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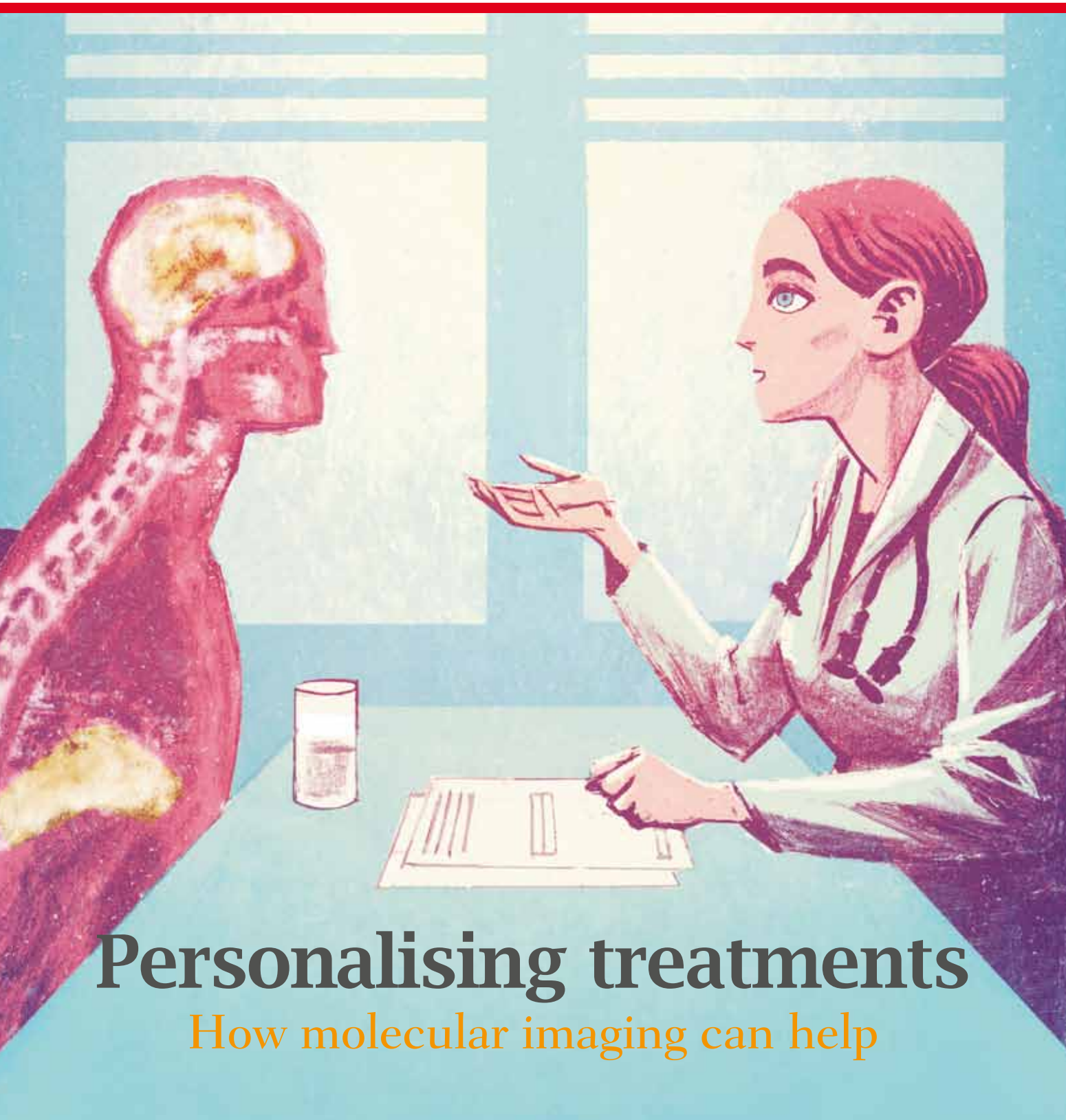
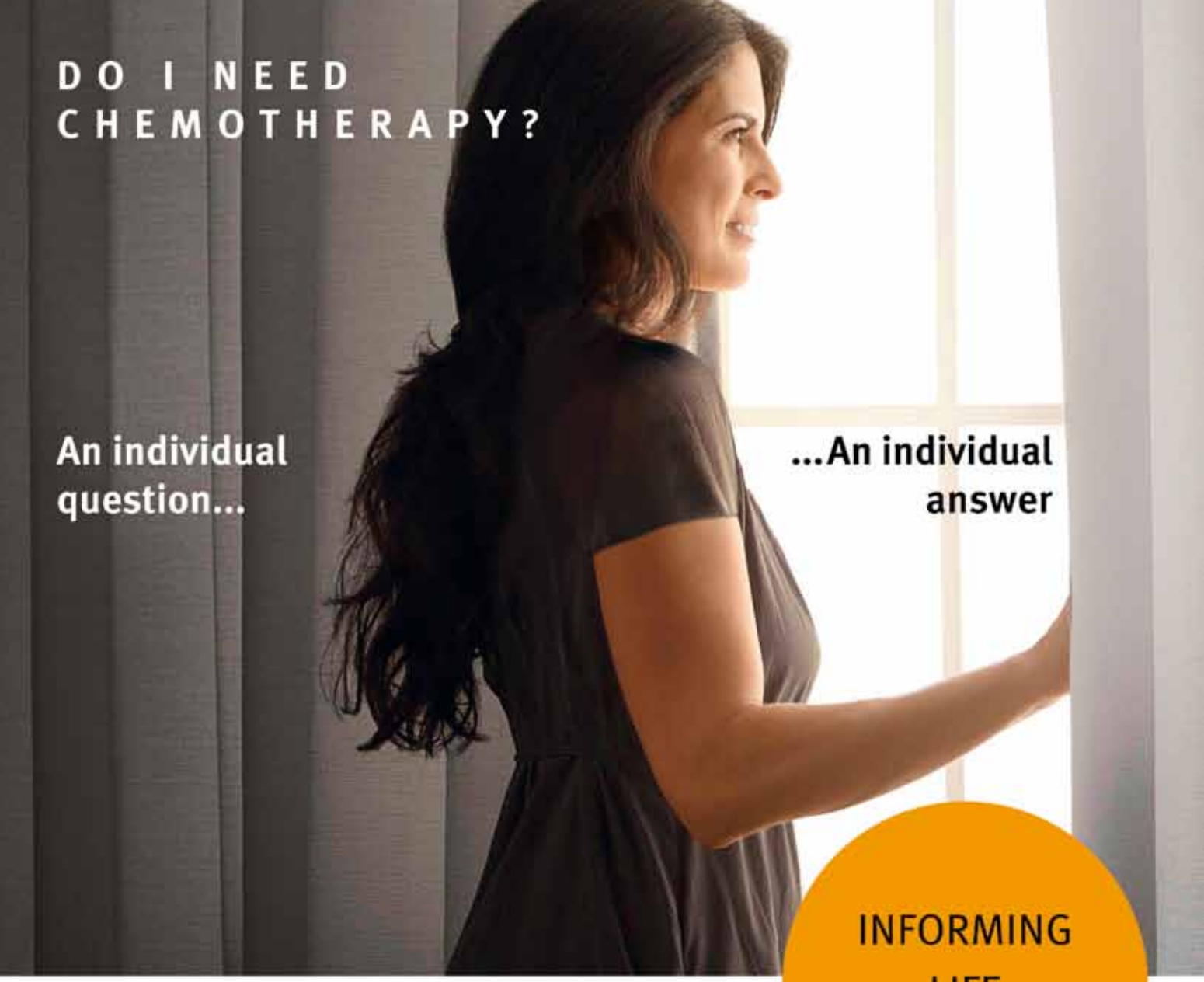


Personalising treatments

How molecular imaging can help



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1. Paik S et al. *N Engl J Med* 2004; 351: 2817-2826; 2. Dowsett M et al. *J Clin Oncol* 2010; 28: 1829-1834; 3. Paik S et al. *J Clin Oncol* 2006; 24: 3726-3734; 4. Albain KS et al. *Lancet Oncol* 2010; 11: 55-65.

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Learning to care

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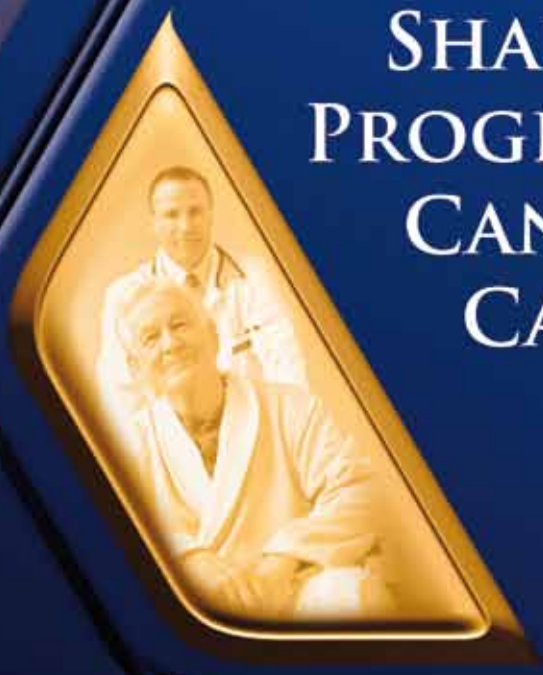

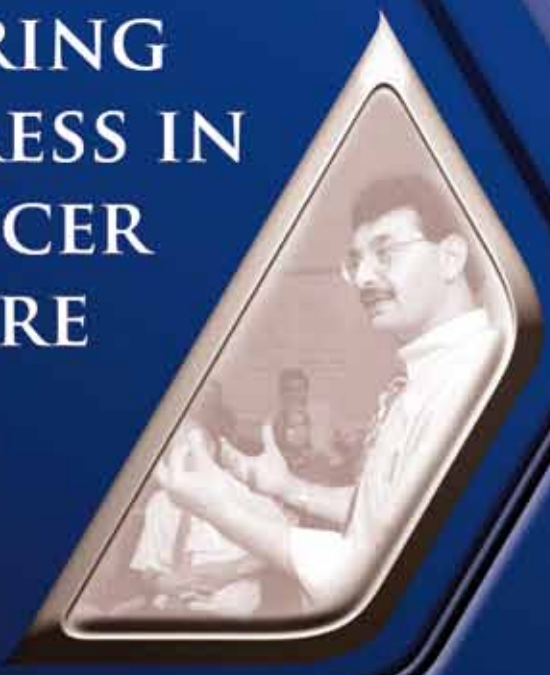

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Time to refocus on risk and prevention

Alberto Costa, Editor

"In the history of cancer research, there has always been tension between those who want to treat cancer and those who think we should prevent it," writes the pioneering medical oncologist and former head of the US National Cancer Institute, Vincent De Vita, in his recent book *The Death Of Cancer*. While they are obviously both important, he says, "The question has always been, where should researchers focus their efforts?"

In recent decades, the lion's share of the research effort has gone to treatment. But three outstanding meetings that recently took place within months of each other, in Europe, the US and India, may signal a change of emphasis.

Last October, 'Prevent the Preventable', the third meeting of the World Oncology Forum, took place in Milan, co-chaired by Michael Sporn, the 'father' of chemoprevention. In early February 2016, 70 top experts gathered in Leesburg, Virginia, to brainstorm on 'Shaping the Future of Cancer Prevention', hosted by the American Association for Cancer Research, and co-chaired by Ernest Hawk and Scott Lippmann. Later that month, in Mumbai, the agenda of the Challenging Dogmas conference, chaired by Indraneel Mittra and Rajendra Badwe, focused heavily on the need to rethink strategies in the light of new knowledge about the process of carcinogenesis.

A key message of these three meetings? That we know very little about cancer prevention and we need to invest in research.

Chemoprevention efforts – the use of chemicals to stop carcinogenesis – have not realised the dream of a magic anticancer pill. Tamoxifen can halve the risk of breast cancer, but for a number of reasons it is not commonly used for this purpose. Aspirin looks promising against some types of cancers, but its impact is still unclear. Some of us may benefit from metformin, but data are not solid enough to move to practice.

Then we need to understand more about risk factors – in particular the big five: smoking, diet, physical exercise, alcohol and sun exposure. Most of our data come from the Anglo-Saxon world, so do not reflect the reality for the rest of the planet. Risk factors vary widely even within Europe, from the Portuguese farmer who exercises a lot in the open air, is genetically protected from sun exposure, eats naturally and well, drinks a bit of Mateus and smokes at least 10 cigarettes a day, to the Irish woman working in a Dublin call centre who does not smoke, has very little sun exposure, sometimes goes to the gym, eats a completely different type of food and often downs a pint or two of Guinness in the evening.

Much of the progress in treating cancer in recent years has come from learning to feed multiple factors into treatment decisions – tumour grade, proliferation, receptor status. Faster progress in helping people stay cancer free now requires that we learn more about individual risk factors and adopt a similar approach to personalising prevention.

Personalising treatments

how molecular imaging can help

Molecular imaging specialists are ready to break out of their research huddles and take their place at the heart of clinical decision making. But can they convince clinicians to welcome them in? **Anna Wagstaff** investigates.

We're in the age of precision medicine. But to the great majority of people with cancer it still doesn't feel that way. Patients and their doctors trying to decide on the best treatment options are still having to gamble on risk–benefit calculations drawn from very broad patient populations, without the personal prognostic and predictive information they need to tell them what their cancer will and won't respond to or how aggressive the treatment needs to be.

As a result, many are still being overtreated, undertreated, or wrongly treated.

The huge research effort invested in developing personalised medicine is in many ways further confusing the picture.

While new generations of 'targeted therapies' are coming onto the market in a steady stream, few of them come with instructions specifying who will and who won't respond, or how they can best be integrated within existing treatment pathways. Immunotherapies, the latest big hope, seem to work in only two in ten of their target population – more commonly only one in ten.

Doctors and patients accordingly find themselves with more options but little guidance on how to choose between them, what combinations work best, and how to time and sequence moving from one to the next.

Now an offer of help is coming from a surprising source, far from the molecular biology labs that have spawned the genomics, proteomics, metabolomics, transcriptomics and other specialist research fields that have so far dominated the precision medicine scene.

The imaging community – specifically specialists in molecular imaging – believe that they can help find answers to many treatment uncertainties, and they are reaching out to the clinical community to see what can be achieved by working together.

Molecular imagers come from two specialties. Nuclear medicine physicians scan using probes labelled with radioactive isotopes to visualise what is going on inside the body. These are the people who brought us PET scans, which use radioactive tracers to reveal the anatomic distribution of cells with a distinctive biology, such as a high metabolic rate, upregulation of different receptors, or hypoxia – all important information for tailoring cancer treatments. The advent of PET–CT scanners made it possible to combine the biological information from the radiotracers with the anatomical precision of CT scans.

Then there are MRI specialists, who in recent years have been pushing the boundaries of their field to provide biological information based on the behaviour of cells when subjected to different magnetic resonance sequences and techniques. While some of these techniques are so sophisticated they will probably only ever be used in a translational research setting, others, particularly diffusion-weighted MRI, can give information about cell density, cell membrane permeability, and hypoxia which could well play a role in tailoring treatments.

Technological developments over the past 20 years have brought the two specialties together, as Wim Oyen, professor of nuclear medicine and molecular imaging at the Institute of Cancer Research, in London, explains.

"PET comes from biology, MRI from anatomy. There is more and more biology coming into MRI and more and more anatomy coming into PET. So they are coming together and provide complementary information. The good thing is that they are talking to each other and developing the technology that helps us image the patient in the most appropriate way."

Good news indeed. But Oyen is well aware that if molecular imaging is to realise its true potential in improving the quality of patient care, the key conversations will be with the academic clinical community. In his capacity as Congress President of the European Association of Nuclear Medicine, he is leading a major charm offensive.

"We are very actively seeking collaboration with clinical societies," says Oyen. "For our annual congress in Barcelona in October we have invited something like 20 clinical societies for joint symposia and discussions, to get clinicians on board about what we can do, and to get our community on board about what clinicians really want from us."

They are reaching out to the clinical community to see what can be achieved by working together

To make sure everyone gets the message, these discussions will take place under the motto, "Go clinical!"

Oyen is aware that imaging specialists have a bit of an image problem themselves. They've gained a bit of a reputation among clinicians for being so proud of the truly impressive power of their technology that they have lost sight of what doctors and patients really need.

Radiomics – biological information *in vivo*

The ability of PET, CT and MRI techniques to visualise different aspects of tumour biology has spawned a new field of research which explores what information from an image can reveal about the prognosis of a tumour and its likely response to different types of therapy.

While genomic and other approaches that rely on tissue or liquid biopsy provide comprehensive 'snapshots' of biological indicators of cancer, imaging can take this information a step further, showing the activity of these markers *in vivo*, in tumours and the microenvironment, and how their activity changes over time.

Research conducted in the Netherlands and the US, for example, recently demonstrated that radiomic information mined from CT scans of 440 patients with cancers of the lung and head and neck correlated with both genomic information and survival (*Nat Commun* 2014, 5:4006).

Fair comment, he says. "A lot of imaging, I must admit, is done just because you can." In some cases the net impact on patient management has been decidedly questionable.

"They don't want a pretty picture that is nice to look at but has no relevance to patient management"

"When we first started looking at FDG-PET for example, one of the things we noticed was that we picked up a lot of little signals in the colon. We reported it and it turned out to be polyps, and we did it again and again, to a level that the clinicians got annoyed, because they had to do all these colonoscopies for something that is really not a colon cancer. Their patient had a lung cancer that required treatment, yet the treatment was postponed because a colonoscopy had to be done first."

It was all part of a learning curve, says Oyen. Today PET–CT continues to play an important role in selecting patients for lung cancer surgery, but the guidelines for reporting have been refined. Signs of polyps are now flagged up as a minor finding that might merit attention once the lung cancer has been resolved.

Oyen learnt from the experience about the importance of working hand in hand with the clinical community to develop the clinical use of imaging.

"They don't want a pretty picture that is nice to look at but has no relevance to patient management. They are looking for a pretty picture that is obvious for them to assess the information, and has a positive impact on patient management and patient outcomes. And that discussion is something that we have to do together." He says the offer they should make to clinicians is: "This is what we can do: what unmet needs do you have that we may be able to help with?"

This is pretty much the conversation that developed with a group of lymphoma specialists in the early 2000s. It's been such a success that lymphoma is being used as a showcase to raise awareness of what imaging can achieve when it addresses clinical uncertainties in an evidence-based way.

Assessing treatment response

Hodgkin's lymphoma is curable in more than eight out of 10 patients – it was the first cancer to be cured by radiotherapy, back in the 1950s, and the first to be cured by chemotherapy, in the 1960s. But treatments can be debilitating, and come with serious long-term effects – studies have shown that, on average, survivors lose 40% of their 'expected work efficiency' for the rest of their lives. This is a particular problem because the majority are diagnosed before they reach 40, many in their teens or twenties.

Finding ways to limit the damage by giving each patient no more treatment than they really need has therefore been a priority for Hodgkin's specialists, which is one reason why, when the first PET–CT scanners arrived in hospitals in the early 2000s, it was used very early in patients with Hodgkin's.

Martin Hutchings, nuclear medicine physician turned clinician, based at Copenhagen's Rigshospitalet, was among the early pioneers. At the time, says Hutchings, CT scans were the mainstay for staging and for assessing treatment response during and after treatment, but it was often hard to tell whether visible lesions represented active tumours or just scar tissue.

"Thousands of publications looked at the value of PET and PET–CT in staging and interim and end of treatment response assessment, and it was invariably found to have a higher accuracy," says Hutchings. Higher accuracy does not automatically benefit patients, he is quick to point out. Indeed in situations where low-risk disease is already being overtreated, using ever more sensitive techniques can exacerbate the problem. In this particular setting, however, studies showed that some patients do indeed benefit in a number of ways. The higher precision provides a more accurate idea of how far the disease has spread, improving the selection of patients for systemic therapy alone, or combined with radiotherapy (only used for more local disease due to the severity of side effects).

It also gives a better idea of response to treatment, and turns out to be highly prognostic. "When you scan a patient after treatment, the results of the PET–CT says more about the long-term outcome of the patient than the original CT scans did."

Hutchings' own studies, published in 2006, provided the key evidence to show that the results of PET–CT during and after treatment strongly predict for progression-free survival and overall survival. "Using PET–CT early during treatment, if the scan was negative, patients did extremely well – almost 100% long-term progression-free survival, and if it was still positive, they did pretty poorly, 70–80% failed in the first year."

