered seriously disabling or life-threatening chronic conditions by the age of 45 – but this figure includes protocols that were more harsh than those used today.

The improving survival rate among patients with childhood cancers presents an important challenge to medical teams: How can late effects be prevented and monitored? As Gabriele Calaminus points out, aside from a few local, isolated initiatives, there is no standard infrastructure to track the health of former patients, beyond the traditional follow-up consultations in the five years after diagnosis. "We know that a long-term follow-up check is required for patients, because they are young and have their whole lives ahead of them. There is no deadline for these late effects. They can occur at any time, or never."

To reduce the frequency, severity and impact of late effects among survivors of childhood cancers is precisely the goal of the PanCare project. Founded in 2008 as a pan-European network of doctors, oncology institutes, former patients and parents' associations, PanCare aims to ensure that every former patient receives the best long term medical care, which it does through developing guidelines, promoting research, and organising conferences, lobbying and exchanges of information

Peter Kaatsch, a member of PanCare, and director of the Deutsche Kinder Krebsregister (KKR), which since 1980 has been centralising incidence data on childhood cancers, emphasises the size of the problem. "While we have made considerable progress in improving the survival rate, the number of childhood cancers is still unfortunately increasing in Europe, by about 1% per year – 11% in the past 10 years," he says.

"This is a terribly frustrating statistic. Despite decades of international research, we still know little about the aetiology of childhood and adolescent cancers. We don't have enough cases to identify the risk factors, which can be environmental, genetic, familial..." Getting answers, he says, requires international cooperation that goes beyond clinical trials of treatment protocols. "There is no place for competition in paediatric oncology," Kaatsch emphasises. "We all work in a team. The PanCare network summarises this spirit: cooperation."

Kaatsch coordinates PanCare Life, which focuses on the long-term effects of cancer treatment on fertility, hearing and quality of life. The project, which aims to establish a European database of late effects, brings together scientists and oncologists from eight European countries, through 16 institutional partners, and is funded by European Union to the tune of €6 million.

There's great enthusiasm for the work, but it is not without obstacles. The starting point is to gather and harmonise statistical data from a cohort of 12,000 patients spread across the eight countries: France, Germany, Czech Republic, Denmark, Italy, the Netherlands, Switzerland and Ireland.

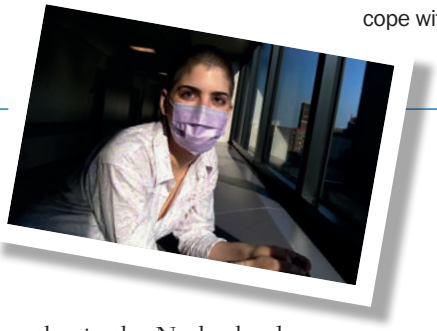
"There is no common evaluation standard yet. If you add in variables such as differences in infrastructure, methodology and language, you can imagine the difficulty! The Czech Republic, for example, saw its medical data completely scattered after the communist period." Other discrepancies include the criteria for being diagnosed as sterile: in Germany this can happen after unprotected sex has failed to lead to pregnancy after 12

MAKING THE MOST OF A LIFE, INTERRUPTED

"I've spent the last year of my life searching for Suleika B.C. (before cancer). I've looked for her all over New York City — the old bars she used to frequent, the coffee shop where she had her first date with the ex-boyfriend, the apartment above the Pearl Paint sign on Canal Street that she shared with 10 roommates her first summer out of college — but the more I look, the more I'm beginning to realize she no longer exists. There is no going back to my old life. The problem is I don't know how to move forward either."

At the age of 22, Suleika's plans to become a journalist and champion the cause of women around the world were interrupted when she was diagnosed with acute myeloid leukaemia and myelodysplastic syndrome. Isolated in an oncology ward, she began to report 'from the frontline' of her hospital bed, first in journals, then in a 'hastily put together' blog, and ultimately in her *New York Times* column and video series, 'Making the most of a life, interrupted'.

Her work, which won her an Emmy award, shines a spotlight on the largely unseen world of young people who are struck by cancer just as they are starting out in life. She writes candidly about fear of the cancer returning, worries that she will never feel 'normal' again, guilt that she doesn't feel more grateful for having survived. Her message to others going through the same thing: "It's not the interruption that matters, but how you cope with it, learn from it and grow beyond it ."



months; in the Netherlands it is 24 months."