This information is particularly valuable in assessing response at the end of treatment. "You want to know if the patient is in complete response, which means that in many cases the patient is likely to be cured, or whether there is unsatisfactory partial response, which might call for additional treatment or maintenance treatment, or a very close surveillance scheme."

Do no harm. Using PET–CT to guide treatment of Hodgkin's lymphoma helps doctors minimise long-term damage to the health of their patients, many of whom are still young

In 2007 clinical guidelines were revised to incorporate the PET–CT scan after treatment as the key determinant for response assessment. In 2014 they were changed again to include PET–CT as standard of care for staging and the interim assessment as well.

Selecting for surgery

PET–CT has also been proving its value in assessing response to treatment among patients treated with chemoradiation for head and neck cancers that have spread to the neck nodes. Recent results from the UK PET–NECK trial show that complete response on PET scans following chemoradiation is as reliable as surgical dissection for confirming that the nodes are free of cancer.

This is great news, says Vincent Gregoire, a radiation oncologist at the Catholic University of Louvain in Brussels, who specialises in head and neck cancer. Most doctors, he says, have been using either palpation or CT scans to assess response to treatment, but both carry a considerable margin of uncertainty, with the result that many patients have to be referred for lymph node dissection to be certain.

Gregoire compares lymph node CT to looking at a dustbin from the outside and guessing whether it is full of rubbish or not. "PET will tell you," he says. One in five patients in this population need to have their lymph nodes removed after chemoradiation to prevent recurrence. PET can be used to identify those patients, sparing everyone else from surgery they don't need, which, as Gregoire points out, is good for patients and saves money.

It's not a major operation compared to some head and neck surgery, he says, but it requires four days in hospital and patients do pay a price. "The neck will be stiffer with neck node dissection after radiation than without, and

in some patients you may end up with more severe complications, affecting the swallowing function, for example."

Gregoire and his colleagues have been interested for many years in the potential of molecular imaging to better tailor treatments for patients with cancers of the head and neck, since treatment often impacts heavily on long-term quality of life.

Having gone almost as far as they can in tailoring their radiation beams to the three-dimensional contours of an individual tumour, they now want to see how far they can go in tailoring radiotherapy to each tumour's individual biology.

Gregoire mentions three biological parameters in particular: hypoxia can be visualised by PET using, for example, ^{18}F-fluoroazomycin arabinoside (FAZA); high cell density can be visualised using diffusion-weighted MRI; high metabolic rate can be shown by PET using ^{18}F-fluorodeoxyglucose (FDG). All are known to be associated with poorer prognosis, and all are typically distributed unevenly in clusters within a given tumour.

It is yet to be proven whether increasing the dose to areas of the tumour showing these biological properties does in fact benefit patients. This is more likely to be the case in head and neck cancers, where loco-regional control is key, says Gregoire, than for instance in breast, lung or prostate, where metastatic disease is the bigger problem.

Two years ago he applied to the EU research programme, Horizon 2020, to fund a trial that he hopes will show that dose escalation tailored to cell density or to hypoxic cells will improve outcomes. Sadly, he says, it was turned down, so for the moment the protocol is sitting on his hard disc, gathering virtual dust.

Reducing futile treatment

Across the city at another Brussels hospital, another potentially important molecular imaging protocol gathers dust on another hard disc, having also had its Horizon 2020 funding application rejected.

Alain Hendlisz, head of the department of digestive oncology at the Jules Bordet Institute, is leading a study that could help reduce the number of cancer patients needlessly exposed to adjuvant chemotherapy.

For the moment, the trial protocol is sitting on his hard disc, gathering virtual dust

This is a toxic therapy, with potentially long-term effects, that is given following curative surgery, to mop up tumour cells that may be lurking undetected. The great majority of people treated with adjuvant therapies gain no benefit – most would not have suffered a recurrence anyway, while in some the disease recurs despite the therapy because the leftover tumour cells do not respond to the treatment.

Finding ways to refine the selection of patients who really need adjuvant therapy is therefore a major unmet need and has been a big focus for translational research, spawning tools like Mammaprint and Oncotype DX, that use gene signatures to define risk of recurrence.

Hendlisz and his colleagues – who include Martine Piccart who led the MINDACT trials to validate Mammaprint – are now taking a slightly different approach. Before giving adjuvant therapy, they want to use PET–CT scans to check that the cancer is likely to respond.

The proposed trial is in patients with stage III colorectal cancer, for whom adjuvant therapy with the FOLFOX cocktail of cytotoxics is the standard of care. The idea is to administer one cycle of FOLFOX before the tumour is surgically removed, and then examine the response by comparing PET–CT scans taken before and after the chemotherapy.

Results from the PePiTA trial (Preoperative chemosensitivity testing as Predictor of Treatment benefit in Adjuvant stage III colon cancer), led by Hendlisz, suggest that selecting patients for adjuvant FOLFOX based on their PET response may decrease the proportion of patients given adjuvant therapy by 40–50% without increasing recurrence rates. But this now needs to be validated in a larger and longer trial – and that is where the funding problems kick in.

Building the evidence

As a leading figure in the community, Wim Oyen is all too aware of how many small exploratory studies have shown potential for helping personalise treatments, but have never broken out of the research setting into the clinic.

He accepts that the problem is not just funding, it's also about attitudes and awareness. Imagers need to recognise that clinicians want strong evidence that a given technique will improve patient outcomes.

"I am now pushing in the nuclear imaging community that we stop entertaining ourselves and convincing ourselves that we have such great innovative imaging techniques, but fail to take the final step into actual

widespread clinical use because the evidence falls short of what clinicians accept as evidence."

He points out that the settings where molecular imaging has really caught on – such as lymphoma, head and neck cancer, and also lung cancer – are where "trials were done in a way that oncologists accepted."

Clinicians, on their side, need to be more aware of the potential of imaging to help personalise treatment, says Oyen, and should do their best to integrate molecular imaging, alongside for instance immunohistochemical and genetic biomarkers, when developing new treatment strategies.

It can be very frustrating, he says, when opportunities to generate this evidence are missed. He cites the example of oesophageal cancer, where a series of trials done at the Technical University Hospital in Munich had shown that early use of PET–CT to assess response to neoadjuvant chemotherapy benefited patients, allowing those who didn't respond to move straight to surgery, thereby saving them from unnecessary delays and toxicity.

"Clinicians should do their best to integrate molecular imaging when developing new treatment strategies"

So far so good, but the standard of care then changed to chemoradiation. However, the trials comparing the two treatments failed to address the question of who benefits, and whether PET–CT could be used in the same way to identify patients who derive no benefit from this even more toxic neoadjuvant therapy, and would do better moving straight to surgery. We'll need a new trial to find out, says Oyen, but he can't see that happening anytime soon. "If the imaging had been in that original trial, you would have had the answer."

He understands that the cost – and complexity – of including imaging in such trials can be intimidating, but as he points out, investing in techniques to personalise cancer treatment not only benefits patients but saves money in the long run. It reduces the direct costs of unnecessary treatment, and by avoiding unnecessary long-term damage to the health, function and quality of life of survivors, it will yield much greater savings from health and social care budgets, while boosting tax receipts.

The question is, who will pay?

Funding research

Some countries are making some public money available for these sorts of studies. The PET–NECK trial, for instance, which showed PET–CT response monitoring can reduce the unnecessary use of neck dissection, was funded by the UK's National Institute for Health Research.

It included a cost-effectiveness analysis, which showed that, over the two-year minimum follow-up period, the per-person cost saving was £1492 (€1900) per person (*NEJM* 2016, 374:1444–54).

In Belgium, however, Gregoire claims that public funding for such studies is increasingly hard to come by. "We have a lot of difficulties in convincing the payers." The typical response from funding agencies, he says, is that this sort of imaging is commonly carried out, "so we shouldn't need funding, because it will be paid by health insurance or whatever."

While that may have been true a few years ago, says Gregoire, nowadays payers won't cover imaging unless it is in use as a routine part of standard care.

Hutchings reports that some of his European colleagues face similar

False economy?

Surgical dissection of neck lymph nodes can affect patients' range of movement and their ability to swallow.

A UK study, funded by public money, found that PET–CT helps avoid unnecessary neck surgery in patients with squamous cell cancers of the head and neck, while at the same time saving almost €2000 per patient within two years *(NEJM* 2016, 374:1444–54).

Many other studies to confirm the value of molecular imaging in guiding treatment decisions are being held up because they can't get funding.

problems "Even in rich countries like Germany, access to PET–CT has been very difficult, I know it's been really difficult both for the German Hodgkin's Study Group and also for the non-Hodgkin's study groups to build trials where PET–CT was part of the trial. They really have to negotiate every single scan, because it's not something that the health insurance agencies naturally pay for. And that's increasingly the way things are going."

"They really have to negotiate every scan, because it's not something insurances naturally pay for"

It is, of course, right and proper that healthcare budgets should not routinely pay for scans whose clinical value has yet to be demonstrated. However, sustainable health systems do need mechanisms to fund trials that could lead to better outcomes and lower costs, which is part of a wider conversation about promoting innovation.

A priority for Oyen, meanwhile, is to ensure that imaging studies are built into the development of all new treatments, so that by the time new drugs come to market, or new therapeutic strategies are adopted, the role that imaging may be able to play in defining who should receive the treatment and when is clear.

"The moment you know a drug is going to be developed, and you know you have something of a signal from molecular imaging, then you should run molecular imaging, not as a side study, which is usually underpowered, but as part of the main protocol, and run it in a way that you enrich the patient population that will benefit from your drug.

"I'm strongly advocating that we start doing research from day 1, to be in a position to identify these molecular imaging biomarkers, because when a drug comes to market it is too late, nothing will change anymore."

He emphasises that he is not trying set up molecular imaging biomarkers as some sort of competition to other types of biomarker that are more commonly investigated in early trials.

"I am totally agnostic about which type of biomarker. If a liquid biopsy is doing the job, that is fine. But so far, the discussion I've seen starts with an indication that something is happening, and then the next question is 'Where is it?' and then you need imaging again. So if a patient with a prostate cancer has a rising PSA, something seems not right, but is it in his prostate, or his lymph nodes or bones?"

The plea he makes is for "a more open mind" towards what genetics and immunohistochemistry can offer in combination with imaging. "I would like nothing more than if we could use, for example, liquid biopsies to preselect the patients on whom we have the most impact on management when we put them through imaging."

Key to moving forward will be convincing the EMA and FDA, the European and US regulators, to acknowledge imaging biomarkers – which is a conversation he and his fellow members on the board of the European Association of Nuclear Medicine are actively engaged in.

He says that being expected to generate the same level of evidence as some of the lab-based biomarkers is hard, because they do not have huge numbers of patients. "We'll have to do smart trials, with smart designs to get the answers."

There is also the question about whether companies are prepared to invest the additional time and money to do these studies.

This too is part of a wider conversation about whether there may be better ways for public and private sectors to work together to deliver personalised medicine, which the current business models seem unsuited for.

The challenge for Oyen and his colleagues is to ensure that the role molecular imaging can play in finding solutions features as an integral part of these conversations.

The plea he makes is for 'a more open mind' towards what genetics and immuno-histochemistry can offer in combination with imaging

That has to start by convincing clinicians that molecular imaging can help them with the specific uncertainties they face in tailoring treatments to patients. He is hoping that his overtures to the clinical community at the forthcoming EANM congress, combined with his exhortation to the imaging community to "Go clinical!" will be a step in the right direction.

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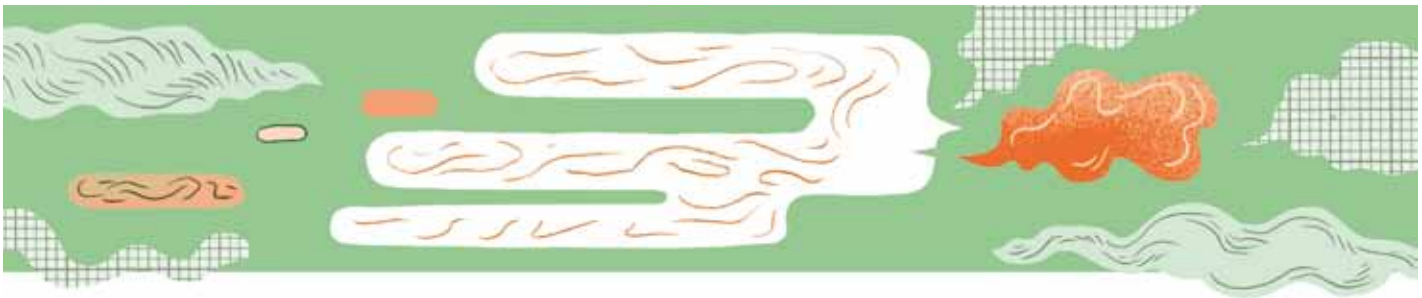

Hello, my name is Kate Granger

Her campaign to bring a human touch to healthcare, which she carries on even through the tough final stages of cancer, has had widespread impact and brought international acclaim. **Simon Crompton** talked to the woman who changed the way healthcare workers greet patients.

Kate Granger is still a bit mystified about how she became a celebrity – a healthcare poster girl, a cancer "rock-chick" as she puts it.

"I'm just a normal Yorkshire lass," she protests. "It's very strange that people want me to sign things and have selfies with me. I'm baffled by it everyday." But to those who meet Kate or follow her regularly on Twitter, it's not such a mystery. Being gloriously normal is at the heart of Kate's success.

With the help of her husband Chris Pointon, doctor and cancer patient Kate set up the #hellomynameis campaign on Twitter in 2013. It is an attempt to get all healthcare professionals to do something very simple: introduce themselves to patients. This, says Kate, who is 34, is not just a matter of basic courtesy. It is about establishing a human connection between a vulnerable human being and someone who wants to help.

Her campaign has taken off in a big way. #hellomynameis has made over one billion impressions on Twitter, with healthcare professionals declaring their support and displaying their #hello my name is… name badges in selfies. The campaign tapped into a wave of unease about depersonalisation in the UK's National Health Service and triggered a new drive for "compassionate care", gaining support from the Prime Minister, the Health Secretary and more than 100 health providers and organisations. It has also been commended in major reports.

The campaign's influence now goes well beyond the UK, with offshoot campaigns in France, Germany, Italy, Spain, the United States and a hugely successful #hellomynameis pledge in Australia.

In the past year the acknowledgements and accolades have come thick and fast. When I meet her at her small home in Wakefield, she's just received an honorary doctorate from London South Bank University. Before that she'd been presenting the Kate Granger Compassionate Care Awards organised by NHS England; before that conducting a speaking tour around 16 hospitals and health organisations; receiving an honour (MBE) from Prince Charles; receiving the Pride of Britain Award; receiving the award for the most inspirational people in health…

In her front room, she proudly points me to the pictures of her husband and nephew and nieces that decorate the mantelpiece and sideboard, but when I ask her of the

A reluctant celebrity. Kate agreed to have her portrait painted to challenge assumptions about what dying looks like. It was painted by Antonia Rolls as part of her exhibition 'A Graceful Death: portraits and words from the end of life'

whereabouts of the awards and certificates, she says they're on a shelf upstairs.

"There are too many of them to show anyway," she says with a blunt, dry charm. That doesn't mean they haven't given her pleasure. This year has also seen her receive fellowships from the Royal College of Physicians of both London and Edinburgh.

"I'm the youngest Fellow in the London college's history, and they've never made a non-consultant or doctor a Fellow before." (She qualified as a consultant geriatrician shortly after I spoke to her.) "I don't know whether they just felt sorry for me and decided to give me the fellowship early," she says with a mischievous grin. "It was a very nice day anyway."

But the reason why Kate is so honoured, widely read, and adored by 42,000 followers on Twitter has nothing to do with feeling sorry for her – even though the desmoplastic small round cell cancer that she lives with is widespread and terminal. Ever since the cancer was first diagnosed in 2011, Kate has assumed she might have just months to live.

The reason is that she is doing extraordinary things with her limited time. But she is also being entirely ordinary. Her Twitter followers know all about her love of baking, her family, her love of the NHS, her band practice (she plays second flute), and her determination (often severely challenged) to stay positive in the face of aggressive chemotherapy and poor prognosis. Through it all, they also see her resolve to keep practising as a geriatrician and leave a wider legacy of health professionals relating to patients as people.

"I think I seem to have developed a very powerful voice, in the sense that it's credible and authentic," she says. "I haven't got it in for every healthcare professional, but I do have a vision of the health service. I have my quality improvement eyes on whenever I'm being a patient, and I guess I can write about that in a way that lay patients

probably can't. I think it's about a simple message delivered by someone with an authentic voice."

Being in the public eye isn't always easy. When I meet Kate, it's just a few weeks after her fourth course of chemotherapy – and she says she hasn't got her confidence back yet. "Some days I don't feel like putting on my make-up and being the public Kate," she says. But she pushes on, aware that the legacy she is working on is important.

She tells me that audience members sometimes cry when she gives talks. What particularly makes them cry? I ask. "The bit when I say that I'm determined not to be remembered as that tragic young doctor who died of cancer, rather than somebody who was creating a legacy. That bit tends to get them bawling." She laughs.

How it started

The story of Kate Granger's cancer journey tells you everything you need to know about the importance of her campaign. "I do have a story," she says. "It's quite an upsetting story at times, isn't it? Nobody really wants to watch a girl in her 30s talking about her own demise or the suffering she's been through, do they? But the story has a message that people can take away with them and use in their own practice."

Kate found out she had cancer while on holiday in California with Chris in 2011. She'd been tired for weeks – which she'd unsurprisingly put down to the 100-hour weeks she was working as a junior doctor – and then she had severe back pain. CT scans revealed that she had tumours in her abdomen and pelvis that were pressing on her ureters, causing kidney failure. She returned to the UK for further tests and MRI scans.

She still finds it hard to talk about what happened next.

> **"I just couldn't believe the impersonal nature of care, and how people seemed to be hiding behind their anonymity"**

"I was in an admissions ward. I never saw the same doctor twice and the nurses weren't coming, so I was in pain. I was by myself, 29 years old, scared, hating the cancer diagnosis and with this vault of uncertainty ahead of me."

"And this junior doctor came to see me and just sat in the chair by my bed. He didn't introduce himself. He just looked out of the window and said: 'I'm really sorry but your cancer's spread.' No checking what I knew already, or whether I wanted someone with me. He couldn't wait to get out of the room. So I said just give me the report, and I looked through it and all these bad words were popping out. Mets? I didn't know I had mets. I had hundreds of questions, but I couldn't ask them because he didn't have any answers. It was just awful. He went and I was just left. I don't want anyone to go through that experience again."

It was the worst experience she has had with cancer, she says, but she is adamant that the doctor was not to blame. He was unsupported by senior staff and simply too junior to effectively deliver a death sentence.

The experience that led to her founding #hellomynameis came later, in August 2013.

It had been a bad few days: Kate had become unwell with an infection following surgery to replace the stents draining her kidneys. So she was admitted "kicking and screaming" to the emergency department. Kate knew from her professional experiences how stressful Accident & Emergency could be for staff, but she'd had no idea how stressful it could be for patients.

"I just couldn't believe the impersonal nature of care, and how people seemed to be hiding behind their anonymity," she says. "It's really really important to me to know who I'm talking to, but it was really hard to extract the name of the junior doctor who was treating me. And it was all so task-orientated. So yes, I got my appropriate tests, and bloods, and got my antibiotics quickly – but there was no personal interraction during that time. And if they'd bothered to interact they'd have found that out that actually I'm quite scared of needles, having spent a couple of years having had little else done to me. But it was just wham bam!"

What happened that evening was in complete contrast. A porter took Kate, still in severe pain with a postoperative infection, on a ten-minute journey from the emergency department to the urology ward. It is significant that Kate still remembers his name.

"Brian introduced himself to me. He had a name. He gave me blankets. He had genuine kindness. And it made a massive difference to me. I was starting to despair and he came along and made the day a little better. Then there were a few more days in hospital, with people not introducing themselves, and the ones who did making me feel better and safer about being in hospital."

So she talked to Chris about her experiences, and he said she should do something about it. So she got onto

Twitter, expecting her spontaneous campaign to amount to a couple of tweets and a chat with a few like-minded health professionals. But the catchy hashtag started to spread. Kate started writing articles about her experiences in national newspapers, blogs and then books and the momentum grew. Today #hellomynameis is arguably the most successful health campaign ever launched by an individual in the UK.

"For me, the campaign comes to life when it reaches out of social media into healthcare organisations, when somebody who's seen it on Twitter says 'I want to bring that to my hospital' – and then does. That's when it really has an impact."

The woman behind the hashtag

Kate, of course, underestimates the impact of her own character on the campaign's success. Originally from Huddersfield, Yorkshire, the daughter of teachers, the young Kate worked in the kitchens of a day centre for older people run by her mother, during school holidays. Those experiences of talking to older people, "realising what an amazing bunch of people they are," fed her interest in becoming a geriatrician when she trained in medicine in Edinburgh. Medicine, for her, was not about the science, but the people – talking to them, finding out about them, working out the clues to their illness.

"I can use my experience to say this isn't right, can you think about this, can we change this so that it doesn't have to happen to other people"

Those family-forged values of helping people are at the heart of #hellomynameis... "I think it's the teacher in me that makes me want to write and share my experiences. I teach juniors, medical students and other health professionals at work, and I think it's part of me because of my family. I have this great frustration when I'm sat in a hospital bed, not being able to be a doctor. I'm thinking: what can I do? I can use my experience to say this isn't right, can you think about this, can we change this so that it doesn't have to happen to

other people. It's kind of teaching on a big scale."

Her experiences as a patient, she says, have made her a much better doctor. In particular, she's learned about the importance of sharing information. "It's so frustrating, as a patient, sitting there all day wondering about stuff, wondering whether it's okay to ask about your blood test, whether there's going to be a scan, what happens next. If that information was just shared naturally, things would be so much easier."

She can't understand why some doctors seem to avoid engaging with patients for fear of being asked difficult questions. "I like the difficult questions!" she laughs. "They're more interesting."

"Sharing my story is getting people to be more open about dying. You walk down the street, you don't know who's got a terminal diagnosis do you?"

Some, I suggest, avoid engagement because of time pressures. She bridles: "That's such a fallacy. It's just so wrong." She tells me she was telling her junior doctors yesterday how her 20-minute conversation with a patient's family had provided clues about his condition and circumstances which would help with discharge planning and save hours of time later on. "If you find out about problems sooner, you have strategies to overcome them and save time later on. We think we don't have time, but we do."

I ask her about her "bucket list", which she started writing the day she learned she had metastases. She's ticked off most of the items, including: watching the BBC *Pride and Prejudice* in one sitting; eating fish and chips at a favourite family seaside resort; getting a tattoo; skydiving; learning to make brioche with Michel Roux Junior; eating at the Fat Duck restaurant; starting work as a fully qualified consultant; traveling to Barcelona, New York, Bruges, and returning to Edinburgh and California. Her partner Chris is very good at organising things for her, she says, adding that he never gets the accolades she does. I promise I'll mention him.

But Kate is very aware that her time for achieving more is limited. She tells me how she's had four courses of aggressive chemotherapy since 2011, each time reluctantly.

"It did cross my mind to never start. Most people would say, just give me the chemo: I want to live longer. But I knew how rough this might be. I'd looked after patients going through similar chemotherapy and I'd seen what their mouths looked like, how they lost all their platelets, how they had fevers that wouldn't get better. But at that early point I had a family that hadn't yet come to terms with my diagnosis. I didn't really have much of a choice. I could have been selfish and not had it, but it would have been no good for them."

So each time she's just "knuckled down", accepted "it's going to be rubbish" and got on with it. Each time the treatment has been less effective, and each time her bone marrow has found it harder to recover. She's not sure she'll do it again, she tells me. But she has. Her fifth course of chemotherapy began on 4th April 2016.

A legacy of kindness

The prospect of death is never very far away. "If I knew I were to die tomorrow, I'd feel proud of #hellomynameis, how far we've come with it, and how hard we've worked on it. And I'm proud of things outside health. I'm proud of those little people there," (she points at the picture of her nephew and niece) "and I'll always be the doting aunty who buys too many presents."

And when she dies, if anyone starts talking about her "losing her battle with cancer" she'll turn in her grave, she says. Someone inevitably will, I suggest. "Don't worry, I've got Chris briefed," she laughs.

I suggest to her that the reason people flock to her talks, and follow her life every day on Twitter, is that she refuses to let there be anything 'tragic' about her at all. It's as if she's acknowledging but defying all the bad things about cancer – not by being superhuman, but by being entirely normal. By asserting the simple things that make life worth living: courtesy, family, friendship… and the joys of baking.

In answer, she shows me a small portrait of her (shown on p 21), commissioned as part of an exhibition called 'A Graceful Death'. It portrays Kate sitting on her sofa, smiling – just the way I've been seeing her now. The picture was, she tells me, exhibited alongside harrowing pictures of thin, ill people about to die. "I wanted to define the face of dying a bit like the girl next door. It doesn't look ill. It has a fairly healthy complexion.

"I guess sharing my story is getting people to think about dying, talk about it and be more open about it. You walk down the street, you don't know who's got a terminal diagnosis do you? We're not all tucked up in hospice beds!"

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EORTC NCI AACR 2016	**29 November – 2 December 2016** *Munich, Germany* ENA2016 28th EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics
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12,000
patients screened

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Explaining Europe's survival gaps

More than 15 years after the Eurocare project revealed the UK and Denmark to be lagging behind their western European peers, both countries are still struggling to catch up. **Marc Beishon** asks why?

Eurocare, the landmark series of studies comparing survival of cancer patients among European countries, has been profoundly important in focusing attention on the quality of Europe's cancer services over the past two decades.

Now in its fifth edition, and including data on 21 million cancer diagnoses held in 116 cancer registries in 30 countries, it graphically demonstrates important variations in survival rates, broken down by cancer type, that had previously been hidden. In doing so, it introduced the concept of 'unnecessary deaths' – deaths that could have been prevented with earlier diagnosis or more appropriate treatment – and gave ammunition to advocates and politicians to press for overhauls of poorly performing cancer services.

One of its more notable impacts has been in the UK, whose poor showing in the Eurocare-2 studies came as a shock to a country that had always seen itself as ahead of the field in cancer (see *Survival of cancer patients in Europe: the EUROCARE study*. IARC Scientific Publications No 132). The data showing survival rates for patients in England and Scotland as consistently below the European average were instrumental in prompting the government to introduce a pioneering cancer plan for the National Health Service in the year 2000.

Denmark, another surprise under-performer, reacted in a similar fashion, drawing up its first cancer plan; while in Germany, a certification system for breast clinics was implemented in 2003 partly because poor survival results were identified by Eurocare.

But while the Eurocare studies have undoubtedly fuelled important policy initiatives, questions remain about how far they have actually led to improvements in patient outcomes.

The narrowing of the major survival gap between western Europe and countries of eastern and central Europe during the first decade of the new millennium would appear to show that they have. Yet the underperformance of the UK and Denmark has continued as a notable feature of successive Eurocare studies, up to and including Eurocare-5, published at the end of 2013 (see, for instance, http://tinyurl.com/eurocare-5).

Attempts to analyse why this is happening have focused attention both on the reliability of the data, and on the need for additional comparative data that could help throw light on what lies behind survival differences, to better inform efforts to tackle them. And the hope is that Europe will have its first unified cancer information system in the next few years, with a first step – an interactive visualisation tool of incidence, prevalence and survival – on track for release by the end of 2016 (see box p 22).

Can we trust the data?

The Eurocare team, based at the National Cancer Institute in Milan and at the Italian National Public Health Institute in Rome, do discuss the limitations – and strengths – of their studies at length in their publications, so there should be no confusion about the interpretation of the findings. In the summary of results for Eurocare-5, they flag up a number of issues. These include the "unexpectedly high" survival rates some countries show for cancer types that are rapidly fatal; variations in case mix for cancers in the same main type (such as small-cell vs non-small-cell lung cancers); the well-recognised problem of the impact of screening in raising incidence and survival rates through overdiagnosis and lead-time bias in prostate, breast and melanoma in particular; and bias introduced by data that comes from cancer registries predominantly in affluent areas of a country (Italy and Belgium are mentioned).

But the key limitation is a big one – that there are no data on major prognostic factors such as stage at diagnosis and treatments. Without these it is not possible to fully assess the reasons behind survival differences, they report. At present, these data are available only on an *ad hoc* basis, as cancer registries do not systematically collect such clinical data and, even if they did, cancer staging practices vary across the continent, which would be another barrier (in Eurocare-5, of the 116 participating cancer registries, 43 did provide stage data for breast cancer but only 12 for prostate, for example).

Another shortcoming inherent in survival studies of this sort is that Eurocare is a retrospective study that records the five-year relative survival rates for patients diagnosed up to 14 years earlier. The current analysis, published in 2013, covers the period 1999 to 2007, and a lot can happen in healthcare systems and

ECIS: A cancer information system for Europe

The European Cancer Information System (ECIS) is a joint project of the European Commission's Joint Research Centre and the European Network of Cancer Registries (ENCR). It aims to provide European countries with a range of indicators that can be compared across registries and over time.

The first aim is an interactive visualisation tool of already published aggregated and anonymous data of incidence, prevalence and survival. But a wider set of possible indicators is already available from the Eurochip project, while others have yet to be developed, and in total could include those shown here.

In essence, the project aims to marry high detail, individual level data from clinics and registries with low detail, aggregated data from demographics/socioeconomics, and health systems.

Of particular importance are 'high-resolution' individual data to bridge the gap between simple description and the effective interpretation and public health use of cancer data (high-resolution studies have originated from the Eurocare database, where sampling of patients with more detailed clinical information has been carried out, and there is now a range of such studies in the Era-Net Transcan-2 Highcare project, and also in Rarecare, on rare cancers).

- **Prevention** – fruit and vegetable consumption, smoking, body mass index, physical activity, alcohol consumption, sun exposure (from sources such as the European Health Interview Survey, EHIS, plus new ones on sun exposure for example)
- **Screening** – mammography, pap smear, colorectal (EHIS and official member state reports)
- **Treatment and clinical aspects** – radiotherapy equipment, CT/PET/MRI scanners, surgical procedures (hysterectomy, prostatectomy, breast conserving/mastectomy etc.), stage, compliance with guidelines, treatment delay (from Eurostat, OECD, Eurochip plus new sources on staging, guidelines and delays)
- **Macro social and economic variables** – health expenditure as % of GDP, anti-tobacco regulation, cancer patient costs (Eurostat, WHO; cost would be a new one)
- **Epidemiology and cancer registration** – registry coverage, incidence, survival, prevalence, mortality (IARC, Globocan/ECO, Eurocare, Haemacare, Rarecare, Europreval, Eurostat)

See also the European Network of Cancer Registries – www.encr.eu and the European Cancer Observatory – www.eco.iarc.fr, for details on 'precursor' projects. www.tumori.net/eurochip has details on the now concluded cancer health indicator project.

cancer guidelines between then and publication. (Eurocare-6, though, will analyse the prognosis for patients with a diagnosis between 2005 and 2012 with a follow-up to 2013, reducing the gap between data collected from registration time and published data.)

As for strengths, Eurocare-5 goes some way to addressing a major criticism of previous versions – lack of coverage. "National registries of Bulgaria, Estonia, Latvia, Lithuania, and Slovakia are now included," write the team, "and population coverage also increased for other countries: from 1% to 23% for Germany, 34% to 100% for Netherlands, 8% to 100% for Czech Republic, 43% to 77% for Portugal, and 27% to 36% for Italy."

And looking back at Eurocare-4, published in 2007, some of the criticisms levelled at the time of publication seem unfounded, in particular on the quality of the data and the lack of coverage.

The increased coverage now in countries such as Germany has not changed their survival ranking; indeed, the Czech Republic, which upped its population contribution to 100% in Eurocare-5, showed increased survival, not less, as might have been expected for a whole-country sample.

The Eurocare team also take pains to explain the rigorous quality control procedures they apply to the datasets. They point out that, even if one were to assume there is a high number of errors in cancer registries, this would still not explain the differences between the UK and other comparable European countries (there is a simulation study on this).

It is natural for oncologists to defend their practices and outcomes, and certainly there are many questions that can still be asked about the applicability of the data. But in the UK, the finding of Eurocare-5 that the country is still lagging behind its western European peers, albeit with a narrowing gap in some cancers, has been broadly accepted.

Finding out more

The issue now is to find out why and take steps to improve the situation. The key, for many, will lie in 'drilling deeper' to get a clearer picture of certain aspects of services and outcomes.

The Eurocare authors talk broadly about the possible explanations for differences between countries, which they say include "differences in stage at diagnosis and accessibility to good care, different diagnostic intensity and screening approaches, and differences in cancer biology". Variations in socioeconomic factors, lifestyle, and general health between populations might also have a role, they add.

They also mention analyses that have been done in the UK to try to explain its relatively poor performance – in particular the role of late diagnosis (which is also a possible factor in Denmark, not least in lung cancer). Unequal access to and underuse of treatments have also been mentioned as contributory factors – older women in England, for instance, have been reported as having more non-standard treatments than younger patients.

For Richard Sullivan, director of the Institute of Cancer Policy at King's College, London, the answers are to be found in joined up thinking about data and processes. "Epidemiological data is vital – you need mortality, survival, prevalence and incidence to tell you different things about your health system. But we have to drill down deeper to understand the differences, such as by adjusting for the stages of cancer that people present with.

"The countries making the most progress, such as the Netherlands, are the ones able to use the data to develop quality systems and processes for the delivery of care, down to factors such as the volume of surgery needed at a centre, the amount of radiation fractions to provide and so on."

This also depends on policymakers gathering the data and understanding how healthcare systems should be organised and prioritised to provide cancer services, he adds. Much of this goes by the board in less regulated countries, particularly in eastern Europe. "Because of the lack of outcome data, people are able to claim what they want without being held to account. A big problem is that epidemiological systems are often poorly funded – registries are just not as sexy as other things such as drugs," says Sullivan.

A number of countries, such as Greece, do not yet have national population cancer registries, or indeed properly implemented cancer plans, and while it is possible to model data across regions and population groups – Eurocare divides its datasets into regions – the type of high-level intelligence that also involves the regulatory and economic issues needed to plan and implement cancer services is often lacking and not prioritised, he adds.

Where's the UK going wrong?

The UK, meanwhile, has different health systems in its four constituent countries, and although much work has gone into developing tumour-based clinical pathways and other processes, most cancer services are carried out in general hospitals, and systems are subject to constant reorganisation and changes in commissioning policy, according to fiscal cycles, notes Sullivan.

The latest cancer taskforce report for England – *Achieving World-Class Cancer Outcomes* – which sets out a strategy up to 2020, once again uses international comparisons, noting that the gap in survival between the highest performing comparable countries (Australia, Canada and Sweden) and the lowest (England, Northern Ireland, Wales and Denmark) remains largely unchanged, except in breast cancer.

"Commissioners consistently report they have neither the expertise nor the time adequately to commission complex cancer services"

It recognises the higher incidence of cancer in deprived groups, but argues that differences in one-year survival among England's clinical commissioning groups cannot be explained only by deprivation levels (although certain factors can be critical, such as the higher incidence of triple negative breast cancer in African–American women). The report also references Eurocare-5 in noting that treatments have become more important in accounting for international differences.

But commissioning of cancer services has become highly fragmented, and the strategy taskforce claims that commissioners "consistently report they have neither the expertise nor the time adequately to commission complex cancer services, many of which are changing rapidly as research drives progress." Fragmentation of services is also cited as a problem by the head of the Danish Cancer Society.

The English taskforce comes up with a number of expected recommendations, such as retargeting early diagnosis efforts, replacing outdated radiotherapy equipment, and rolling out a national molecular

Drilling down for explanatory data

Survival data indicate that older women in the UK have poorer survival than their peer group in neighbouring countries. Drilling down to look at treatment data reveals that the poorer survival could be because in the UK they are less likely to be treated according to guidelines. Drilling down further, to look at the use of geriatric assessment, could reveal whether they are being undertreated because of unwarranted assumptions about their fitness, or whether this generation of women really is more frail in the UK than in neighbouring countries, in which case less aggressive treatment could make sense.

diagnostic service. But possibly one of the most interesting proposals is to provide better metrics that give more rapid feedback through a 'dashboard' that will include regularly updated data on the vital statistics of a service, which could help address complexity.

For Sullivan, this is fine, but he argues that reports like this one are too often written by insiders rather than external experts, and there is resistance to taking the hard decisions to act on data. He gives as an example research carried out by Henrik Møller's group at King's College, which found that hospitals in England that carry out high volumes of surgery for non-small-cell lung cancer have more patients who are older, of lower socioeconomic status and have more comorbidities – and yet achieve better survival. "But despite this we seem to be unable to consolidate thoracic services in England," says Sullivan.

This is the type of study that interests Lars Holmberg, a breast cancer surgeon turned cancer epidemiologist, who also worked at King's but is now back home in Sweden at the Uppsala/Örebro regional cancer centre. Holmberg has led epidemiological studies such as a comparison of prostate cancer survival in England, Norway and Sweden (*Cancer Epidemiol* 2012, 36:e7–e12). His view of the international comparative studies is that they do have major limitations, and "making far-reaching conclusions from them is a mistake". They do, however, provide important indicators to drill down into to try to discover reasons. "And maybe it's not that useful to keep on doing these broad comparative studies – perhaps we should ask more specific questions about possible interventions," he suggests.

Holmberg points out that attempts to improve the data by which to compare countries, such as adding the stage at diagnosis, may not be very productive, as clinical variation may be great, even if the quality of the data is fine. And patients in one country who present late may get better treatment than in another country, which could confound comparisons.

During his time in the UK, Holmberg recognised that later diagnosis, especially in cancers that are curative when caught early, is one explanation for the country's poorer outcomes. He also echoes other commentators in flagging up undertreatment of older patients as a possible contributory factor. "When comparing England and Sweden, England appears to recommend active treatments for older people less frequently, although that may have changed now," he says. He cautions, however, that lower rates of active treatment could be appropriate if older people in England have more comorbidities, in which case, he says, "it wouldn't be reasonable to put them through the stress of treatment."

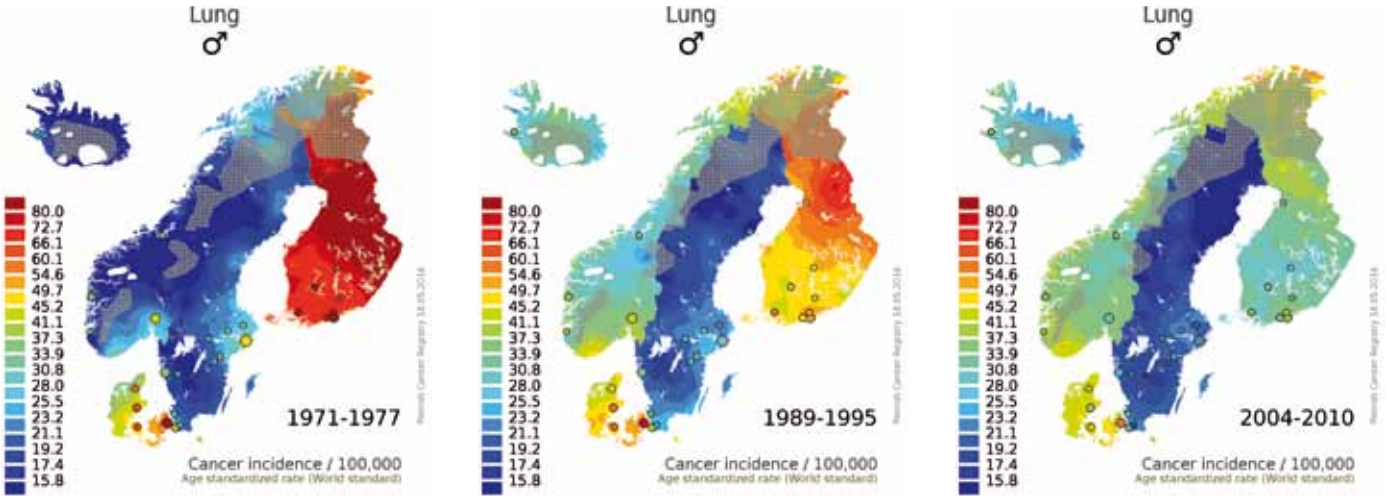
> **"Perhaps we should ask more specific questions about possible interventions"**

Holmberg suggests that a study on geriatric specialists assessing older people for treatment would be a good example of research that is worth performing across a select group of countries. "What I've seen in epidemiology is that pure data gathering is often over-emphasised, and hypothesis testing under-emphasised," he says.