Oncogenetics is also delivering promising results, says Kaatsch. Studies have shown that genetic analysis can be used to determine which children are at high risk for specific long-term side effects, which makes it possible to plan ahead. "For heart disease, for example, to know and assess this risk in advance allows the doctor to determine the least harmful dose for his treatment." A small revolution is coming, he adds. "These cured patients are a real treasure that will direct research. We want to gather and disseminate this new knowledge to the medical community, but also to them. They have a right to know."

What do survivors want?

Knowledge is power. But oncologists have to bear in mind that their former patients may feel ambivalent about being followed up all their lives. How can they be effectively monitored, without constantly reminding them of their former 'ill' status?

How can their psychological and social wellbeing be supported in addition to their physical wellbeing? How can a global prevention programme be set up? After finishing their treatment, most patients vanish from the medical system.

Many never want to set foot in a hospital again, they want to move on. Once they turn 18, survivors will tend to look to general practitioners for their healthcare, but many GPs have no idea about the kind of follow up that is needed.

In 2013, the Institut Gustave Roussy in Paris launched a free follow-up consultation for their former

Oncologists have to bear in mind that former patients may feel ambivalent about being followed up all their lives

Going all the way. Kai-Yan Ly, vice-president of the French teenage cancer survivors group *Les Aguerris*, says the experience of going through cancer twice by her mid-twenties taught her to follow her dreams

childhood cancer patients, funded by the National Cancer Institute INCa. "After an extensive survey of this population, we realised that our former patients did not know about their special medical needs after cancer," oncologist Odile Oberlin explains, "so we wrote to them and advised them to make an appointment for a free and comprehensive check-up." Since 2013, 800 people who had been treated at Gustave Roussy as children or adolescents came for follow-up visit – around one third of all eligible patients.

"It was both moving and exciting to reconnect with them," says Oberlin. "We learned that there are no small cancers. Patients treated for cancer without any long-term effects will cry when they talk about it, even decades later; others who experience terrifying side-effects tell us how life is beautiful. Experiences of cancer differ. Sometimes it leaves traces inversely proportional to the severity of the treatment."

Another promising European initiative could make a big difference to post-cancer healthcare. This is the 'survivorship passport', an initiative led by Riccardo Haupt, an oncologist at Genoa Hospital in Italy, and one of the founders of PanCare. Available in print and online, it is a standardised document where a patient's entire medical history can be recorded – the type of tumour, the treatment received – together with a list of associated risks and general recommendations for monitoring. A prototype of the passport is currently being tested at the University of Cineca, Italy, though issues of cost, as well as data protection remain a challenge.

"Thirty years ago, the word 'cancer' was banned," says Oberlin. "This attitude has drastically changed; cancer is no longer seen as synonymous with death. We can heal it. We are used to giving patients the correct name for their disease, so they can make sense of it. The important thing now is for patients to finally be able to reclaim their own history."

Taking back control

Many former patients are now taking back control over their adult lives. At the start it was parents' associations that took the lead in advocating for the health interests of their children. Today, those young patients have grown up and are starting to find one another; a community of 'survivors' is being born.

It was the first time this topic had been aired in public. Laughing, she describes it as a kind of 'outing'

They have an ambitious agenda: they want to organise themselves, inform their peers, improve communication with medical teams, and improve systems of follow-up, harmonising guidelines across Europe. Many associations of childhood cancer survivors have been set up, using social networks – Facebook, Twitter, websites and online forums – which are a great source of solidarity and support.

Online activism is also spreading fast, one impressive example being the work of US journalist and patient advocate, Suleika Jaouad. Diagnosed with leukaemia at 18, she chronicled her experiences for the *New York Times*, documenting her chemotherapy treatment on Instagram, building up a huge online following, which in turn led to invitations to speak out about paediatric cancer at many high-profile events. "Making the most out of my life, interrupted" is her motto, which seems now to have crossed the Atlantic.

In France, it was the Gustave Roussy invitation to a free follow-up consultation that triggered the creation of the first association of childhood cancer survivors, in 2013. They called themselves "*Les Aguerris*", which sounds like 'cured' (*guéris*), but also means 'strengthened' by the fight. Its members want to lobby the government to address the challenges facing the growing number of people like them. Discriminated against in the job market, turned down for loans and insurance... there are many battle fronts in the fight for survivors to be treated the same as everyone else.

"It's been several years since I first felt the need to meet with other former patients and share what I myself had experienced," says Kai-Yan Ly, who found *Les Aguerris* by chance on the Internet, and is now vice-president. Diagnosed with lymphoma at the age of 7, and then with a second cancer at 23, Kai-Yan, now 26, has a calm voice and a Buddhist demeanour. "Having faced this disease twice reminded me of the essential value of a life: do not forget yourself," she says. Today, she wants to have the same rights and responsibilities as other people, without denying her particular history.

"Talking about cancer is still a strong taboo in our society. When it comes to children, the stigma is even stronger. When you have cancer, shame is a very strong feeling. You are ashamed of being ill, ashamed to be hurting the people close to you, ashamed of your reactions sometimes. The feeling of guilt is always there."

How can it be released? How can it be turned into a positive force? In November 2014, Kai-Yan participated in a television broadcast about life after childhood cancer. It was the first time this topic had been aired in public. Laughing, she describes it as a kind of 'outing' – a terminology first suggested by her oncologist. "I had never imagined I could talk publicly on TV, I was afraid of being blamed. I thought about the consequences for my personal life; it was not easy to talk about such an intimate experience. But when I thought about the people who had lost one of their relatives or about the patients who didn't survive, my decision was clear. I spoke out and my feeling changed from shame to a sense of personal pride." ■

CANCER WORLD JOURNALIST GRANTS

This article was financed by a *Cancer World* journalist grant, a scheme set up to encourage journalists who work in print, online or broadcast mass media to explore systemic issues that have a significant impact on cancer patients. The author, Prune Antoine, is a freelance journalist who writes for a variety of publications including *Le Monde* magazine, *Géo*, *Madame Figaro*, *Elle*, and *XXI*. Publication of articles financed by a *Cancer World* grant is not exclusive to *Cancer World*, and authors are encouraged to publish the original or variants in other outlets.
More information about the grant can be found at http://www.cancerworld.org/Media/Journalist_Grants.html.

newsround

Selected reports edited by Janet Fricker

Elderly breast cancer patients do not benefit from radiotherapy

■ European Journal of Cancer

Most elderly patients with pT1 breast cancer treated by quadrantectomy do not benefit from radiotherapy, the results of 15 years of follow-up of a prospective trial have found.

Whether radiotherapy is beneficial for patients older than 70 years undergoing conservative surgery for early breast cancer has long been controversial. A meta-analysis of 10,801 breast cancer patients from 17 randomised trials, published in 2011 by the Early Breast Cancer Trialists' Collaborative Group, showed that radiotherapy after breast-conserving surgery not only reduces the risk of breast cancer recurrence but also improves overall survival. However, although around 40% of breast cancers occur in women over 65 years, most of the randomised trials assessing postoperative breast radiotherapy excluded patients over 70 years.

In 1987 Gabriele Martelli and colleagues, from the Milan National Cancer Institute, initiated a prospective non-randomised study to investigate whether radiotherapy of the breast can be safely avoided in elderly patients (over 70 years) undergoing conservative surgery (quadrantectomy) and prescribed tamoxifen.

For the study the team evaluated 627 consecutive patients with pT1/2 breast cancer treated by quadrantectomy and tamoxifen and assigned non-randomly to postoperative radiotherapy (n=207) or no postoperative radiotherapy (n=420). Altogether 430 patients had pT1 tumours (<3 cm) and 197 had pT2 tumours (>3 cm). Whether or not radiotherapy was given depended on both patient preference and the opinion of the treating surgeon.

Results show for patients with pT1 disease, the 15-year cumulative incidence of ipsilateral breast tumour recurrence, distant metastasis and breast cancer death in the radiotherapy group were indistinguishable from the no radiotherapy group. For patients with pT2 disease, 15-year cumulative incidence of ipsilateral breast tumour recurrence was much higher in those not given radiotherapy (14.6% vs 0.8%, P=0.004), although the two groups did not differ significantly for breast cancer mortality (radiotherapy 20.2%, no radiotherapy 22.5%, P=0.784) and distant metastasis (radiotherapy 15.7%, no radiotherapy 17.2%, P=0.806). The team did not analyse the effect of ER status on ipsilateral breast tumour recurrence, as there were too few events and too few patients with ER-negative disease.