Even Sweden needs to drill down…

Sweden has good data, through mandatory cancer registration and clinical audit of hospitals, and is among the top-performing countries for cancer. But even here, clear differences in outcomes are apparent between regions and between socioeconomic groups, says

Analysing trends



Interactive maps on the Nordcan site (http://www-dep.iarc.fr/nordcan.htm) allow you to track trends over time in continuous sequences – shown here are snapshots of male lung cancer incidence at three time periods. The method used, "small-area based smoothing method for cancer risk mapping", is described by T Patama and E Pukkala (*Spat Spatio-temporal Epidemiol*, in press)

Holmberg. It is the deeper study designs that are needed to root out the causes, he argues, mentioning a prostate cancer clinical database project in Sweden, PCBaSe, which found, for instance, that the diagnostic assessment of patients can differ by socioeconomic status. "Higher status men get a more thorough work-up," he says. Again, this could be the basis for a cross-country study.

A similar story has been reported for breast cancer, where Swedish counties with less good results have been found to differ from others, again through the intensity of diagnostic work-up. "Maybe the women with less good outcomes got the right treatment based on what the oncologist knew, but maybe the information was wrong," says Holmberg. Was socioeconomic status a factor? It is a question worth answering, he feels.

The extent and quality of multidisciplinary working is another factor suggested by Holmberg as a possibility for investigation. "My view is we tend to look at surgeons and their volume of work, but we have neglected to look more deeply at teamwork, all the way from diagnosis to follow-up. It doesn't help to have a high-volume hospital if processes are disorganised."

The Eurocare team adds that studies on process, such as organisation of care, are indeed important, and also mentions survivorship and quality of life research, and outcome research, which identifies short-term outcomes as surrogate endpoints of survival. But they stress that large-scale comparisons remain important to study the overall impact on survival over time and regions.

Putting data to work

Someone who is well-placed to pull much of this discussion together is Alexander Katalinic, director of the Institute of Cancer Epidemiology at the University of Lübeck, Germany. He is in charge of the regional cancer registry (Schleswig–Holstein), chair of the Association of Population-Based Cancer Registries in Germany, chair of the steering committee of the European Network of Cancer Registries (ENCR), member of the Eurocare steering committee and, not least, one of the team behind the nascent European Cancer Information System (ECIS).

"It doesn't help to have a high-volume hospital if processes are disorganised"

He confirms that Eurocare has been important for Germany, especially in stimulating the setting up of registries that now cover the whole country, as well as a 2013 law that compels all regions to collect more clinical data to do more quality assurance. Speaking about the Schleswig–Holstein registry, Katalinic says it has complete data for the region.

"And we really use the data – it isn't a graveyard as some are," he says. "We have good contacts with the clinicians in the region, and of course they want good results for their patients, and the registry enables them to discuss the quality

of their clinics. Benchmarking means learning from the best in an atmosphere of trust – no one, especially the hospital managements, wants to see their clinic's data exposed as poor in the newspapers." As a cross-border example, Schleswig –Holstein ran a project with neighbouring Denmark comparing lung cancer survival. It found that those Danish patients who survived more than six months had the same survival as patients in the German region, which could prompt hypothesis-driven research into possible socioeconomic, comorbidity and other factors that Holmberg advocates.

"Benchmarking means learning from the best in an atmosphere of trust"

Katalinic though is much more bullish about the potential for large-scale comparative data as a policy tool. The ECIS has grown out of various European projects including Eurocare, Eurocourse (on the development of population-based cancer registries), the Eurochip cancer health indicators initiative, and in particular the information and data work package of the European Partnership for Action Against Cancer, led by Milena Sant of the Eurocare team at Milan's Istituto Nazionale dei Tumori.

It aims to provide a single interactive platform for exploring comparative data, by country, age, gender and time point, on incidence, mortality, prevalence and survival, together with a range of additional cancer health and system indicators (see box p22). Importantly, says Katalinic, it will be set up to be sustainable, with a project team at the European Commission's Joint Research Centre in Italy committed to its development. There is much to do on data analysis and quality, and the project should also highlight 'white spots' around Europe where there is no or limited registry data.

One of the first tasks of the new information system will be to publish data on cancer incidence, which Katalinic says can translate into public health action. "Countries can benchmark incidence in the same way as we are doing survival – take colorectal cancer, where, if you monitor where screening is in place, you can now see clearly where incidence is falling."

One of the aims, he says, is to create an interactive tool, similar to Nordcan, which is already up and running for the Nordic region, hosted by the International Agency for Research on Cancer, IARC.

One such tool (see p 25) enables users to see comparative trends in incidence and mortality, through an animated colour-coded map, operated by a digital slider that moves from one time period to the next. The information can throw light, for instance, on how lung cancer incidence has responded to anti-smoking policies, says Katalinic.

In the longer term, the key aim for ECIS is to make available individual-level data, like the US SEER – Surveillance, Epidemiology and End Results – programme, which researchers can draw on for high-resolution studies to explore the impact, for instance, of compliance with guidelines on survival or mastectomy rates.

Key to it all will be ensuring high-quality data, says Katalinic, who adds that, despite reservations by some, it is possible to collect more clinical data such as tumour stage that will be amenable to comparative analysis.

Indeed, a new data protocol for European epidemiological cancer studies has already been defined, which envisages the collection of standard data on stage at diagnosis and summary treatments, so that over the next few years, incidence and survival by these factors will be available for research (see ENCR's data call 2015, www.encr.eu/index.php/activities/2015-call-for-data).

What can data do?

Will this give countries like the UK and Denmark – or indeed countries that rank even lower – the information they need to address the problems that dog their cancer systems? The indications so far would suggest probably not.

Given the complex interactions where social inequality and differential access to resources may be overriding factors, it is unlikely that focusing on individual disparities, for instance in late diagnosis, or access to new drugs, or hospital systems, will make a big difference. Indeed, the Eurocare team stresses that interventions that address the whole system, rather than measures for selected groups of patients, are likely to make the most impact on survival. But in the future, ECIS data could be essential to generating hypotheses that could be tested in the sorts of studies advocated by experts like Lars Holmberg.

It could also provide an invaluable audit service. As well assisting policy makers in teasing out the implications of five-yearly reports of survival data, it will aim to provide other comparative information on a range of quality indicators that are not routinely collected by cancer registries, and which could be available much sooner, so that problems can be picked up quickly and the impact of remedial actions on those indicators can be monitored effectively.

But health policymakers across Europe do need to support cancer registries in collecting more basic clinical data to pave the way for a wider indicator set.

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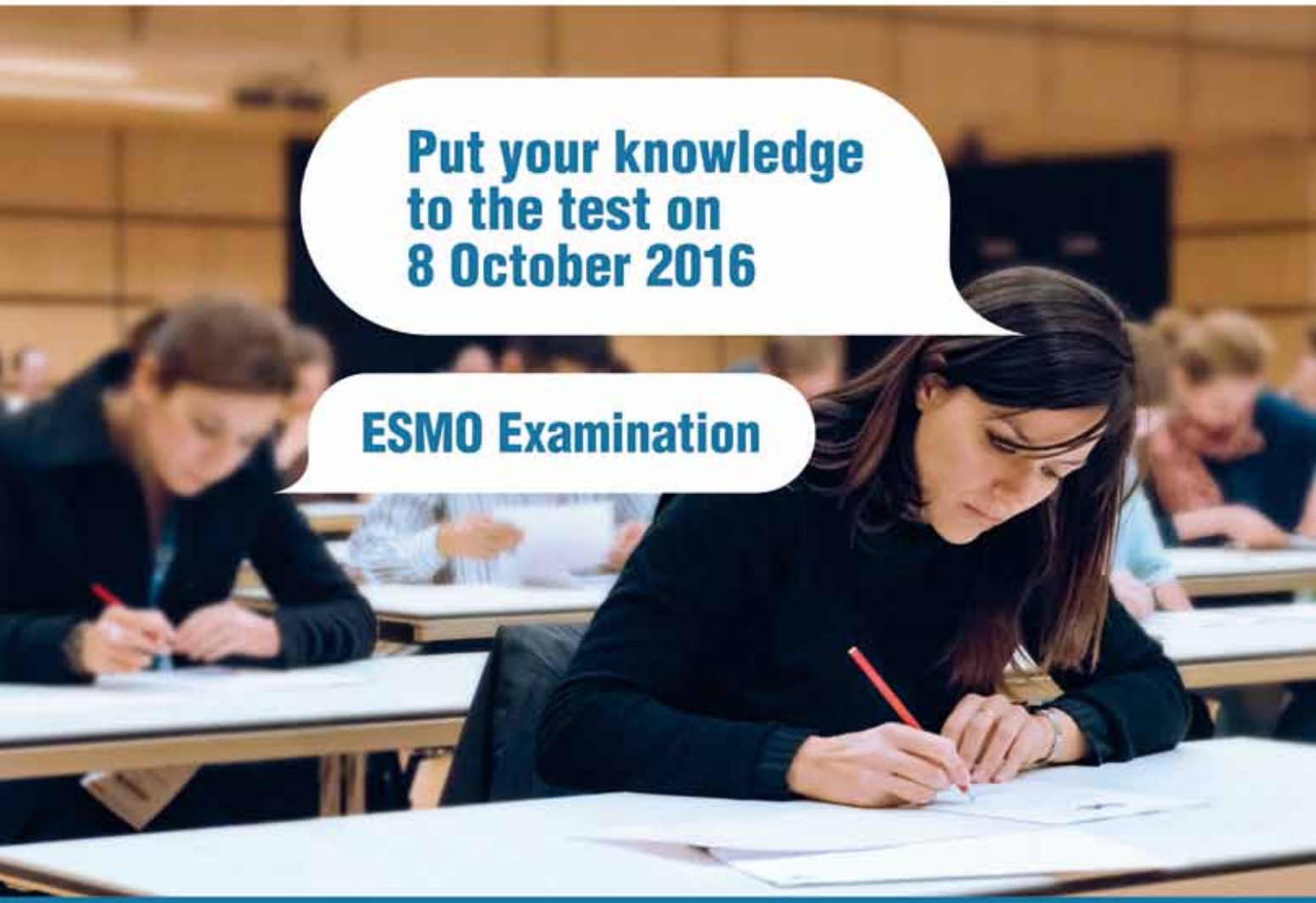

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Doctors and nurses:

We work as a team – why not train as a team?

Patients get better care when doctors and nurses communicate well and each profession understands and respects what the other contributes. So shouldn't their training prepare them for teamwork? **Maria Delaney** reports.

Mr Lloyd is angry! His elderly mother is getting no treatment for her metastatic lung cancer, and he doesn't want to hear what the doctors and nurses are saying…

…A different approach by a new face. They understand why he is angry. Their rationale make sense. His anger fades…

"What is happening now?" facilitator Anne Arber, cancer and palliative care lecturer at the University of Surrey, asks the participants. They are a mixture of oncology nurses and registrars, and have been asked give feedback on the method that their colleagues used to communicate to the relative. They are then asked to put themselves in the place of the patient's son. Denial to acceptance. Anger to sadness. Suggestions come in from across the semi-circle of seats facing the mock consultation room.

The facilitator then turns to 'Mr Lloyd'. "And is that how you feel?" Christopher Webber, an actor-facilitator who assumed the angry relative role twenty minutes before, answers in detail. His 25 years of experience enables him to immerse the nurse or doctor sitting opposite him in the interaction. He is acting, so that they don't have to.

This communication skills session was part of the masterclasses in clinical oncology (ESO–ESMO), and oncology nursing (ESO–EONS), which took place jointly and in parallel in Switzerland in March. The participants come up with the role that the actor plays. Common themes are breaking bad news to a patient, dealing with an angry relative, and interacting with a difficult colleague.

This sort of multiprofessional training works well for communication skills, according to Andrew Hoy, retired UK-based palliative medicine physician, who facilitated a session at the same time as Arber. "Although some of the detail may be different for different professional groups, the generality of skills and attributes is much the same," he says, adding that, "the professional groups learn from each other."

Instead of 'Mr Lloyd', the participants in Hoy's session were interacting with 'Mrs Jones', a cancer patient, played by actor Debbie Manship. She agrees with Hoy. "Because it is communication-skills based, the difficulties for the participants, regardless of what their profession is, are very often common," she explains.

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Lena Sharp, president elect of the European Oncology Nurses Society (EONS), and co-chair of the nursing masterclass is a big believer in interprofessional learning – the term used, she says, to describe two or more professions learning with and from each other. Interaction is key, she explains. "It's not sharing the same lecture room. That's not enough."

Sharp feels that it's an issue in healthcare that, once you finish your education, you're supposed to be very good at interprofessional communication, despite not having been educated together. It's a real problem, she says, and she would like to see more interprofessional training developed.

The concept is not a new one. The WHO first identified interprofessional education as an important component of primary healthcare as far back as 1978, and issued its technical report on this subject in 1988.

The report made a number of recommendations, including that communication between health professionals at all levels should be encouraged and improved, and continuous joint in-service training should be provided for all members of the health team, with a view to strengthening the team approach in the field.

"I've seen progress but it's too slow," says Sharp, who adds that only a few universities have developed medical education that encompasses interprofessional learning. When it is added, it is often voluntary or only a small part of the curriculum, she says.

This fact is evident in the ESO oncology masterclass. It is the first time that many of the doctors and nurses have trained with other professions, despite years of medical training. "It's not a common practice. I've only seen it here," says Cypriot nurse participant Loizos Hadjulois. He feels that it should be more common because they are part of the same team and need to cooperate all the time. "But for some reason, we don't train together."

"It was useful in the communication skills session to get input from the nurses," says English oncologist participant Michael Davidson. He believes that there is scope in medical school to include other professions.

ESO's Scientific Director, Fedro Peccatori, says the 'silo culture' in oncology, and other specialties, where "the doctor is the doctor, the pharmacist is the pharmacist, the nurse is the nurse" needs to be changed. He argues that, from the last year of medical school, "it would be best to have the notion and the idea that multi-professionality is the way that medicine is going."

A specialist in women's cancers, Peccatori feels that, while the practice of medicine has changed dramatically

Benefits of interprofessional education

World Health Organization

The WHO advocates interprofessional development to improve the education of health professionals and consequently health outcomes. Its 2010 report, *Framework for Action on Interprofessional Education and Collaborative Practice 2010*, identifies key benefits accruing from health professionals learning together. It also presents strategies and ideas that have been designed to help health policy makers implement the elements of interprofessional education and collaborative practice that are likely to be most appropriate for their particular setting.

Educational benefits

- Students have real world experience and insight
- Staff from a range of professions provide input into programme development
- Students learn about the work of other practitioners

Health policy benefits

- Improved workplace practices and productivity
- Improved patient outcomes
- Raised staff morale
- Improved patient safety
- Better access to healthcare

Source: WHO Framework for Action on Interprofessional Education and Collaborative Practice 2010 (www.who.int/hrh/resources/framework_action/en/)

over the past few decades, and there is a strong feeling in the medical community that integration is a positive thing, much more progress is needed in this area. "The knowledge and capabilities are there, but the integration is still something that happens in some [areas] but not everywhere," he says.

Ahead of the field

One university in southern Sweden embraced interprofessional learning thirty years ago. The dean of the Linköping medical faculty was inspired by a WHO conference where he learnt about multiprofessional education, as they called it then. The different professions in the department began working with each other, and it was integrated into the curriculum in 1986. Tomas Faresjö, professor in the Department of Medical and Health Sciences at Linköping University, explains that they made the change, "because the challenge for future healthcare needs cooperation between disciplines and occupations."

Faresjö distinguishes between what they do, and 'multiprofessional education', which he defines as different professions attending a course or lecture together, and is, he says, quite common.

Each group has three weeks to identify a quality improvement in healthcare, in a challenge set by clinics

"We decided that we should have more integration, and that's why we call it 'interprofessional education'."

The interprofessional education of undergraduates is divided into three stages. In each of these, all professions in the medical department work together. This includes medics, nurses, physiotherapists, occupational therapists, and biomedical science students.

"In the first semester, 30 years ago, we devoted a lot of time," says Faresjö. All students in the medical department attended courses together for 10 weeks. "We're breaking down borders early, and I think that's important."

The department then decided that more shared learning was required further into the undergraduate education. After two years, the professions once again work together. This time as part of a base group of eight students and one tutor.

Each group has three weeks to identify a quality improvement in healthcare, in a challenge set by clinics in primary care or at the university hospital. "What is interesting is that they go very quickly into their roles and work together in teams," says Faresjö, who is a tutor on these challenges.

Finally, at the end of their time as undergraduates, they move onto a training ward, where they practice working together professionally, as a team, with supervisors. "They are responsible for finding their own roles in the team, for example supporting elderly people in the orthopaedic clinic," says Faresjö. He proudly reports that they

were the first in the world to start this programme of clinical wards for student training.

Sharp has been to Linköping and says that she can see a difference in the hospital. "This is impacting healthcare a lot, because you don't have the strong hierarchical structures [in Linköping] that you have in other hospitals," explains the nurse trainer. This is because the staff train together, she says, so they know the competencies of the other groups, which improves collaboration.

"If you can educate people early on in their training, then it's natural," says Sharp. She adds that there are traces of this type of education in other universities in Sweden, but Linköping is the only university to do it so systematically.

Team work. Doctors and nurses discuss how to handle difficult conversations with patients, relatives or colleagues, after watching a role play at the ESO masterclass

Oncology education

Shared training can be seen in action at the ESO oncology masterclass. Here the two professions work together during interactive interprofessional sessions such as communication training, and they also share many lectures. They are trained separately for more technical sessions, which are geared towards either doctors or nurses.

This method is also used by the École de Formation en Cancérologie (EFEC), which offers training to healthcare professionals caring for patients with cancer in France.

The majority of their courses are interprofessional. These include courses related to supportive care – nutrition and cancer, sexuality and cancer, fatigue and cancer, psychological social and intercultural aspects of care, palliative care – as well as communication skills and organisation of supportive care. Other courses are aimed at a single profession, because the learning outcomes are different and specific to that profession.

For some courses which address the organisational aspect of care, such as setting up the patient pathway, it is strongly recommended that two healthcare professionals from the same hospital but different professions attend the course, according to Françoise Charnay-Sonnek, president of the European Specialist Nurses Organisation (ESNO) and education head of the EFEC School for Continuing Training, specialising in cancer. She explains that this is because the aim of the course is to facilitate the implementation of the new organisation in the hospital.

Charnay-Sonnek says that it is difficult to attract doctors to these interprofessional courses, as three days may be too long for physicians, and some of them can be a little reluctant to be mixed with nurses. She adds, however, that when they do attend, their feedback is very positive, as this kind of course offers them the opportunity to get know other professions and be more open to listening to them. Doctors and nurses have a very rich experience, says Charnay-Sonnek. "They gain knowledge, and can exchange tips and tricks."

The school runs courses in setting up patient pathways, and learning from error. For these, doctors, nurses and other healthcare professionals attend from the same hospital. Charnay-Sonnek says that when participants are out of the hospital and in the training venue, they are much more open to listening to other professions.

Sharp argues that subjects such as communication, safety, ethics, and some disease topics can be adapted well to shared training. "You can't say that safety is the responsibility of one profession – it's everybody's," she says.

To encourage different professions to interact, she suggests a method called the 'flipped classroom', where a student or participant presents to their peers. Case methodology is a good way of doing this, she says.

Peccatori agrees. Case presentations are currently done by each profession

separately at the ESO masterclass. However, he feels that, when discussing a case, "there are some nuances that you can only get if you have a multiprofessional discussion."

Challenging hierarchies

Routine evaluation of the impact of interprofessional education on health outcomes and service delivery are rare. However, a WHO questionnaire that elicited almost 400 responses from 42 countries, highlighted a number of benefits (see p 30). These include raised staff morale, improved patient outcomes, and students having real-world insight.

This questionnaire was part of a 2010 follow-up report, the *Framework for Action on Interprofessional Education and Collaborative Practice*. The WHO report identifies interprofessional collaboration in education and practice as an innovative strategy that will play an important role in mitigating the global health workforce crisis.