"Data from the present prospective non-randomised study and randomised trials strongly suggest that in most elderly patients with pT1 cN0 ER-positive breast cancer treated by conservative surgery and tamoxifen, the contribution of RT [radiotherapy] to disease control is minimal and its omission does not impact on breast cancer mortality," write the authors.

Data from the study, however, add the authors, suggests that patients with pT2 disease should receive radiotherapy to limit the number of local recurrences. "The novelty of our study is that tumour size (pT status) interacted significantly with the relation between RT and IBTR [ipsilateral breast tumour recurrence], and the 15-year CCI [cumulative incidence] of IBTR was much higher in the no RT than RT group in pT2 patients."

The main limitation of the study, write the authors, is the possibility of bias in selecting patients for radiotherapy versus no radiotherapy. Although all patients were eligible for radiotherapy, it is likely that those in poorer general health tended not to receive it.

■ G Martelli, P Boracchi, E Guzzetti et al. Omission of radiotherapy in elderly patients with early breast cancer: 15-year results of a prospective non-randomised trial. *EJC* July 2015, 51:1358–64

Health professionals need support to deliver less optimistic messages

■ JAMA Oncology

Patients perceive a higher level of compassion from, and also prefer, physicians who provide more optimistic messages versus those who provide less optimistic messages, a US study has found.

Physicians often have difficulty delivering bad news, finding the process stressful and demanding. Factors influencing their reluctance to deliver less optimistic messages to patients with advanced cancer include fear of being blamed, destroying hope or provoking emotional distress, and of confronting their own emotions and death. A further concern is that conveying less optimistic messages will make them be perceived as less compassionate.

Eduardo Bruera and colleagues, from the University of Texas MD Anderson Cancer Center, set out to compare patients' percep-

tions of physician compassion after viewing videos showing two different scenarios. One showed a physician conveying an empathetic and more optimistic message about possible future treatment options to a patient with advanced cancer, and the other showed another physician conveying to the same patient an equally empathetic but less optimistic message about lack of future treatments. Each video lasted approximately four minutes and showed professional actors playing both the physicians and patient. The physician actors, who were both male, middle aged and white, made an identical number of empathetic statements (five) and displayed identical postures. In all the videos, the patient was portrayed by the same white actress, aged approximately 50 to 60 years.

For the study, 100 patients with advanced cancer were randomised to view video A (the less optimistic video) with physician 1, video A (the less optimistic video) with physician 2, video B (the more optimistic video) with physician 1 and video B (the more optimistic video) with physician 2.

The primary outcome was patients' rating of physicians' compassion using five-item tool on a scale of 1 to 10, assessing warm/cold, pleasant/unpleasant, compassionate/distant, sensitive/insensitive, and caring/uncaring to give a final score representing physicians' compassion on a 0 to 50 scale (0 = best, 50 = worst).

Results show that patients reported compassion scores of 15 for the more optimistic video versus 23 for the less optimistic video (P<0.001). There was also a sequence effect favouring the second video on both compassion scores (P<0.001) and physician preference (P<0.001). Physicians delivering the more optimistic message were ranked as more trustworthy – 63 patients viewing the more optimistic message ranked the physician as trustworthy compared to 39 viewing the less optimistic message (P=0.03)

"The finding that patients perceived a higher level of compassion and preferred physicians providing a more optimistic message may explain physicians' reluctance to give bad news because of fear of being perceived to be less compassionate," write the authors.

The study, they add, favoured the second video on compassion scores and physician preference. "A possible explanation… is that dialogue on difficult topics may need to be repeated and processed to become acceptable," write the authors.

Further research and educational techniques in structuring less optimistic message content, they suggest, would help support professionals in delivering bad news, as well as decreasing the burden of feeling less compassionate in such instances.

■ K Tanco, W Rhondali, P Perez-Cruz et al. Patient perception of physician compassion after a more optimistic vs a less optimistic message: a randomized clinical trial. *JAMA Oncol* May 2015, 1:176–183

Clinician enjoyment has little bearing on biopsy precision

■ The Breast

The diagnostic precision of breast biopsy is not influenced by whether or not pathologists enjoy the technology, a US study has found.

In many medical specialties research has demonstrated positive correlations between job satisfaction and confidence in clinical skills and better patient outcomes. Conversely, a study among medical residency programmes reported that depressed physicians had a medication error rate six times higher than their non-depressed peers; while physicians with low career satisfaction report more difficulties in caring for patients. Other academic fields, such as education, cognitive psychology and sports science, have reported positive links between enjoyment of a task and enhanced performance.

In the current study Natalia Oster and colleagues, from University of Washington, Seattle, surveyed 252 pathologists to evaluate the relationship between their enjoyment of interpreting breast pathology and their diagnostic precision. The team hypothesised that pathologists who enjoy interpreting breast pathology would have a "higher diagnostic acumen" compared to those who did not enjoy breast tissue interpretation.

For the study, pathologists, who were recruited from eight US states and had been interpreting breast cases for at least one year, reported on a six-point scale how challenging they found breast cases to interpret, their confidence in assessment of breast cases, and their enjoyment of interpreting breast pathology, from 1 ('very easy') to 6 ('very challenging'). Diagnostic performance was then determined by comparing pathologist assessments of a set of archived tissue samples in glass slide only or digital slide only formats with consensus assessments of the same cases from a panel of three experienced pathologists (the consensus reference diagnosis).

Results showed that 83% of pathologists surveyed (n=208) reported that they found interpreting breast tissue enjoyable, while 17% (n=44) did not. In comparison to pathologists who did not enjoy breast case interpretation, those who did were more likely to review more than 10 breast cases per week (38% vs 13%, P=0.003). They were also more likely to report that colleagues considered them an expert in breast interpretation (24% vs 13%, P=0.003), and to have a high degree of confidence in interpreting breast pathology (95% vs 80%, P<0.001).

However enjoyment was not found to be associated with diagnostic performance. When those who found interpreting breast tissue enjoyable were compared to those who did not, there were no differences in over interpretation (P=0.14), under interpretation (P=0.34) or misclassification (P=0.82).

"A majority of pathologists who currently interpret breast cases enjoy this sub-specialty. Reassuringly, although nearly a fifth of pathologists who interpret breast tissue do not enjoy it, their performance does not differ from their peers," conclude the authors.

A lack of enjoyment among even a small percentage of pathologists, write the authors, has the potential to contribute to future workforce shortages. But the development of whole slide digital technology for primary diagnosis, they add, may allow pathologists to outsource breast pathology to specialised laboratories and lessen future workforce concerns.

■ N Osler, B Geller, P Carney et al. Demographic and practice characteristics of pathologists who enjoy breast tissue interpretation. *The Breast* April 2015, 24:107–111

Favourable parenthood prospects for female Hodgkin survivors

■ Lancet Oncology

Women younger than 18 years undergoing treatment for Hodgkin lymphoma can be reassured that pregnancy is possible. The German study following Hodgkin lymphoma survivors for more than 30 years after diagnosis found that parenthood was similar between survivors aged 20–39 years and the general population. Parenthood was, however, reduced among women aged 40–44 years and those receiving pelvic radiation.

Treatment of Hodgkin lymphoma in children and adolescents has become increasingly successful, with 80–90% now surviving longer than 20 to 30 years. Survivors are likely to consider pregnancy as they grow older, leading to concerns that gonadotoxic chemotherapy with procarbazine and cyclophosphamide, and radiotherapy to the abdomen or pelvis, could cause transient or permanent ovarian dysfunction.

In the prospective, longitudinal study, Jürgen Brämswig and colleagues, from University Children's Hospital, Münster, Germany, compared parenthood in female survivors of Hodgkin lymphoma enrolled in five concurrent studies in Germany and Austria, (each assessing different chemotherapy and radiotherapy combinations) with parenthood in a female population control group. Altogether, 590 female patients who had been younger than 18 years at diagnosis and had been treated for Hodgkin lymphoma at one of 86 participating centres were compared to the female population reported in the 2012 Mikrozensus survey, which reached 802,000 people living in Germany and documented parenthood in five-year intervals among women aged 16–49 years, born between 1963 and 1996.

Results showed that the cumulative incidences of parenthood for survivors of Hodgkin lymphoma were 67% (95%CI 64–75%) at 27.7 years of follow-up (the longest number of years that a patient was followed up before she had her first child) and 69% (95%CI 61–74%) at 39.8 years of age (the oldest age of a patient before she had her first child). The incidence of parenthood did not differ between the Hodgkin cohort and the female German population for women aged 20–24 (P=0.53); 25–29 (P=0.96); 30–34 (P=0.84); 35–39 (P=0.76); and 45–49 (P=0.13). It did, however, differ for women aged 40–44 (P=0.001). Parenthood was significantly reduced in survivors receiving pelvic radiation compared with those who received abdominal and supradiaphragmatic radiation (HR 0.76, 95%CI 0.61–0.95; P=0.01).