Hoy, who facilitates communication sessions, cites another benefit: removal of status differences between the professions. Hoy believes that "it's a great mistake to feel that some healthcare professionals are intrinsically lower status than others." Shared education, he says, is one of the ways around this.

Lack of confidence, especially among nurses, is a big issue, says actor-facilitator Webber. When people are empowered to stand up independently, and come out with an opinion in a role play situation, he says, "You quite often see a bit of light dawning in people's minds."

Being unable to speak up can be tackled through shared training, says Sharp, who knows people in management positions who say they will not question doctors directly. "That is really important to lift… especially in healthcare, when we are handling life or death situations."

Sharp knows people in management positions who say they will not question doctors directly

Improvements in self-confidence and perception have been shown in a small study of medical and nursing students who participated in a three-hour interprofessional learning session (*Nurse Educ Today* 2014, 34:259–64). Separate research (*J Hosp Med* 2014, 9:189–92) has also shown that it improves knowledge and teamwork.

There are also many challenges faced by those implementing or teaching interprofessional education. The main one is the attitude of both doctors and nurses, says Sharp.

In France, you still have physicians who feel superior to nurses, according to Charnay-Sonnek, who says that some doctors prefer not to train with nurses, but those who do "are always very happy, and come back with new ideas… not only knowledge, but also a new multiprofessional vision in all of their care."

Retired doctor, Hoy, believes senior professionals, particularly doctors, may feel more inhibited if other professionals are present during training. "They take some comfort from a uni-professional group," he explains, but he thinks this attitude is quite rare.

When facilitating groups with more than one profession, he says, it's important to be as inclusive as possible to encourage the quieter members to contribute. Erika Juhlin, a nurse participant from Sweden, said that she would have preferred it if there was one case for nurses and one for doctors, because they often had different perspectives. She thinks it would be a learning experience for the doctors to see how her nurse colleagues would handle it, "because they are rarely in the room together with a nurse and a patient without being in control of the conversation."

Making the change

Many points voiced about interprofessional learning by the participants of the ESO masterclass agreed on one thing – that more time was needed so that all participants from all professions got the opportunity to contribute, and voice their opinion.

Securing enough time for interprofessional education is a challenge the medical department in Linköping had to address from the very beginning. "The main criticism is that you're taking a lot of time from the normal curriculum, especially for medical students," says Faresjö.

He looks to national evaluations to prove the critics wrong. Despite providing many weeks of interprofessional training, he says that Linköping came out best in Sweden in every type of test. "That speaks for itself. It can't be true that we are taking a lot of knowledge away from the normal curriculum, and [the students] get less education," says Faresjö, who argues that the reverse is true. "They get more education."

So where could a medical department start? Boundaries within the department need to be broken down, according

The Linköping way. Interprofessional learning is built in to the curriculum of this Swedish teaching hospital, fostering mutual respect and breaking down hierarchies

to Faresjö, as every faculty within the department has its own system of education which, "like a guardian, they want to protect." This often means starting from the beginning with a new curriculum, rather than trying to add time slots into an already full schedule.

Most medical faculties might say that they can't devote a day, perhaps only an afternoon, warns Faresjö, when asked about barriers to implementation. In order to get around such obstacles, he recommends looking at existing subjects that could be integrated.

The communication training at the ESO masterclass was first given just to oncology nurses. "It was quite provocative to even suggest that we do the communication skills together," says Sharp. "When we first raised it, we were met with, not resistance, but questions: Could we really do that? Can we really mix these two groups?" Sharp said that these queries were answered when some of the doctors observed the nurse-only session. The mixed session is now in its third year.

Despite providing many weeks of interprofesional training, Linköping came out best in Sweden

"In oncology, this masterclass is important because we are getting further and further," explains Sharp, who welcomes the advances in interprofessional learning being made each year, and says that they need to keep pushing forward with it.

Though some progress has been made across the world, there is still much to do to achieve the goals that the WHO recommended almost thirty years ago. Peccatori, who is in charge of shaping ESO's educational programme, says that "innovation in education is really difficult to achieve in a short time, and it takes almost a generation to do that, but it is changing."

Awareness of the problem is key, according to Peccatori. "If there is more awareness of the need for integration between the different professionals, I think that this will become easy to implement."

Caught between cancer and a conflict zone

Conflicts in the Middle East have all but destroyed some functioning national systems of cancer care, while refugees who have cancer now depend on structures that are not designed to meet their needs.

Richard Sullivan is Director of the Institute of Cancer Policy and Conflict and Health Programme at Kings Health Partners

Cancer is not the first thing that springs to mind when one thinks about conflict and refugees, but bear with me and I will explain why this is such a problem now. Back in the 2000's I was involved with a European Investment Bank initiative to fund, build and resource two new cancer centres in Syria; one in Aleppo and one in Homs, which respectively saw 36% and 14% of all cancer referrals. Despite being a demographically young country, 73% of avoidable mortality in Syria was due to non-communicable diseases (NCDs).

Syria had not only fully transitioned from a low- to a middle-income country, but it was also host to an influx of refugees from Iraq, and by July 2007 it hosted some 1.4 million, which was increasing at a rate of 30,000 per month.

Outside some stable urban centres, cancer control and care has now ostensibly been wiped out across Syria. With an estimated two thirds of healthcare professionals now refugees (see www.sams-usa.net/foundation/), rebuilding any sort of 'national' cancer control system will take a generation, or more.

Across the Middle East and Africa, protracted armed conflicts, some now lasting more than a decade, are having dramatic effects on migration. By the end of 2014 the UN estimated that there were some 19.5 million refugees, of which 2.9 million were not under UN protection. Internal displacement had also reached nearly 40 million.

What has been so different over the last decade is that this is happening to demographically transitioned countries like Iraq, Syria and Libya, with ageing populations and high burdens of cancer prior to the outbreak of conflicts. In many cases these countries had reasonably developed levels of cancer care.

The new humanitarian space is one in which NCD control and management is now absolutely necessary. The problem is that humanitarian models of care have developed around delivering acute care for infectious diseases, trauma and maternal and child health.

Cancer is a completely new care paradigm for the likes of Médicins sans frontières and the Red Cross. Less obvious impacts of conflict include the likes of Palestine, where isolation and counter insurgency tactics have meant little infrastructure and expertise is available for treating cancer (*Med Confl Surviv* 2014, 30:4–10). A blogpost by Shayma al-Waheidi about the challenge of improving breast cancer outcomes in Gaza gives one some idea of what this means for the average cancer patient (thecancerblog.net/closing-the-40-survival-gap-in-gaza). Even non-traditional conflicts, such as

No cover. Only a small fraction of refugees with cancer get access to the treatment they need

the drug wars in Latin America, have reduced access to cancer care in some regions of Mexico to almost zero, as healthcare professionals have left.

Good cancer care requires all the attributes of a functioning healthcare system, and these are exquisitely sensitive to conflict. But the nature of today's conflicts – protracted duration, intrastate, fought by irregular armed groups, and fuelled by economic opportunities and ethnic rivalry – have created an even more toxic environment for any sort of cancer care during the conflict or in the long tail of the post-conflict period (*Lancet* 2010, 375:341–345).

Prevention policies for cancer and other NCDs also dramatically suffer. Smoking prevalence, for example, has jumped to over one third of the population in Iraq, with a parallel collapse in governance and legislation around anti-tobacco measures. The UN Refugee Agency, UNHCR, has continued to struggle with the burden of cancer in refugee camps under its care.

Health services for refugees are nominally capped at $1,000–$2,000 per person per year, which is far short of even the cheapest cancer treatment. Refugees diagnosed with cancer have to have their cases reviewed on a per patient basis by the UNHCR's Exceptional Care Committees.

In Jordan, between 2010 and 2012, only 511 of the cases reviewed were for cancer (only a fraction of what would be projected to be diagnosed in the camps). Of these, breast, colorectal and soft tissue cancers made up the majority (44%), but only half were authorised for treatment, with poor prognosis a major cause of rejection (*Lancet* 2014, 15:e290–e297).

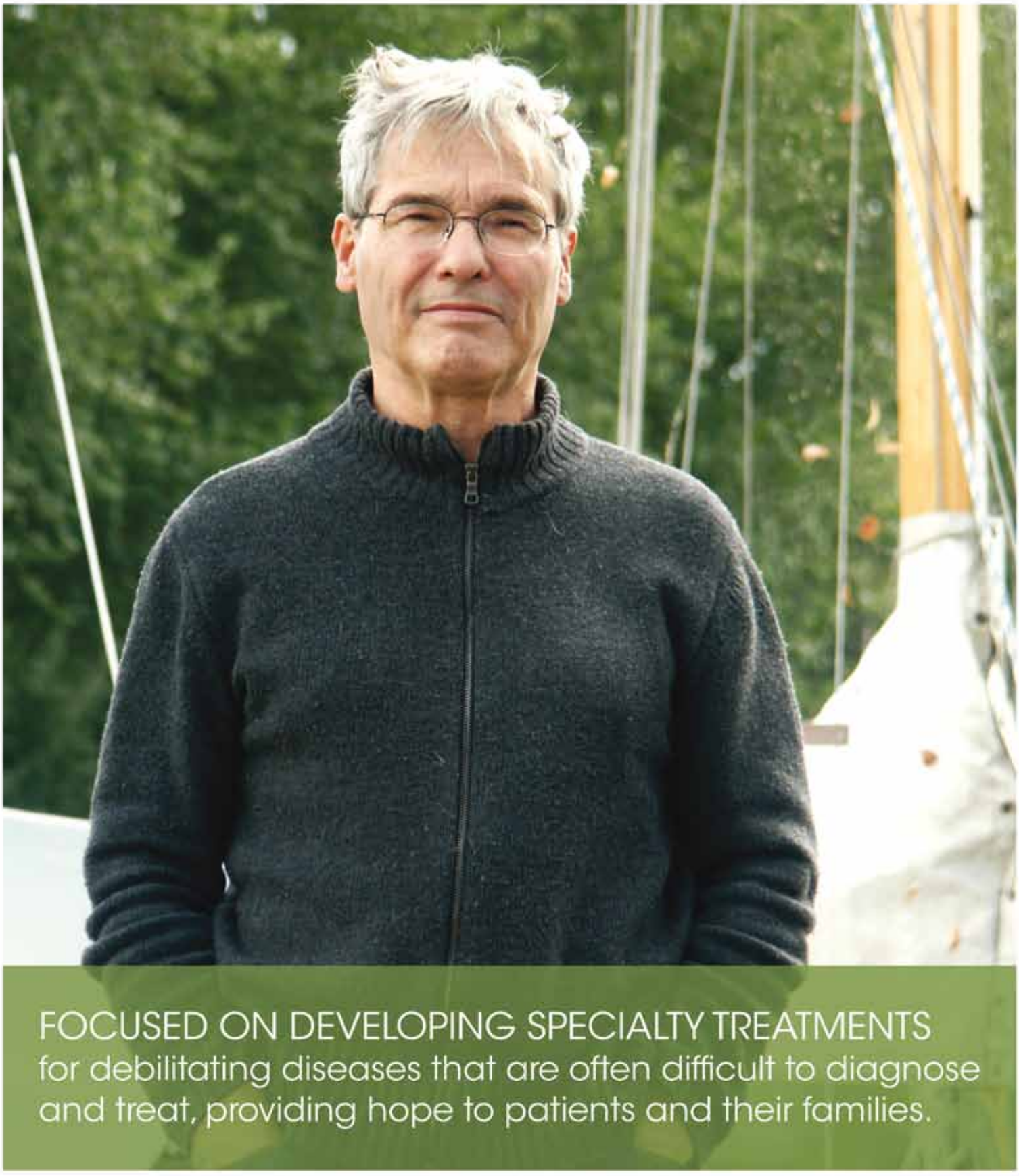
All the evidence points to a massive deficit in both funding and processes to address cancer within the UNHCR system. However, the impact on countries like Jordan, looking after both registered and unregistered refugees, is even more profound, placing a huge burden on an already overstretched cancer system. Institutions like the King Hussein Cancer Foundation have been left to support many refugees diagnosed with cancer through zakat (charitable) funds.

But this is clearly not a sustainable situation. Further afield, Tunisia is also feeling the impact of the collapse of security in Libya, with an estimated 2 million refugees, and as migration continues across Europe, more refugees will be diagnosed with cancer with no clear models of care in place.

Cancer is a completely new care paradigm for the likes of MSF and the Red Cross

Cancer policies and interventions have not kept up with the profound global changes in conflict settings in the last decade. Old paradigms of camp-based refugee care, focusing only on infectious diseases, malnutrition and child-maternal health, are no longer sufficient.

Tackling NCDs, and cancer in particular, is complicated and expensive relative to other areas. However, cancer enjoys substantial funding from both public and private sectors in high-income countries, and there is an ethical duty to help countries and organisations deliver and rebuild cancer control and care. This will require far better cancer intelligence in refugee settings, and the post-conflict environment, and new financing and referral models.



ECCO

EUROPEAN CANCER ORGANISATION

Shaping the delivery of quality cancer care

ECCO, the European CanCer Organisation, aspires to improve outcomes for all cancer patients in Europe through multidisciplinarity. Together with our member societies, we will focus on quality assurance and organisation of cancer services, to help raise awareness of the importance of multidisciplinarity, registries, outcomes research and quality control, and to influence policy making across Europe.

The work that has already been done on improving the delivery of quality cancer care in Europe has been produced chiefly by ECCO member societies through a multidisciplinary effort. The first example was the requirements of a 'specialist breast centre', which were developed by the European Society of Breast Cancer Specialists (EUSOMA). The second example relates to specialist prostate units, initially defined by the European School of Oncology (ESO) task force, which included the European Association of Urology (EAU), the European Oncology Nursing Society (EONS), the European Society for Radiotherapy & Oncology (ESTRO), the International Psychosocial Oncology Society (IPOS), the Organisation of European Cancer Institutes (OECI) and the patient advocacy group Europa Uomo.

More remains to be done for other tumour types. While currently available guidelines on cancer care define the medical content of optimal treatment for a given type of cancer, they do not indicate how to organise this treatment or measure its outcome. High-quality cancer care requires regularly updated evidence-based medical guidelines, but it also needs verified models of care delivery, quality assessment and organisational systems.

To fill the gaps, with the support of its member societies, ECCO is working towards defining organisational criteria for delivering optimal care to each patient and the minimum requirements for quality cancer care. Because of its uniquely multidisciplinary nature, ECCO aims to produce and publish recommended care delivery procedures for selected tumour types, thus complementing most of the available clinical guidelines. Cancer professionals will then be able to count on not only evidence-based treatment guidelines for each tumour type but also indications of best practice in delivering quality care. In 2016, we will focus on colorectal cancer, and child and adult bone and soft tissue sarcomas, with the recommendations being published and presented at the ECCO2017 European Cancer Congress on 28 January 2017.

The outcomes of the ECCO Quality Cancer Care activities will feed in to ECCO's efforts to promote policies that underpin the successful realisation of multidisciplinarity in cancer care.

ECCO is engaged in ensuring that the oncology value chain is optimised for all cancer patients by finding synergies between different members' expertise and knowledge, and addressing disparities and inequalities in cancer outcomes across Europe.

Ecco-org.eu

Peter Naredi – President of the ECCO Board of Directors (2016/2017) and Professor of Surgery and Chairman of the Department of Surgery at the Sahlgrenska Academy, University of Gothenburg, since 2013

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Radiotherapy-related skin reactions

Acute skin reactions associated with radiotherapy can be distressing and can lead to treatment interruption. Anticipating, assessing and managing the problem according to best evidence can make a big difference.

This grandround was first presented by Lena Sharp, from the Stockholm-Gotland Regional Cancer Centre, in Stockholm, as a live webcast for the European School of Oncology, in collaboration with the European Oncology Nursing Society. It is edited by Susan Mayor. The webcast of this and other educational sessions can be accessed at e-eso.net.

Radiotherapy-related toxicity occurs because of the effect of radiotherapy on normal tissue that divides rapidly, such as the skin and mucous membranes. Acute toxicity occurs during treatment and 2–3 weeks after completing radiotherapy, while late toxicity occurs from weeks to years after treatment.

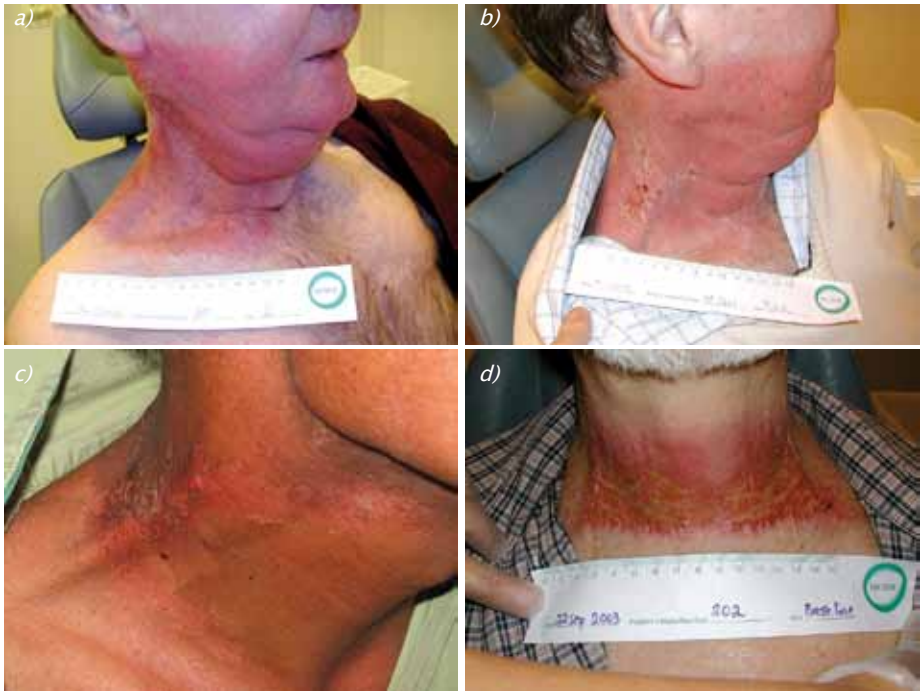
Skin tolerance was one of the limiting factors in the early days of radiotherapy and can still cause treatment interruptions. It was partly overcome by fractionation – dividing the dose of radiotherapy into several smaller, often daily, doses. Repeated small doses are less damaging than a single fraction with the same total dose. However, despite fractionation there are still problems with skin tolerance, and it remains a reason for treatment interruptions, which can negatively affect treatment outcome with radiotherapy.

Acute skin reactions

Acute skin reactions to radiation are very common, affecting 80–100% of patients treated with adjuvant or curative radiotherapy. Most patients have mild reactions with limited impact on their quality of life. However, some patients, particularly those having radiotherapy to the head and neck or pelvic area, experience more severe reactions. These are associated with symptoms including pain, itching and infections, and in the worst cases lead to treatment interruptions.

Epidermal skin cells are continuously shed from the skin surface and new skin cells are produced in the basal layer below the epidermis. At four to five weeks into radiotherapy, the production of new

Acute skin reactions



Acute radiation skin reactions start as erythema (*a*). If the reaction continues, dry desquamation occurs (*b* and *c*), which may be followed moist desquamation (*d*)
Figures courtesy of Lena Sharp

cells is reduced, and it stops altogether if treatment continues. Skin cells keep peeling off from the surface, with no new cells produced below. In the end, the whole of the epidermis can be lost, and moist desquamation occurs, with the basal layer and dermis exposed. It takes a few weeks after treatment ends before the process of skin cell growth and turnover returns to normal and the skin can heal.

Acute radiation skin reactions occur (see figure above), initially as erythema, ranging from light pink to dark red skin. If the reaction continues, dry desquamation occurs in which the skin appears broken. The next stage is moist desquamation, which is likely to cause infection. In very rare cases nowadays the reaction continues to necrosis.

Risk factors

Risk factors for acute radiation skin reactions include factors related to the treatment itself, to other treatments or to the patient.

Radiotherapy-related factors

Radiotherapy-related factors include dose (the higher the dose, the higher the risk), overall treatment time, volume treated and radiotherapy technique. Using intensity-modulated radiation therapy (IMRT) reduces the risk of severe skin reactions, while the risk is increased by using bolus (material applied to the irradiated area to adjust the dose received at depth and on the skin surface) or by boosting the dose to a specific part of the irradiated area, or using an immobilisation device.