"The results of this study document an overall favourable prognosis for parenthood in female survivors of Hodgkin's lymphoma. They will assist counselling of female survivors about their positive potential for future parenthood," write the authors.

That parenthood was similar to the general population until the age of 40, write the authors, can probably be best explained by the higher number of primordial follicles in the pre-pubertal and pubertal ovary than in more mature ovaries. "By contrast, gonadotoxic treatment in adult female patients carries a higher age-related risk of infertility, probably due to the decreasing number and increased vulnerability of oocytes," they add.

In an accompanying commentary W Hamish Wallace, from the University of Edinburgh, writes, "Current challenges remain to avoid radiotherapy without compromising survival in selected patients with Hodgkin's lymphoma, and, for those in whom radiotherapy cannot be avoided, to provide fertility preservation counselling and consider ovarian tissue cryopreservation under the auspices of a clinical trial."

■ J Brämswig, M Riepenhausen, G Schellong et al. Parenthood in adult female survivors treated for Hodgkin's lymphoma during childhood and adolescence: a prospective, longitudinal study. *Lancet Oncol* June 2015, 16: 667–675

■ W Hamish Wallace. Parenthood in female survivors of Hodgkin's lymphoma. *ibid* pp 601–603

Caution urged over selenium supplements in prostate cancer

■ JNCI

Selenium supplementation after diagnosis of non-metastatic prostate cancer may increase the risk of prostate cancer mortality, a US study has found. Caution is warranted regarding use of such supplements among men with prostate cancer, the authors conclude.

The Nutritional Prevention of Cancer (NPC) study reported in 1996 that men randomised to selenium had a lower risk of prostate cancer compared with those receiving a placebo. The effects were most marked among men in the lowest tertile for baseline selenium; while for those in the highest tertile, supplementation was positively, but not statistically significantly, associated with prostate cancer risk. In 2009 the SELECT trial reported no effect of selenium supplementation on prostate cancer incidence, somewhat dampening the enthusiasm for primary prevention. The effect of selenium supplements taken after diagnosis or prostate cancer progression, however, are unknown.

In the current study, Stacey Kenfield and colleagues, from the University of California, San Francisco, prospectively followed 4,459

men diagnosed between 1988 and 2010 with non-metastatic prostate cancer in the Health Professionals Follow-Up Study. Subjects completed a validated semi-quantitative food-frequency questionnaire (FFQ), including information on vitamin and mineral intakes. Brand information was used to calculate selenium intake from multivitamins.

During a median follow-up of 8.9 years the team documented 965 deaths, 226 (23.4%) because of prostate cancer and 267 (27.7%) from cardiovascular disease. In multivariable analyses, men who consumed 1–24 µg/day of supplemental selenium had an 18% increased risk of mortality from prostate cancer compared to non-users, those taking 25–139 µg/day had a 33% increased risk and those on 140 µg or more per day had a 2.60-fold greater risk (*P* trend = 0.001). There was no statistically significant association between selenium supplement use and biochemical recurrence, cardiovascular disease mortality, or overall mortality.

"These data underscore the potentially complex and variable role that lifestyle factors may play in the long etiologic time course of some cancers, in particular that risk factors for incidence may be very different than those for mortality," write the authors.

A U-shaped relation may exist between selenium supplementation and cancer, they suggest, whereby persons with low selenium status benefit from supplementation because of increased expression of selenoenzymes, thereby increasing antioxidant protection; persons with somewhat higher levels have maximum antioxidant protection, but may benefit from supplementation because of apoptosis upregulation; and persons with high excess levels may be vulnerable to adverse effects.

Such results, they add, may not be generalisable to all populations, because selenium status differs widely across the world because of soil content and selenium supplementation behaviour. In the US men consume on average 134 µg/day, while in Europe they consume an average of 40 µg. The recommended daily dose is 50 µg.

In an accompanying commentary Theodore Brasky and Alan Kristal, from Ohio State University College of Medicine, write, "Urologists should query their patients about use of selenium supplements and recommend avoiding any supplement containing more than the US recommended dietary allowance of 55 µg/d."

■ S Kenfield, E Van Blarigan, N DuPre et al. Selenium supplementation and prostate cancer mortality. *JNCI* January 2015, 107(1): dju360

■ T Brasky, A Kristal. Learning from history in micronutrient research. *ibid*, dju375

Statins have no effect on mortality in colorectal cancer

■ JNCI

Statin use was not associated with reduced mortality among patients with colorectal cancer, a prospective German population based cohort study has found.

In addition to lowering cholesterol, statins are thought to have pleiotropic effects which may contribute to cancer prevention and influence apoptotic, angiogenic, proliferative, and inflammatory processes. While studies have found an association between statin use and moderate reductions in mortality among patients with colorectal cancer, such studies have lacked adjustment for some potentially relevant confounders, such as stage of disease.

For the current study, Michael Hoffmeister and colleagues, from the German Cancer Research Centre, Heidelberg, undertook face to face interviews with 2,697 patients from southern Germany diagnosed with colorectal cancer between 2003 and 2009. Information was gathered on statin use, therapy details and recurrence, and data on vital status and date of death were obtained from population registries. Overall information about molecular pathological subtypes of colorectal cancer was available for 1,209 patients. Cox proportional hazard regression models were used to estimate adjusted hazard ratios (HRs).

Among the study population, which had a mean age of 68 years, 412 patients used statins (15%), and 769 died during follow-up (29%). Simvastatin was the statin used most frequently (56%), followed by atorvastatin (22%), pravastatin (11%), and fluvastatin (7%).

After a median follow-up of 3.4 years, a multivariable analysis adjusting for major clinical and epidemiological factors found use of statins was not associated with overall survival (HR=1.10, 95%CI 0.85–1.41), colorectal cancer-specific survival (HR=1.11, 95%CI 0.82–1.50), and recurrence-free survival (HR=0.90, 95%CI 0.63–1.27), respectively. However, an association between statin use and recurrence-free survival was found for early-stage carcinomas (stage I+II: HR=0.50, 95%CI 0.26–0.95). Analyses stratified by molecular subtypes of colorectal cancer suggested no association of statins and overall survival among patients with the more common tumour subtypes including microsatellite stable tumours, CIMP-low/-negative tumours, tumours with negative or moderate expression of ER-beta, *KRAS*–wild-type and *KRAS*-mutated tumours.

"The results of the present study do not support suggestions of beneficial effects of statins for CRC [colorectal cancer] prognosis derived from registry-based studies and suggest that such effects reported in previous studies might partly reflect the lack of or incomplete control for stage at diagnosis and other factors associated with the use of statins such as better medical surveillance," write the authors, adding that, to their knowledge, the study is the first to report associations of statin use and survival by pathological subtype.

The findings of better recurrence-free survival associated with use of statins among early-stage patients, they add, may be due to chance and need confirmation.

■ M Hoffmeister, L Jansen, A Rudolph et al. Statin use and survival after colorectal cancer: the importance of comprehensive confounder adjustment. *JNCI* March 2015, doi:10.1093/jnci/djv045

The moment medical students discover a profound appreciation for humanity

AAMAAN ROWTHER

"Your First Patient: The opportunity to dissect a human body is a once in a lifetime opportunity. The cadaver that you will use for dissection was donated by a person who wished to make a contribution to your education as a physician. It is not possible to put into words the emotions experienced by that individual as he or she made the decision to become a body donor. It goes without saying that the value of the gift that the donor has made to you cannot be measured, and can only be repaid by the proper care and use of the cadaver. The cadaver must be treated with the same respect and dignity that are usually reserved for the living patient."

– Grant's Dissector, 15th edition

Your first patient. These were the first words I would be assigned to read when I began my first year of medical school. They are the opening words of the introduction to *Grant's Dissector*, a dissection manual used by medical students around the world, and are intended to frame students' understanding of the cadaver from which they will derive their first lessons in human anatomy and medicine overall.

I found the notion – that we would perceive the deceased body as our first patient – to be comforting and disconcerting at the same time: comforting because I was hopeful that the standards of our treatment of the cadaver would be raised to the level of respect and compassion that would be owed to a live patient, but disconcerting because I dreaded that the standards of our treatment of patients would instead be lowered to the level of dispassionate objectification and dehumanisation that the anonymous, embalmed body might evoke.