Factors related to other treatments

There may be risk factors related to previous or concomitant chemotherapy, hormone therapy, or targeted therapy. Data from studies are conflicting, however. Some studies show these treatments to be risk factors, while others do not.

Patient-related risk factors

Quite a few studies show high body mass index (BMI), as well as smoking, to be risk factors for acute radiation skin reactions. Age, skin type, genetic variation, comorbidity and alcohol consumption may be risk factors, but the evidence for this is weak.

We published a study on 390 women with breast cancer who were treated with adjuvant radiotherapy after mastectomy, chemotherapy and/or hormone therapy according to guidelines. Their skin was assessed using an assessment tool (RTOG/EORTC scale) and patients reported symptoms.

Data were also collected on health-related quality of life, sleep disturbance and clinical factors including smoking status (measured by carbon monoxide in expired air), BMI and treatment data (*The Breast* 2013, 22:634–638).

Results showed that 21% of women had severe acute radiotherapy skin reactions at follow-up, 10 days after radiotherapy. Total radiotherapy dose, high BMI, older age and smoking were statistically significantly associated with severe acute radiotherapy skin reactions. High BMI ($P<0.001$) and smoking ($P=0.027$) showed the strongest associations. Women who smoked had twice the risk compared to non-smokers. Patients with severe acute radiotherapy skin reactions reported higher levels of pain and increased problems with sleeping.

Management

Research over the last 10 to 15 years has shown that few, or even no, skin care products are effective in preventing or reducing acute radiotherapy skin reactions. A lot of skin products are used that have not been evaluated, and there is wide variation in practice, with many centres using local remedies that have not been tested.

Basic strategies, such as keeping the skin clean with soap and water, seem to be more helpful than particular creams. The goals for skin care are to:

- ☐ Keep the skin clean
- ☐ Control pain
- ☐ Provide comfort
- ☐ Avoid friction and trauma from clothes, weather etc
- ☐ Prevent infections.

Measures that can help with skin care include pain management and good nutrition to support wound healing. Smoking cessation is one of the most important measures a patient can take to reduce their risk of severe skin reactions. It is important to be careful with sun exposure, to maintain good hygiene and to avoid skin care products just before treatment. Patients should not use make-up on the irradiated area while having radiotherapy, and should use electric rather than manual razors.

What skin care products should patients use?

First of all, patients should use soap and water for washing the skin. Several studies show that soap and water are better than using water alone, because this is associated with higher risk of moist desquamation. The type of soap is not important, but a mild soap is preferable, and highly perfumed soaps should be avoided.

Most creams that have been tested, including those containing Aloe vera or camomile, show no effect. Conflicting results have been seen with creams containing hyaluronic acid, topical steroids (although many centres use these) or calendula. A recent small study showed that olive oil reduced the risk of severe skin reactions (*Int J Clin Exp Med* 2015, 8:11000–06), while others showed some effects with a sandalwood and turmeric-based cream (*Br J Radiol* 2014, doi: 10.1259/bjr.20130490) and with a boswellia-based cream (*Eur Rev Med Pharmacol Sci* 2015, 19:1338–44).

There is a question about whether to use a skin cream or not. At least one study has shown a difference between patients who used a skin cream and those who did not (*Radiother Oncol* 2004, 73:153–162). It does not hurt to use a skin cream, and I think it can provide a way to keep the skin soft and intact for longer, although there is limited evidence on this.

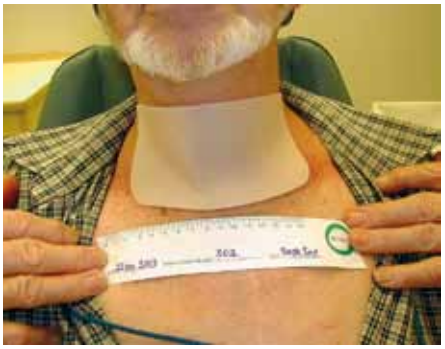
One of our studies compared calendula cream (marigold extract) with aqueous cream – the standard care at our centre – in 420 patients with breast cancer who were randomised on a blinded basis. The patients' skin was assessed using the RTOG/EORTC scale, and they were asked to report symptoms. Patients were also asked about their experiences with the skin creams. Results showed no statistically significant difference between the two creams, with slightly higher severe reactions with calendula cream, which was more difficult to apply and more expensive than aqueous cream (*EJON* 2013, 17:429–435).

Use of topical steroids is a hot topic. There are conflicting data, with some studies showing a reduction in itching and erythema, but no reduction in pain or moist desquamation, which are two major problems (*Int J Rad Oncol Biol Phys* 2011, 79:1460–66). One study has shown improved quality of life by using topical steroids from the outset of radiotherapy, but there were very few severe skin reactions in the placebo group (*Int J Rad Oncol Biol Phys* 2014, 90:748–755). There are no data on long-term effects of topical steroids on irradiated skin. I would recommend against using topical steroids for all patients, but to assess the risk factors for each patient, and use steroids if appropriate. Soft silicone dressings can help to prevent trauma and friction (see figure above). In most cases these can be left on during radiotherapy, although this should be discussed with the radiotherapy team.

There may be a risk of increased dose to the skin surface, if the dressing is left in place during radiotherapy, but this is not clinically relevant. A problem with these dressings is that they are expensive, and are therefore not available to all patients.

Question: Do you think intensity modulated radiotherapy (IMRT) is more effective in the prevention of acute radiation skin reactions than 3D radiotherapy?

Soft silicone dressing



Dressings like these can help prevent trauma and friction, but are generally used only in acute cases, because of their cost

Courtesy of Lena Sharp

Answer: Yes, I think so. But a lot of factors have to be taken into consideration. Using IMRT for all breast cancer patients would increase treatment time, which may cause problems. However, I think it would definitely be better for the skin.

Question: Is the pH of soap relevant? If yes, what is the evidence on optimal pH for soap?

Answer: It doesn't seem to matter. It seems to work with any mild, preferably perfume-free soap. I think we focus too much on things like that.

Question: Is steroid therapy really not applicable?

Answer: You can definitely use it, but I don't think you should recommend it for all patients from the start of therapy. There are not a lot of data on long-term use. Consider using it if a patient develops a severe skin reaction early in treatment, or if they have other risk factors. There are studies showing it might improve quality of life and itching, but my advice is that steroids are not for general use.

Question: If you are trying to solve itching, would you be better using an antihistamine rather than a topical cream, if appropriate for a patient?

Answer: Yes. Good idea.

General recommendations

Patients with erythema should wash the skin with mild soap and water daily and apply a perfume-free lotion. Dry desquamation is treated in a similar way, washing with mild soap and water daily, in addition to avoiding friction and trauma, such as rubbing of shirt collars. Silicone dressings or silver dressings can be used to cover the irradiated area to reduce friction, although silver dressings should not be left on during treatment. Moist desquamation is treated in the same way, ensuring that any infections are treated with antibiotics.

Combined treatments: radiotherapy and targeted drugs

Targeted drugs can cause skin rash, and it is important to consider the combination of this with the skin toxicity associated with radiotherapy. One of the problems with combined treatments is that more severe skin reactions can occur, particularly with higher doses of radiotherapy. The patterns of skin reactions to targeted drugs also differ from those associated with radiotherapy. Skin toxicities from targeted therapies can start much earlier, and there is currently limited understanding of the late toxicities with the combination with radiotherapy, because it has been used only relatively recently.

These skin problems need to be treated with antibiotics immediately, because it is even more important to avoid treatment interruptions for patients on combined treatments. Many patients with colorectal cancer have targeted therapies, and are advised to cover up the skin reactions to these drugs with makeup. Patients receiving radiotherapy for head and neck cancers, however, should avoid makeup on areas of irradiated skin. There is limited evidence on management, but a recent literature review in head and neck cancer treated with radiotherapy plus chemotherapy or EGFR inhibitors provides some information (*Crit Rev Oncol Haematol* 2015, 96:167–182).

Assessing skin reactions to radiotherapy

Many of the assessment tools currently used are not validated. Assessments should include, or be combined with, patient-reported data, because the most important factor is not how red a patient's skin is, but how the reaction and symptoms affect them. You should assess the patient's skin before, during and after radiotherapy to enable comparison.

It is important to consider inter-observer variability. We tested two different tools used independently by two very experienced nurses in patients with breast cancer, and found inter-observer agreement of 50–60% (*EJC* 2011, 47 2665–72). In some cases the difference was two steps on the measurement scale. When we explored the reasons for the difference, we found that many nurses assess the redness differently. Education is essential and, after our study, we held workshops with all of our staff on the use of skin assessment tools, and found we could increase inter-observer agreement to 90%.

Question: What online assessment tools do you recommend?

Answer: It is important to see whether your department is already using an assessment tool and to use that, particularly if the department is using it in research. A useful measure for assessing patient-reported symptoms, and for staff to assess the skin, is the RISRAS scale, and we have used the RTOG/EORTC scale, which has been widely used in Europe. However, with any measure it is important to include patient-reported symptoms. A useful overview of assessment tools for acute radiation skin reactions has been published in the Clinical Journal of Oncology Nursing (vol 15, pp 481–492).

Question: What about areas of the skin where you can't apply dressings, such as for patients treated for rectal or gynaecological cancers, who can develop quite severe skin reactions? How should these patients be managed?

Answer: This is really difficult, but should include the same management as for other areas of the skin. We have used silicon dressings in these situations. They

will fall off and need to be changed, but would need to be changed several times in these areas anyway. There are sprays and other preparations that could be used after the treatment period, but not during treatment. Gauze may be placed in skin folds, to try to avoid skin–skin contact. A hand shower should be used to keep the skin clean.

Question: Given the variation in practice between different centres and the lack of evidence for one product compared to another it is difficult to develop institutional guidelines. Do you have any recommendations on this?

Answer: I think it is important to keep it simple. Although there is a lack of evidence, that does not mean a product is harmful, and if an institution finds something works, then that is fine. Use any type of moisturiser that works and is available locally. One approach is to ask the patient about the moisturiser they normally use, and recommend they continue, as long as it is perfume-free. I think we put too much focus on the type of cream, but this does not really matter.

Question:. Is there any evidence on the use of sucralfate in ulcerated lesions in radiodermatitis?

Answer: A very well-designed UK study showed no evidence of benefit in colorectal and breast cancer patients (Radiother Oncol 2004 73:153–162).

Question: Is there any recommendation on when patients should start applying skin care products – before or after onset of the skin reaction?

Answer: There is no strong evidence, but I would recommend starting when treatment starts. This also provides a good way of checking the skin. The skin reaction will occur anyway in response to radiotherapy, but it is important to help the patient continue with treatment so they don't have interruptions.

Take home messages

Most patients experience acute skin reactions from radiotherapy, mostly mild to moderate

Patients should be advised to keep their skin clean with soap and water.

A lot of remedies are used by different centres but with little or no evidence.

Using a simple moisturiser could be helpful; however, there is no strong evidence in favour of any particular type of skin care product.

Smoking is the most important patient-related risk factor for skin reactions, and starting radiotherapy provides a useful teachable moment to help people stop.

High BMI is also a risk factor.

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Unlocking progress: why we need to change the culture of biobanking

Progress in understanding resistance and learning how to combine and sequence therapies most effectively is being stifled because specimens donated by patients, and related data, are being hoarded and not shared. **Peter McIntyre** reports.

There are growing calls across Europe to make more effective use of tissue, blood and other specimens that patients have donated for research to speed up progress in treating cancer. These specimens, together with the linked clinical data about the patient they came from, offer an invaluable resource for researchers trying to identify biological traits that could help guide decisions on the best treatment options for each patient.

But failures to share data, and the hoarding of precious biomaterials, are leaving clinicians and patient advocates increasingly frustrated at the lack of coordination in research.

Patients who give permission for their tissue and blood products to be used are often unaware that it has effectively become the 'property' of a single research team or pharmaceutical company.

Denis Lacombe, Director General of the European Organisation for Research and Treatment of Cancer (EORTC), says that, despite rapid increases in understanding the genetic causes of cancer, lack of collaboration is hindering progress in treating the disease.

It is only possible to fully understand the biology of cancer, including the mechanisms of relapse, recurrence, and resistance, if researchers have access to biological material and the capacity to link it to clinical data about the patient and the course of the disease, he argues.

Without that knowledge, clinicians are left guessing at how best to use new treatments. "In the real world, we need combinations and sequences of drugs, but the way we function is industry brings drugs to the market one by one.

"Melanoma doctors don't know the optimal duration of a checkpoint inhibitor, how long you have to treat a patient and how to sequence a checkpoint inhibitor with a BRAF, or MEK or CTLA inhibitor."

The industry is not going to address these questions, says Lacombe, so three years ago he spearheaded the launch of a bold EORTC collaborative programme.

SPECTA (Screening Patients for Efficient Clinical Trials Access) is a network involving clinicians and researchers from academia and industry, which seeks to channel patients quickly into relevant clinical trials, which it does by screening material from patients treated at participating institutions using high-quality next generation sequencing, gene expression and genomics.

Trial sponsors looking to enrol patients with specific mutations can find them through the SPECTA database, avoiding the need to screen thousands themselves to identify the subgroup they require. This can benefit sponsors and patients. But the wider cancer research effort also benefits, because the biomaterials from patients recruited for those trials remain in the SPECTA database, and their data are regularly updated, which builds up vital information about progression, recurrence and survival along the entire patient journey.

If patients progress on one trial and move on to another, their longitudinal data can reveal important information about resistance, the impact of sequential treatments, and how that relates to tumour biology, which would not be available if data for each trial were locked away under the control of the separate sponsors, as typically happens today.

Lacombe believes that the SPECTA system of holding materials and data within its collaborative research network could also facilitate clinical trials combining two drugs that are in development in two different companies, which has so far proved impossible. "Potentially, by more sharing we can change this paradigm," he says. "Patients would maximise their chances to benefit from treatment, because we would be following them from recurrence to recurrence."

Lacombe has criticised researchers who keep the equivalent of "butterfly collections" of tissue materials in freezers and cupboards, as wasting precious resources. "Butterfly collections decorate your room, but that is it," he says. "And they fade away with time."

"In the EORTC, we have banned this notion of ownership which I think is very detrimental. We speak about: 'Who is responsible for the chain of custodianship?'

"Personally I feel more and more that it is unethical for commercial silos to keep biological materials. The reason is that, if a clinical trial is negative, the company will close the programme overnight and all the materials they have been collecting are difficult to access, if not impossible."

Access. The patients who run the PATH biobank, including co-founder Ulla Ohlms pictured here, ensure that the specimens from 8,300 patients currently banked here are used to progress cancer research, not just commercial interests or individual careers

Martine Piccart, Medical Director of the Jules Bordet Institute, Brussels, agrees. "If we look at what we have done over the past two decades, it has been incredibly disappointing. It is very difficult to find the biomarkers for response or lack of response to the new drugs, and the reason is that we never share results and put them in the public domain. So-called translational research is restricted to a single study of a few hundred patients, while it is obvious that the way to make progress in this very complex area is by at least sharing data. Companies do very good work as they have very good scientists. But they never share data with other companies.

"It is disappointing that even academic investigators are sometimes very negative towards sharing, and that has something to do with the need to publish. That must now change because it is a disservice to patients. I think it is not completely honest.

"It is a real nightmare and patients are totally unaware of this. They donate their material to science because they trust this will help future patients, not in my view a particular company or investigator."

Piccart, who raised this issue at the European Cancer Congress last year, says that industry and academics need exclusive access to tumour material for a limited period to develop new tests and products, after which there should be open access to the material, with data uploaded to a public platform.

She is calling for a cultural shift towards the clinical trials equivalent of The Cancer Genome Atlas (TCGA), which has collected samples from more than 11,000 patients across 33 tumour types. "The CGA project is a fantastic resource for scientists, but it is not connected to trials. Can you imagine if we could do something like that in trials, where data are connected

Getting consent. At the European Institute of Oncology, nurses spend a lot of time talking to patients about why their tissue is a valuable resource for research, how it may be used, and how their privacy will be protected

to the clinical outcome of the treatment? That would be absolutely phenomenal. That is the only way we are going to move towards personalised medicine."

The costs of such collaboration could be shared. "We are all partners: the patients, the physicians the companies and the governments."

Good biobanks share

Many biobanks are organising to share materials better. The Jules Bordet Institute has one of the oldest biobanks in Europe, with 15,000 samples collected over the past 25 years. The biobank steering committee is open to sharing for good proposals, especially for research into rare cancers. Biobank manager Ligia Craciun says that academic research is the first priority but there are also opportunities for collaborating with pharmaceutical companies.

Craciun sits on the steering committee of the Belgian Virtual Tumourbank, which catalogues samples from 11 partners across the country, and the Jules Bordet also supports the European Research Infrastructure Consortium (BBMRI-ERIC), which promotes data and sample sharing across Europe.

Another good example is the Biobank for Translational Medicine at the European Institute of Oncology in Milan, which over the past four years has collected materials from 2,500 breast cancer patients and 500 patients with lung cancer, matching tumour tissue with normal tissue, blood serum and plasma. It is the European biobank for collaborative studies conducted by the International Breast Cancer Study Group (IBCSG) and for the ALTTO HER2 trial, coordinated by the Breast International Group, which compared two HER2 blockers used separately, in combination or in sequence in an adjuvant setting.

As co-chair of the IBCSG translation research committee, Pruneri says that researchers involved in the studies do have the first call on tissues, but it is possible for other researchers to access them if they put a convincing enough case to the steering committee.

Calls for proposals to use biomaterial collected in the ALTTO trial is currently restricted to participating researchers, but Debora Fumagalli, scientific adviser to the Breast International Group, says that they eventually will open this up. "Researchers have invested tremendous energy and time into the trial and it is fair to give them some 'protected' time to propose research ideas that they have. However, our final goal is to open the access to the wider community in order to make the most benefit out of this precious data."

Pruneri suggests a number of ways to improve the use of material for research. He believes that if hospital pathology departments can become biobanks – with all the quality control, consenting, anonymisation and safe data storage that entails – then material from about 30,000 breast cancer patients could be available across Europe for further research. Centres could use the fees they receive to cover the costs of data managers and specialist nurses.

He also agrees with Lacombe about the need for a shift from traditional clinical trials towards studying multiple samples from single patients at different stages of recurring or continuing disease. "This is a new avenue of targeted research that can be accomplished only in a biobank that is actively banking tissue."

Patient inspired biobanks

Some biobanks have been directly inspired by patients to improve research and treatment. When Ulla Ohlms was diagnosed with breast cancer in 2000, molecular tumour biology and biobanks were in their infancy. She became a founder member of Foundation PATH – Patients' Tumor Bank of Hope, dedicated to improving research and treatment.

The PATH biobank collates breast cancer materials from a network of seven centres in Germany. It has biomaterial from more than 8,300 patients, almost 6,900 fresh frozen tumour samples with matching normal tissue and 15,000 blood serum samples. It comes with clinical data and often with several years of follow up data.

The biobank has a majority of patients on its board and supports breast cancer research in academic centres and in industry.

Tobias Anzeneder, manager director of the biobank, says: "We have seven of the best breast cancer centres in Germany that are very big on enthusiasm and engagement. Everybody is happy to make a contribution to research and form part of a successful resource for breast cancer. Gynaecologists and pathologists from the PATH breast cancer centres do all this work of consenting, labelling, data acquisition and sharing completely voluntarily. That is a very big plus."

Patient advocate Jayne Bressington was instrumental in starting a UK national GIST tissue bank after her daughter was diagnosed with a rare form of the disease, PAWS–GIST. She was dismayed to find little research into her daughter's condition and no organised collection of material. When she took her daughter to the USA for specialist treatment, the UK hospital where she had been treated was willing to send tissue samples, but reluctant to send a second batch when the US hospital asked for it.

Jayne Bressington said: "Patients are often are invited to sign a consent form about using their tissues for research. Most often a sample of tissue is stored in the hospital pathology lab, and that is where it stays. A researcher can only track materials down if they can connect with patients who are sufficiently proactive to say 'I have had some tissue collected and it is in the hospital.' My experience suggests that it takes strong determination on the part of the patient to make that happen."

Working with supportive clinicians in the UK, Jayne Bressington has helped to establish a national GIST tissue bank at the Northern Institute for Cancer Research in Newcastle, but it is proving difficult to build a national network of contributing clinicians.

"My vision is that when these operations happen, the surgeon and patient will sign a consent form that automatically says that tissue can be transported to the national GIST tissue bank. That does not happen at the moment."