"THE ANATOMY LESSON" BY REMBRANDT – LICENSED UNDER PUBLIC DOMAIN VIA WIKIMEDIA COMMONS

Rite of passage

The first day was unforgettable. One of my lab partners broke into tears upon unzipping the body bag lying on the stainless steel table before us. Such raw emotions were apparent across the lab, which was otherwise dead silent in those first moments. For some, it was the first time seeing a dead body, while for many others it was the nearest they had ever been to one. While our first patient may have not been alive for months, the unique features of her face and contours of her hands made the living person she once was feel palpably near; even speaking seemed to violate the solemnity of the scene.

For several hours a day, five days a week for eight weeks, we would dissect, transect, and strip our first patient down to the bones, literally. Progressing from region to region of the body, we would be responsible for identifying various anatomical features. Beyond mere naming, this involved perceiving each structure with multiple senses: seeing the blood vessels branching through the limbs, touching the hard stones discovered in the gall bladder, smelling the partially digested material seeping out of the intestines. Needless to say, the task at hand required that our raw emotions from the first day be tempered, our visceral reactions subdued. In a word, we had to become desensitised.

The meaning of this word, desensitised, changed through the course of anatomy lab. At the start, it denoted a process of growth out of fear and disgust and into curiosity and awe, from hesitating to even speak to confidently removing layers of fascia as a team, relying on one another's skills and knowledge for collective success in a novel and challenging task of learning. The value of such a transition in one's medical training is enormous.

Yet, by the end of the eight weeks, desensitised had taken on an entirely different meaning for some students. These were the students who would begin handling their cadavers with the delicacy of a rag doll, who would make inappropriate jokes during the genitourinary section, and who ultimately would treat their 'first patient' like one would an object that had never been alive.

The language of medicine

Todd Olson, PhD, an anatomist at Albert Einstein College of Medicine, said that "anatomy is the foundation for the language of medicine: the language health-care professionals use for communicating about patients." Dr Olson was most likely referring to the basic anatomical vocabulary of medicine, the *terminologia anatomica* that one first learns in the anatomy lab and that subsequently forms the foundation of concise and accurate discourse between physicians about the health and disease of patients. Yet, in the wake of recent attention on how doctors speak of patients, generated by a conversation secretly recorded by a sedated patient undergoing a colonoscopy, one cannot help but wonder about the other possible meanings of the statement.

Is the language of medicine that is learned in anatomy lab limited to anatomical vocabulary, or does it extend to our less technical conversations about patients, and even the extent to which our words respect and humanise the people in our care?

This question is often left out of debates about the need for cadaver dissection in medical training, yet it represents some of the most important lessons and formative experiences of anatomy lab. In interactions with their 'first patient', some students discover a profound appreciation for humanity and a humbling reminder of the unique privileges and responsibilities we shoulder as physicians. Others merely learn mechanisms of coping during this encounter with death, how to suspend their emotional reaction and physical repugnance while distancing themselves from any sense of the human life that the cadaver once had.

Regardless of what we take with us from anatomy lab, apart from the smell of formaldehyde, the experience imparts much more on our language and training than the names of anatomical structures, and this contribution to our medical education deserves both caution and attention.

This piece was originally published on the Medical Madrasa blog (http://medicalmadrasa.blogspot.co.uk/) on 28 June 2015, and is republished with permission from the author

Armaan Rowther is currently studying toward a combined MD-PhD in public health under the Johns Hopkins University Medical Scientist Training Program

WE'RE REACHING OUT TO MEDICAL STUDENTS

ESO has teamed up with ESMO to help convince more of the brightest and best young medical students to go into medical oncology. A newly launched summer course, held in the Spanish town of Valencia, offers students in their fourth or fifth year of medical school the chance to spend an intensive five days interacting with international experts; learning a practical approach to cancer diagnosis, staging, prognosis and therapy; getting to grips with the basic principles of medical oncology; and discussing how to plan their careers.

The first course, held this July, had such a high standard of applicants that 50 of the nearly 300 who applied were given a place, rather than the 40 that had initially been envisaged.

Encouraging more medical students to consider a career in medical oncology will be essential to ensure that the patients of tomorrow will have enough top-quality doctors to care for them and to keep pushing up standards of clinical practice.

Applications for the 2016 course open in September 2015. For further details check out the ESMO and ESO websites, www.esmo.org and www.eso.net