The plan now is to move the biobank to the Royal Marsden in London, which has the highest concentration of GIST patients in the country and an established biobank.

Promoting a culture of sharing

The UK is investing in biobanking at a national level. UK Biobank – a charity supported by the National Health Service – has collected blood, urine and saliva samples from 500,000 people who have also agreed to have their health followed. In another project, Genomics England, is sequencing the genomes of 100,000 UK citizens, half of whom have cancer, with the aim of supporting efforts to develop therapies and diagnostic tests. The anonymised data is made available to academic and industry researchers.

But a great deal of valuable material is also held in a myriad of biobanks belonging to different institutions or research groups. In 2007, the National Cancer Research Institute initiated a UK Confederation of Cancer Biobanks to raise standards, which included a statement promoting sharing and collaboration.

Those working with tissue products, it said, "should use these samples, or make them available to others for use, in the best interests of the public and not solely in the interests of themselves or their organisations."

Derek Stewart, the patient advocate who first chaired the Confederation said, "If we are funding a biobank from the public purse or charities that have raised money through public efforts, then I personally think it is unacceptable that those tissues are not being shared. If you receive the funding, there should be an onus to show what you are doing for the patients and public."

In 2011, the National Cancer Research Institute and the Medical Research Council published a UK Funders' Vision for Human Tissue Resources, under which research groups are expected to consider how to link with existing studies or trials that already have collected high-quality clinical data, rather than collect their own. If they do collect tissue, they should seek generic consent from patients so it can be used for a range of research, and make access possible through a publicly accessible directory. The vision says: "Sample collections must then be made more easily discoverable and accessible for use in high quality, ethical research."

"My vision is that the consent form automatically says that tissue can be transported to the national GIST tissue bank"

In May 2016, the first national directory of UK biobanks was published. Philip Quinlan, Director of the Tissue Directory and Co-ordination Centre, says they are encouraging 250–300 tissue banks in the UK to sign up. "There is a need to know more about what is going on. We are still in the discovery phase of making it possible to find the resources."

The long-term aim is to improve research access to the biobank materials. "Members of the public and patients are incredibly generous and usually make donations with no strings attached. With that there is a duty to make sure they are used – not to do so is almost misuse.

"If people need to reserve them for a particular research study, that is fine, but in the longer term there is a real need to make sure those samples are used for the purpose they were collected."

The Centre is also working with software companies to improve the technical ability of biobanks to share materials. "If a biobank wants to share, it should be as easy as flicking a switch."

While there may be logistical and technical challenges in sharing biomaterials, there's less of an excuse for failing to share the data generated by studies that use those materials, and here again there seems to be a need for a cultural change.

Most biobanks ask researchers to provide feedback on the quality of the samples, but few require feedback on the research results or are equipped to handle this information.

However, they put varying degrees of pressure on researchers to make their results known. Genomics England, for example, says "access may cost them less if they make their results available to all other researchers."

Ligia Craciun from the Jules Bordet institute says that researchers who fail to publish their results would find it harder to win access to the materials in future.

In Munich, Anzeneder says: "PATH will always encourage you to publish. I ask how the research is going and when results will be published. As a biobank founded by patients, PATH has a big interest in seeing as much data shared as possible."

Team science

As the Cancer Genome Atlas closes its data collection phase in 2016, Director Jean Claude Zenklusen counts the development of 'team science' as one of the most valuable outcomes, enabling researchers to uncover patterns and investigate questions that were not even imagined at the start of the project.

Martine Piccart says this kind of team work is too rare in medicine, where reputations are based on publications, and collaboration is not fully recognised – being 'et al.' in a publication does nothing for your career.

The situation is not much better in north America, where Lillian Siu, director of the phase I programme at Princess Margaret Hospital, Toronto, Canada, was recently asked to help the US National Cancer Institute (NCI) and a pharma company develop an antibody towards a biomarker for a rare lymphoma. The task was urgent and biobanks are reluctant to allow rare tumour samples to be used for pre-clinical analysis. After making 20 calls to pathology labs, Siu had to buy samples on the Internet for preliminary testing.

"I think it is a pity because there are tons of data and samples out there if we had made a collective effort to biobank them. If there was a vision to do that many years ago, I would not have to go through so much to find the rare samples."

In a presentation to the Cancer Therapy Evaluation Program in Maryland, Liu highlighted the importance of effective biobanking in improving the speed and effectiveness of research in the Experimental Therapeutics Clinical Trials Network (ETCTN), established by the NCI and partners to evaluate new therapies.

She argued for the network to establish a virtual biobank with an inventory of tumour samples at different ETCTN sites, complete with histology and molecular genotype, and with clear guidance on how to obtain samples, including conditions under which ethics approval could be waived.

She flagged the importance of including rare tumours, and also emphasised considerations of sustainability, which can be a big issue particularly with biobanks that serve broad clinical trials networks, rather than individual clinical trials. "You can do all this but if you don't bank you have got nothing. We really have to think about how to do this in a way that is sustainable. To bank tumours you have to have core funding institutional support. It is not like it comes free."

Lacombe, meanwhile, has been pursuing the EORTC vision for collaboration around its central platform for gathering biological and clinical data, by holding one to one conversations with "the big four" stakeholders in Europe: the European Medicines Agency, the European Federation of Pharmaceutical Industry Associations, the European Commission and the Innovative Medicines Initiative.

So far there are no signs of a breakthrough. "It is extremely difficult to provoke such a major change because it requires that people completely think out of the box, to share collections and so on. It is work in progress and we keep talking. Not everyone has necessarily understood the need for changing the way we are doing things."

So far, SPECTA has recruited 1,000 patients with colorectal cancer and 150 lung cancer patients and is now recruiting for melanoma, neuro-oncology and rare tumours. It is steady progress, but Lacombe contrasts the situation in Europe with the NCI-MATCH trial in the US, which will base cancer treatment for 5,000 patients on individual molecular profiling. Supported by the NCI Clinical Trials Network, MATCH took just four months to reach its first recruitment target, and began its main phase of recruitment at the end of May 2016.

Lacombe says NCI-MATCH has credibility because it is seen as independent and is backed by a trusted governmental body. "It has big visibility and it is very successful. They are getting a lot of trials and the programme goes well, and I think that here we are paying the price of a fragmented Europe."

This information is intended for healthcare professionals in the European Union

ACT IN TIME...

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- **For the treatment of adult patients with unresectable or metastatic GIST who progressed on or are intolerant to prior treatment with imatinib and sunitinib[1]**

Reference: 1. EU SmPC 2014

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Stivarga® 40 mg film-coated tablets. (Refer to full SmPC before prescribing.)

Composition: *Active ingredient:* 40 mg regorafenib. *Excipients:* Cellulose microcrystalline, croscarmellose sodium, magnesium stearate, povidone (K-25), silica (colloidal anhydrous), iron oxide red (E172), iron oxide yellow (E172), lecithin (derived from soya), macrogol 3350, polyvinyl alcohol (partly hydrolysed), talc, titanium dioxide (E171). **Indication:** Treatment of adult patients with: 1. metastatic colorectal cancer (CRC) who have been previously treated with, or are not considered candidates for, available therapies. These include fluoropyrimidine based chemotherapy, an anti-VEGF therapy and an anti-EGFR therapy; 2. unresectable or metastatic gastrointestinal stromal tumors (GIST) who progressed on or are intolerant to prior treatment with imatinib and sunitinib. **Contraindications:** Hypersensitivity to the active substance or any of the excipients. **Warnings and Precautions:** It is recommended to perform liver function tests before initiation of treatment and monitor closely (at least every 2 weeks) during the first 2 months of treatment. Thereafter, periodic monitoring should be continued at least monthly and as clinically indicated. Mild, indirect (unconjugated) hyperbilirubinaemia may occur in patients with Gilbert's syndrome. Close monitoring of the overall safety is recommended in patients with mild or moderate hepatic impairment. Stivarga® is not recommended for use in patients with severe hepatic impairment (Child-Pugh C). When prescribing in patients with KRAS mutant tumours, physicians are recommended to carefully evaluate benefits and risks. Blood counts and coagulation parameters should be monitored in patients with conditions predisposing to bleeding, and in those treated with anticoagulants or other concomitant medicinal products that increase the risk of bleeding. Permanent discontinuation should be considered in the event of severe bleeding. Patients with a history of ischaemic heart disease should be monitored for clinical signs and symptoms of myocardial ischaemia. In patients who develop cardiac ischaemia and/or infarction, interruption of Stivarga® is recommended until resolution. The decision to restart Stivarga® therapy should be based on careful consideration of the potential benefits/risks of the individual patient. Stivarga® should be permanently discontinued if there is no resolution. In patients developing posterior reversible encephalopathy syndrome (PRES), discontinuation of Stivarga®, along with control of hypertension and supportive medical management of other symptoms is recommended. Discontinuation of Stivarga® is recommended in patients developing gastrointestinal perforation or fistulae. Blood pressure should be controlled prior to initiation and during treatment and it is recommended to treat hypertension. In cases of severe or persistent hypertension despite adequate medical management, treatment should be temporarily interrupted and/or the dose reduced. In case of hypertensive crisis, treatment should be discontinued. For patients undergoing major surgical procedures it is recommended to interrupt treatment temporary for precautionary reasons, and to resume treatment based on clinical judgment of adequate wound healing. Management of hand-foot skin reaction (HFSR) may include the use of keratolytic creams and moisturizing creams for symptomatic relief. Dose reduction and/or temporary interruption, or, in severe or persistent cases, permanent discontinuation of Stivarga® should be considered. It is recommended to monitor biochemical and metabolic parameters during treatment and to institute replacement therapy if required. Dose interruptions or reduction, or permanent discontinuation should be considered in case of persistent or recurrent significant abnormalities. Each daily dose of 160 mg contains 2.427 mmol (or 55.8 mg) of sodium and 1.68 mg of lecithin (derived from soya). **Undesirable effects:** *Very common:* infection, thrombocytopenia, anaemia, decreased appetite and food intake, headache, haemorrhage*, hypertension, dysphonia, diarrhoea, stomatitis, vomiting, nausea, hyperbilirubinaemia, HFSR, rash, alopecia, asthenia/ fatigue, pain, fever, mucosal inflammation, weight loss. *Common:* leucopenia, hypothyroidism, hypokalaemia, hypophosphataemia, hypocalcaemia, hyponatraemia, hypomagnesaemia, hyperuricaemia, tremor, taste disorders, dry mouth, gastroesophageal reflux, gastroenteritis, increase in transaminases, dry skin, exfoliative rash, musculoskeletal stiffness, proteinuria, increase in amylase, increase in lipase, abnormal International normalized ratio. *Uncommon:* hypersensitivity reaction, myocardial infarction, myocardial ischaemia, hypertensive crisis, gastrointestinal perforation*, gastrointestinal fistula, severe liver injury*, nail disorder, erythema multiforme. *Rare:* keratoacanthoma/ squamous cell carcinoma of the skin, PRES, Stevens-Johnson syndrome, toxic epidermal necrolysis.
*fatal cases have been reported

Classification for supply: Medicinal product subject to restricted medical prescription. **Marketing Authorisation Holder:** Bayer Pharma AG, D-13342 Berlin, Germany. **Date of the underlying Prescribing Information:** December 2014. Bayer Pharma AG, 13342 Berlin, Germany.
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Drug repurposing in oncology

patient and health systems opportunities

Repurposing established drugs for oncology patients offers the potential to deliver cheaper and faster drug development. This could help close the widening gap between patient expectations and healthcare budgets, as the cost of medical anticancer therapy escalates. In this review, **Francesco Bertolini** and colleagues consider barriers to drug repurposing and suggest ways to overcome them, in the interests of patients and society globally.

This is an abridged version of F Bertolini et al (2015) Drug repurposing in oncology – patient and health systems opportunities. ***Nat Rev Clin Oncol*** *12:732–742. It was edited by Janet Fricker and is published with permission ©2015 Nature Publishing Group. doi:10.1038/nrclinonc.2015.169*

nature REVIEWS CLINICAL ONCOLOGY

There is growing recognition that the budgets of most national healthcare services will be unable to support the current explosion in costs of new oncology drugs for much longer. The worldwide spend on oncology drugs in 2013, for example, was US$ 91 billion, with global sales of the 10 biggest selling oncology drugs reaching $ 43 billion (*Global Oncology Trend Report*, 2014, IMS Institute for Healthcare Informatics).

Increasing evidence suggests combination therapies are more likely to be effective against advanced neoplastic lesions than single agents or sequential drug combinations. This is because the number of cancer-inducing DNA mutations is larger than originally anticipated, and evidence suggests complex variations between and even within tumours in each patient. Tumour microenvironments also play a major role in tumour growth, and immunotherapies such as checkpoint inhibitors, which target the tumour stroma, look promising. In the majority of cancer patients, testing combinations of therapies offers the opportunity to target multiple derailed cellular machineries.

Repurposing the arsenal of drugs approved for non-cancer indications, for which preclinical and clinical safety data are available, might offer effective treatment options for cancer patients. In theory, drug repurposing allows faster development, reduces costs, and leads to safer preclinical and clinical validation protocols. However, reports of successful repurposing of drugs as anticancer agents have been limited.

Identifying repurposing opportunities

A variety of technologies can be used to identify drugs preclinically for repurposing from the existing armamentarium of approved drugs.

Knowledge mining

The vast majority of drugs possess off-target effects that might contribute to therapeutic benefits (*Nature* 2009, 462:175–81). By interrogating existing scientific databases, researchers can identify drugs that recognise specific targets. The identification of tricyclic antidepressants (imipramine and clomipramine) for treatment of small-cell lung cancer offers an example of this approach. An alternative strategy is to select agents assuming that drugs with similar side-effect profiles share targets (*Science* 2008, 321:263–66).

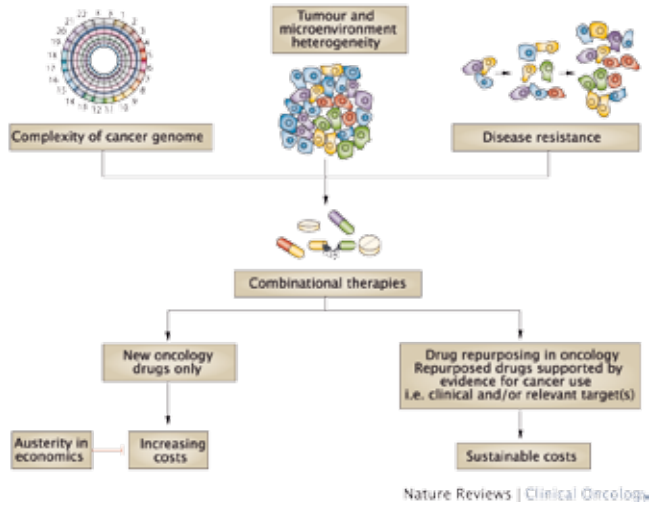
In silico approaches

This strategy combines knowledge mining and molecular modelling, using algorithms to screen a wide range of molecules to see how they interact. Once a shortlist has been identified, validation steps can be performed *in vitro* and *in vivo*. Although successful examples of *in silico* screening exist, the approach has yet to be validated in drug repurposing (*Drug Discov Today* 2013, 18:110–15). Virtual screening, for example, showed that simvastatin interacts with oestrogen receptors (*PLoS Comput Biol* 8:e1002503 2012).

In vitro assays

High-throughput screening allows identification of existing drugs active against cancer, with both phenotypic (cytotoxicity) and target-based assays used in drug discovery. *In vitro* phenotype screening of synergistic combinations also carries promise (*Proc Natl Acad Sci* 2003, 100:7977–82).

Combinatorial therapies and drug repurposing



Factors intrinsic to cancer biology suggest the need for combinatorial therapies for effective treatment and how drug repurposing in oncology can meet this need, leading to the availability of novel and affordable therapies.

Animal experiments

While extensive *in vivo* screening of agents in animal models is currently not possible, it is recognised that testing drugs in animals could provide important scientific validation for drug repurposing. Investigators who screened 182 drugs in a glioblastoma xenograft model, for example, identified anticancer activity for candesartan, risedronate and terbinafine (*PLoS ONE* 2014 9:e101708).

Treatment in companion animals

Well-conducted clinical trials in pets diagnosed with cancer can offer insights and provide information on the potential of drugs to treat human cancers. The combination of piroxicam with metronomic cyclophosphamide in dogs with soft tissue sarcomas provides an example deserving possible consideration in humans (*J Vet Intern Med* 2008, 22:1373–79).

Clinical observations

Patient reports of unexpected side effects or clinician observations of unexpected outcomes provide opportunities for repurposing. Observations from 'off-label' use of drugs can give preliminary signals of activity, especially in paediatric oncology (*Drug Discov Today* 2013, 18:4–10).

Epidemiological and post-hoc analysis

Epidemiology studies can be used to determine associations between use of drugs and specific outcomes. A case-control study, for example, first suggested a possibly reduced cancer risk in diabetic patients treated with metformin (*BMJ* 2005, 330:1304–05). Additionally, epidemiological evidence suggests the beneficial effects of aspirin on overall mortality are mainly through reductions in cancer deaths (*Lancet* 2011, 377:31–41). Later studies suggest the *PIK3CA* mutation serves as a predictive biomarker for response to adjuvant aspirin therapy in colorectal cancer (*Br J Haematol* 2002, 121:768–71).

Two-way drug development rationale

In-depth sequencing of tumour DNA can identify mutations, deletions and gene amplifications as well as new targets with

Potential candidates for repurposing

These generic drugs have shown anticancer activity in at least one randomised trial

- Aspirin
- Cimetidine
- Clarithromycin
- Propranolol
- Disulfiram
- Itraconazole
- Etodolac
- Nitroglycerine
- Pravastatin
- Verapamil
- Chloroquinine
- LMW heparin
- Arsenic

the potential to be druggable. One example was the in-depth-characterisation of the genetic landscape of patients with Philadelphia chromosome-like (Ph-like) acute lymphoblastic leukaemia, revealing that the majority had genetic alterations responsive to tyrosine kinase inhibitors (*NEJM* 2014, 371:1005–15). The repurposing of drugs already approved for patients with neoplasms has advantages, including the availability of dose-finding data, and information on side effects and interactions with drugs already used in cancer patients.

Matching drugs with disease subtypes

This approach explores how drugs already used in other medical fields can be repurposed for oncology. One of the best examples here is thalidomide, withdrawn in the early 1960s after evidence of severe teratogenicity, which was later found to have possible anti-angiogenic effects. The finding prompted a trial in which thalidomide was found to have response rates ranging from 25% to 35% in relapsed/refractory myeloma (*NEJM* 1999, 341:1565–71). Subsequent trials exploring thalidomide in combination with other agents active against myeloma cells showed response rates of 50% when used with steroids (*Br J Haematol* 2003, 121:768–71) and 70% with steroids and alkylating agents (*Hematol J* 2002, 3:43–48). More recent initiatives include development of thalidomide analogues, such as lenalidomide and pomalidomide, to overcome toxicity, and biomarker studies to predict which subpopulations benefit.

Strategies to increase success

Drug repurposing programmes in oncology have so far achieved limited success. While examples of drug repurposing can be found in neuro-psychiatry (*Nat Rev Drug Discov* 2004, 3:673–83), in oncology, if new cancer indications for known anticancer drugs (such as the repositioning of imatinib for GIST tumours) are excluded, success stories have been limited.

The reasons are multifactorial. Firstly, no data exist suggesting failure rates of repurposing projects would be any different from other new drugs (*Drug Discov Today* 2013, 18:523–32). Establishing the recommended dose required to achieve anticancer activity is another issue. Some drugs demonstrate benefits for doses recommended for other indications, while others require higher doses to exert anticancer effects. Some preclinical experiments with fluvastatin, propranolol, omeprazole or candesartan in oncology required higher doses than those recommended for different indications.

Intellectual property and patent protection are important considerations, with problems and solutions depending on whether drugs are proprietary or already available as generics. Lack of commercial interest can impede efficient clinical research on use of drugs (*JCO* 2014, 32:720–21).

For proprietary drugs, extending life cycle is in the company's interest, since any new indication will bring additional years of market exclusivity – three years in the USA, one year in Europe, and four years in Japan. However, cancer trials have long follow-ups and high failure rates, making them less attractive.

For generic drugs, the ability to patent new uses is theoretically feasible, but investors often prefer drug development projects with stronger legal protection, avoiding possible future commercial competition. Paediatric indications and orphan diseases are two notable exceptions, where financial incentives exist in the form of market protection (*Access Health Policy* 2014, 2:22813). Justifying a dramatic price increase for a cheap generic drug to recoup investment can be problematic.

While at first glance, promotion of comparative effectiveness research offers a great opportunity for generic drugs, the cost of non-inferiority trials comparing traditional with new agents can come in at around US$ 68 million. As a consequence, repurposed drugs may not demonstrate the expected favourable cost-effectiveness ratios compared to new entities.

Several drugs show clinical benefits in randomised clinical trials that are supported by additional preclinical evidence, but lack strong patent protection, making them unattractive for company-driven drug development (see table).

Concrete action to implement effective solutions is necessary to ensure that the scientific community does not repeat mistakes or miss opportunities from the past. One of the most promising solutions is offered by public–private initiatives that encourage research into shelved compounds to identify potential new targets for diseases (*Nat Rev Drug Discov* 2011, 10:397). As intellectual property exists in this case, commercial drug development may be possible.

Take home message from the authors

Francesco Bertolini (left) is from the Laboratory of Haematology–Oncology, European Institute of Oncology, Milan, Italy. Vikas Sukhatme (centre) is from the Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, Massachusetts. Gauthier Bouche (right) is from the Anticancer Fund, Brussels, Belgium.



"Considering the large arsenal of potentially effective drugs that are available for repurposing studies, we believe scientists, clinicians, regulatory agencies and patients should evaluate together how to promote a fast-track and adequately budgeted roadmap for drug repurposing in oncology, both at the bench and the bedside.

Clinical implications

More preclinical studies and clinical trials might be designed to include repurposed drugs. The EMA and FDA will need to modify current regulations to enable official licensing of combinatorial therapies using repurposed drugs.

Further studies

Considering the possible and unexpected synergies between repurposed drugs, *in vitro* approaches for single-drug evaluation in multiple cancer types might be refined to investigate multiple combinatorial therapies. And, of course, we would like to see more high-quality clinical trials conducted on repurposed drugs funded through innovative mechanisms."

Not-for-profit foundations (especially those focusing on rare cancers, orphan or neglected diseases), health insurance companies and governments all have crucial roles to play in drug repurposing. Yet governments seem unaware of the potential for drug repurposing to lower cancer treatment costs, and to offer additional therapeutic options to cancer patients. One therapeutic strategy for patients in low- and middle-income countries, where the price of new drugs makes them unaffordable, is to perform trials of repurposed drugs in patients with cancer for whom no other options are available.

There are a number of ways to promote drug repurposing:

Financial incentives encouraging companies to take the risk of repurposing non-cancer drugs could include rewarding them with options for longer market exclusivity and/ or re-negotiating prices for new indications.

Agents abandoned after being found ineffective for non-safety reasons in non-oncology indications should be systematically discussed by teams from different therapeutic domains.

'Social impact bonds' could be developed, where any organisation performing generic drug repurposing trials has pre-agreed financial incentives.

To make phase III trials of repurposed drugs affordable, central funding bodies could dedicate budgets to co-fund necessary trials when contacted by smaller funding bodies. Governments could provide incentives to not-for-profit foundations by providing matched funding for trials. Governments or health insurers could then commit to reimburse costs of trials to funding foundations where results are positive.

To facilitate the process of getting regulatory approval for new indications, governments, investigators and not-for-profit organisations could be allowed to submit dossiers, rather than just the drug manufacturers as at present. The EMA/FDA could provide scientific advice.

Conclusion

Academic and independent-driven preclinical and clinical research programmes, we believe, should be promoted both nationally and internationally. For such programmes to prove successful and ultimately bring benefits to cancer patients, the design and quality of repurposing trials will need to be optimised. Broad communication of the results of well-performed repurposing trials will be necessary to ensure they become practice-changing. Where no interest can be raised from the private drug development sector, non-commercial drug development strategies will be required. Not-for-profit drug companies have emerged to address problems of the developing world, and we, like others, believe such companies could positively affect the outcomes of patients in economically developed countries as well.

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Challenging cancer dogma in Mumbai

Are we optimistic or just complacent? For its 75th anniversary, India's Tata Memorial Centre invited the research world to take a fresh look at whether we are on track for defeating cancer. **Vineet Gupta** reports.

As an oncologist with a busy practice in the Indian city of Bangalore, I find myself frequently confronted by disappointed patients and their relatives, who ask me when we will finally find a cure for cancer. I evade and dodge some questions, and I answer others, hiding behind platitudes and power points to show that we are making progress in kicking this scourge on its heels.

But I cringe, because I know that envisioning a time when we'll be able to cure almost all cancers, with an ever-improving stream of engineered pharmaceuticals and yet-to-be-discovered cutting-edge treatments, seems so naïve, so utopian...

Just like the seductive headlines I read on a daily basis, which reek of scientific bravado, bordering on hubris, as they inform us that a cure for cancer is just around the corner. I read them with a resigned shrug, staggering from the vastness of the problem – a game whose rules we don't even understand, so we play checkers while cancer is playing chess – and I wonder aloud whether everyone is inhaling these half truths.

So I was thrilled when I chanced upon an editorial in *Lancet Oncology* co-authored by Rakesh Jalali, a neuro-oncologist I know rather well, who works at the venerable Tata Memorial Centre in Mumbai – easily South Asia's leading cancer centre (*Lancet Oncol* 17:140–141).

The editorial captured my frustration with paltry victories against cancer and the preoccupation with the hype generated from so-called molecular and genetic 'breakthroughs' that are translating into neither a

Enquiring minds. 1000 people spent three days peering into cracks in the foundations of the war against cancer

meaningful understanding of the malignant process nor a clinically relevant relief for our patients.

It also brought home to me how far cancer has become draped in ribbons of every hue, while we stand awestruck by the glitz and blinding promises of targeted 'omic therapies, seemingly forgetting that cancer remains a formidable challenge as ever.

On a brighter note, it flagged up a conference that promised to take a critical look behind the glitz. Titled 'A Conference of New Ideas in Cancer – Challenging Dogmas', it had been called by the Tata Memorial Centre to celebrate its 75th anniversary, and would be held later that month in the iconic setting of the National Centre of Performing Arts, on Mumbai's famous Marine Drive.

The three-day meeting, supported by *Lancet Oncology*, the American Association of Cancer Research (AACR) and the US National Cancer Institute, promised an eclectic mix of several bold keynote addresses, symposia and lively debates.

So it was that I found myself among an interesting and diverse body of 1000 delegates, who converged on Mumbai from 23 countries.

The brief the organisers had given to the speakers was simple: we are unhappy with the little that has been achieved against the scourge of cancer; we find it difficult to sit complacently with this 'rah–rah' scientific culture, amplified in public media by headlines of war-cry-like rhetoric enshrined by the ever so sexy 'moonshot'.

The meeting lived up to its title for sure – it stirred the pot, adding much-needed zing to the stale ale, and the science kept us glued to our comfortable seats from morning till early evening.

In essence it was about bridging the cancer divide – between the entrenched zeitgeist and starkly contrarian points of view; between seductive statistics and meaningful benefit to patients; between activity and achievement; between those who may naïvely believe that cancer can be conquered with their understanding

of a piece of the molecular jigsaw and those who struggle at the fringes of traditional, often ridiculed, conventional cancer care.

Unlike most scientific meetings of this scale that are awash with industry money, this meeting by design steered clear of support from industry and special interest groups. The result – a nonpartisan gathering that had the moral courage to address hard-hitting questions that are often forgotten in clouds of commerce.

Crisis in mainstream biology

A leitmotif that ran through this meeting was that there is a crisis in mainstream biology. The linear, deterministic computer models that grew out of our cultural fascination with the genetic code, beginning with the discovery of the DNA structure in early 1950s, no longer serve us well as explainers and predictors of modern biology and cancer. Yet no better alternative has yet emerged to make sense of things.

The first keynote speech, titled Cancer Research in Need of a Scientific Revolution, challenged the basis of our current understanding of the nature of cancer. Carlos Sonnenchein, from Tuft's University, Boston, argued that cancer is a defect of tissue architecture, and that the predominant theories that see it as a cell-based disease could therefore be leading us up the wrong path. He argued the case for the 'tissue organisation field theory', which he has been developing over many years, alongside Ana Soto, his longtime colleague who holds the prestigious position of Blaise Pascal Chair at the École Normale Supérieure in Paris.

Dominant theories about mechanisms of DNA damage came in for critical scrutiny by Indraneel Mitra, director of the translational research programme at the Tata Memorial Centre. Another iconoclast venerated for his original thinking, Mitra proposed a new model which focuses on the patho-physiological role played by circulating fragments of DNA and chromatin, which act as DNA damaging agents when they are freely uptaken by healthy cells. These circulating fragments are released into the blood from dying cells during the programmed cell death process, apoptosis. The causal link proposed between these bits of biological detritus and DNA damage could throw new light on what causes cancer, and open up potential new avenues for prevention and treatment.

For those of us who live by the edict "In God we trust, rest please bring data," the unassuming Ian Tannock from the University of Toronto, Canada, gave an engaging keynote on the relevance of randomised controlled trials in clinical practice. He exhorted the audience not to be over-impressed by a successful single trial, and to interpret practice-changing randomised placebo-controlled clinical trials with particular caution. "Repetition of important results is essential before changing practice," and "clinicians should expect less benefit and more toxicity when applying the results of clinical trials in routine practice," were his two central messages.

The profound, urbane Ronald DePinho, President of the MD Anderson Cancer Institute, Houston, gave a rousing keynote speech on The Cancer Moonshot – Making Cancer History. He detailed the monumental efforts of the US Government, and MD Anderson in particular, to conquer the scourge of cancer in our time. He surveyed the current landscape of available services at the MD Anderson, and talked about how investments in technology, personnel and time are pushing the scientific community closer to an all-out cure.

> **"We find it difficult to sit complacently with this 'rah–rah' scientific culture"**

His was a bold, exhortation – a tad political – that stood somewhat alone against the more sceptical, insistent view that we need to reassess our outmoded view of this disease. These sorts of claims about the death of cancer, aka moonshot, aka making cancer history, which seem to stand exposed by the triumphant march of this disease, are what prompted the organisers to call this conference questioning the grounds for such certainty. But DePinho's sincere yearning for cure and commitment to getting the science right struck a chord with the audience.

The meeting closed with a lineup of the distinguished faculty taking the stage to deliver a circumspect but sobering narrative on the three-day marathon.

To me, the Mumbai conference on New Ideas in Cancer was a provocative, eye-opening preview of the glaring, and obvious cracks in the foundation of the war against cancer; a laudable effort by a handful of creative, intrepid, and bold academic clinicians, who are urging us to look where nobody else is looking.

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'We've been there'

the Metaxa oncologists who went public about their lives as patients

Doctors get cancer too, but not many of them choose to make a documentary film about the experience. **Vasiliki Michopoulou** talked to some who did, and asked them why?

It's October, 2004, and Nikos Karvounis, director of the First Oncology Clinic at Metaxa cancer hospital in Piraeus, Greece, is signing his own medical notes. He is 55 years old, and has just been informed that he has cancer in his intestine. It is the hardest time of his life. He feels that time is starting to run backwards, and for the first time he finds himself in the position of his patients. He asks his colleagues to operate on him, fighting his own battle with cancer among his cancer patients, whom he keeps encouraging, while trying at the same time to encourage himself.

The emotions and insights generated by this 'two-way' battle would later be captured in a documentary by film director Stavros Psillakis. First shown in April 2012,

> "I feel so familiar with the disease that I think of it as a normal part of life, as a bell that reminds you that the countdown has started"
> *NIKOS KARVOUNIS*

Metaxa: Listening to Time heard not just from Karvounis, but from six other doctors at the cancer hospital who had themselves been diagnosed with cancer.

The film created quite a stir. Because, as Psillakis comments, we all think that doctors are invulnerable, "something like little gods".

"Working at a place where everything reminds you of your illness is scary," says Karvounis, who today is back in good health. A father of six, with a love of cinema – he's a particular fan of Tarkovsky – it was his idea to make this documentary. "Imagine looking at a case similar to your own. You examine your patient's medical file and you wonder why they are still alive, or why they are doing so poorly. You can't control it. I had never imagined that I would get cancer. It's hard because, as an oncologist, you know the biological course of the disease, you know how these people die, you can imagine what the end of your own life will be like. The worst thing is that you do not know if you're 'finished' or if you will live a little bit longer."

Karvounis believed that that he would be able to expose his life to the camera without appearing either to wallow in misery or to preach. "I saw it as exposing my inner self in a creative way," he explains, "allowing people to interpret the film in their own way and extract messages for themselves." He discussed the idea with a group of colleagues at the hospital, who had all been treated for cancer, and introduced them to the director, and the project grew from there. Despite its harrowing subject, the documentary comes across as a hymn to life, through the voices of the doctors diagnosed with cancer.

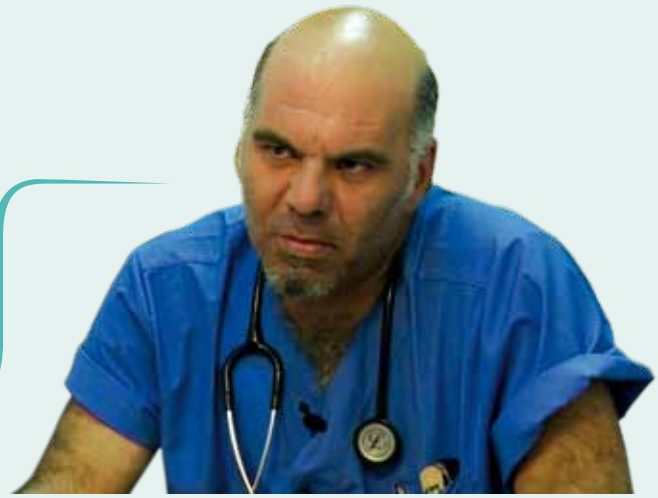
In the film, time acquires tremendous value. After the first shock of the cancer diagnosis, learning to live with the threat of the disease becomes a lesson in life, underlining the importance of every moment. Karvounis returned to his work as an oncologist within two months of surgery. Today, 11 years on, he says his attitudes have not changed, either towards patients or to himself.

"You do not change the existential anxiety you always have. I know well how cancer patients feel and react. I studied that before I became a patient. You do cry, if necessary for yourself and for the patient. But I'm not shocked by cancer. I feel so familiar with the disease that I think of it as a normal part of life, as a bell that reminds you that the countdown has started, that's all. We will all die, but for some of us the end is unknown. I even knew how I would die [if the cancer proved fatal]. I have seen the same story unfold for the last 29 years."

Nikos Bountouroglou is one of the three radiation oncologists who featured in the film. He was just 37 years old when, in 2008, he was diagnosed with cancer in the kidney. He had his own reasons for wanting to participate.

"This film is not a self-help guide for cancer patients and their relatives," he stresses. "It talks about the power of the human mind, for the collectivity, the social colour of each individual adventure. It talks about the existential condition of man when he faces extreme situations. I participated because I wanted to send the message that the doctor is a human being and has the same problems that you have, so we are the same. People hide their illness and my participation was a battle against that. There is no need to hide it. We need to come out and say it in public. Yes, I got sick!"

> “It’s that ‘click’ that you feel for the patients when you have experienced how they feel. It brings you closer to them”
> *NIKOS BOUNTOUROGLOU*



In contrast to Karvounis, Bountouroglou has noticed a change in his attitudes and his behaviour. “After my cancer, my relationships with people became more qualitative. I think of them first as human beings and then as a doctor. I have my phone available 24 hours a day for my patients. Unfortunately, I have lost patients, and I have cried many times thinking about what I could have done for them.”

He does try keep a distance, to avoid identifying too closely with his patients, but says he finds it hard to stay uninvolved. “It’s that ‘click’ that you feel for the patients when you have experienced how they feel. It brings you closer to them, and you fight alongside them in a double battle.” He says he always tells his patients about his own experience with cancer, and urges them not to let the disease take over their lives. “Do not lose a minute of what you are offered at any moment.”

The value of time, and regrets over wasted time, was something that also preoccupied his wife, Aphrodite, after his cancer diagnosis, Bountouroglou remembers. She thought about all the time the two of them had not used to the full, he said, and worried about the many things they might not manage to do.

Time also matters in other ways when you have cancer. Bountouroglou, who is vice president of the Metaxa hospital staff association, is acutely aware of the long and stressful delays in accessing treatment, and worries about the impact on patients. It starts, he says, with a four-month waiting list just to see a specialist. It can then take up to three months to get the results of diagnostic tests, followed by a further two-month wait for surgical treatment. Adjuvant radio- or chemotherapy, which should start soon after the surgery, also has waiting lists of typically around three months.

“The health system does not function properly, because of budget constraints, which is putting patients at risk,” he says. “There are many cases with fatal outcomes. While the number of new cancer cases is increasing, the public health system is deteriorating, and access to healthcare is becoming increasingly restricted. People are constantly being asked to pay for essential drugs or radiotherapy treatment or for diagnostic tests.” Health cannot be treated as a commodity, he says. “It is a social good.”

While Bountouroglou’s concerns about the state of cancer services are shared by many of his colleagues, they did not get an airing in the documentary. The intention, says Maria Pulizzi, a fellow radiation oncologist, and survivor of kidney cancer, was to create something positive.

When she was asked to participate in the film, less than two years since her cancer was diagnosed, metastases had already spread to her lung and bones. She was looking for drugs in early trials that could help her. She describes her participation in the film as a painful, but liberating, experience. When she finally agreed, it was for two reasons: “I wanted something optimistic to come out of this film, because everything around cancer is dark and miserable. We all agreed on this and I think that this was our great achievement. Moreover, this was for me a personal need.”

The second reason, she says, is that it brought people together. “We shared what was happening to ourselves and to other people, especially with colleagues, and we became very close.” This, can be seen in the film, she says, because, while each person spoke to the camera without

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knowing what any of the others had said, “when we finally saw the film, we found out that we had complemented each other like the pieces of a puzzle.”

Pulizzi feels the people with cancer suffer an added burden and isolation due to the stigma surrounding the disease. “Patients feel that they are being punished for something by God or fate. They can’t accept cancer as a pure coincidence.”

As a result, some people don’t even talk to the people closest to them about their cancer. This can lead to lasting problems, she says, because, however successful the treatment, the sense of a threat of recurrence never really goes away, so people need continuing support. Pulizzi was particularly pleased, therefore, by feedback from many patients who said the film had helped them speak more openly about what they were going through.

“We succeeded through the film in helping people talk about their illness with the people around them. They did share, those who were ready to do so.”

Some of her patients, she says, are so overwhelmed by fear that they retreat into a shell and find it difficult to talk. She finds that by talking about her own story she can help restore in them some sense of hope and confidence. “I always tell my patients, particularly young people who are scared or showing passive behaviour, that I had cancer. It’s a myth that there is no salvation. It’s now been seven years since my diagnosis, and for the last three and a half years I have been without medication. Completely cured. Even my colleagues didn’t believe it. There is great progress nowadays in cancer treatments. It’s not true that nothing can be done.”

Pulizzi believes that one’s attitude toward cancer is one’s attitude to life itself. But she recognises that she used to be too hard on patients when she pressed them to adopt a more positive attitude. When she got ill she understood how it felt not to be so brave.

“Fear is fear, whether you are a doctor or patient. The disadvantage is that, as a doctor you know what comes next, and you are more vulnerable, while the patient seems to be more protected in their ignorance. If you are someone who has learned to fight in life, you will be prepared to do it. But you cannot demand it. I demanded that of my patients and it was wrong.”

That fear, as she knows, spreads well beyond the person with cancer. Her son Andrea was only 13 years old at the time she was diagnosed, and Pulizzi describes it as the worst period of his life. “He became distanced, because of the fear of pain. He didn’t visit me in hospital. He didn’t even call me because he was afraid of what he would hear.”

The film, she says, helped Andrea, “because for the first time he heard me talking about my cancer.” And the story she told wasn’t all bad. “Cancer helped me too,” says Pulizzi. “It changed my attitude towards life and my priorities. I understood the true significance and value of things. I needed to be ‘slapped’ in order to recognise the real essence of life.”

Metaxa: Listening to Time, is available on DVD, with English subtitles, from *www.tetraktysfilms.com*, price €238 plus shipping.

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