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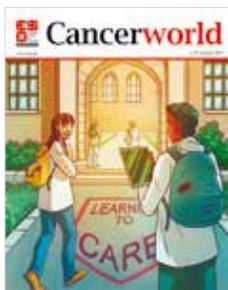


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Printed by

Grafiche Ambert, Verolengo (TO)

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Published by

European School of Oncology

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Registrazione Tribunale di Roma
Decreto n. 436 del 8.11.2004

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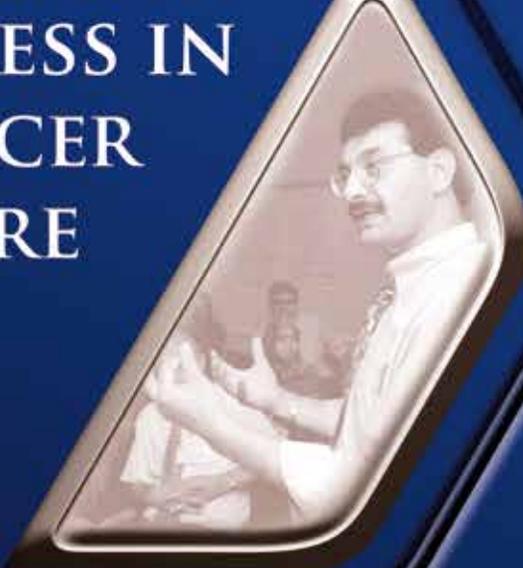
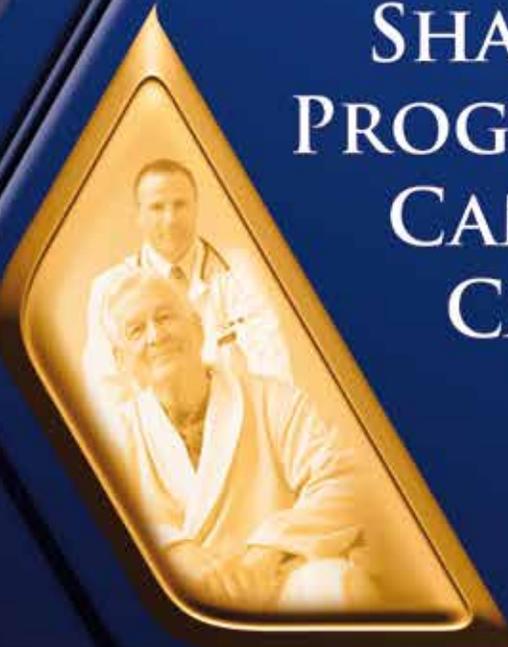
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Cancer World is published four times a year by the European School of Oncology. It is distributed at major conferences, and mailed to subscribers and European opinion leaders.



SHARING PROGRESS IN CANCER CARE



Sharing Progress in Cancer Care (SPCC) is a pioneering partnership between ESO and some of the world's leading pharmaceutical companies. Unrestricted grants from SPCC partners support a spectrum of innovative projects implemented by ESO such as *CancerWorld* magazine and the Masterclass in Clinical Oncology. The SPCC partners confirmed as of February 2019 are acknowledged on this page.

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Major changes ahead

Alberto Costa, **Editor**

Last year we asked you to let us know how you would like to continue reading *Cancer World* articles. You told us that, while some of you still prefer holding a print copy in your hands, the great majority now read the magazine on your laptops, phones or tablets. Responding to this, beginning in January 2020 we will become an online magazine, making use of the connectivity and flexibility that digital publishing offers, while retaining our critical, independent and broad approach to covering the cancer care stories that matter, on a weekly basis. This is just the latest step in an evolution that has been going on since we first launched.

I have always felt very proud of having come up with the idea for a scientific magazine on oncology, when I was Director of the European School of Oncology. Participants in our educational events would often say, “We can’t read *The Lancet* or *The New England* even when we’re sitting on the train going back from work!” They were asking for something lighter – summaries of articles, interviews, reports, investigative articles.

We started in 2001 with *Cancer Futures*, published by Springer Verlag, which quickly became known for its cover stories, with a picture of a well-known leader of the European cancer scene illustrating an article detailing their lives, achievements, hopes and aspirations. That experience came to an end when we understood that we needed proper journalists – articles written by doctors often left a lot to be desired

– and that ESO had enough experience to take on the role of publisher.

Cancer World was born in 2004 and, under its founding editor Kathy Redmond, it attracted a strongly motivated team of journalists from across Europe.

From next January, *Cancer World* will be published by a new non-profit organisation set up by ESO’s two independent foundations, called SPCC (Sharing Progress in Cancer Care). SPCC will take on responsibility for all activities that ESO previously ran with the support of unrestricted grants from pharmaceutical companies. ESO will limit its activities to those programmes of career development in oncology that are funded exclusively by its private donors.

As part of these changes, I’m delighted to be handing over the role of editor to Adriana Albini, Professor of Pathology at the University of Milan Bicocca. She will continue to work closely, as I did, with our dedicated team of editors and journalists, to ensure the magazine continues to provide our readers with the independent and challenging scientific coverage that you rightly expect of us.

Being editor of *Cancer World* has been a fascinating experience. I have greatly enjoyed the opportunity to redesign the magazine, making wider use of cartoons and illustrations and overseeing the transition to a primarily digital publication, cancerworld.net, thus extending our reach. Thank you for your attention and... stay with us!

Cancer World articles are published online weekly. If you receive *Cancer World* in print only, please sign up to our online version at http://bit.ly/CW_subscription to ensure you continue to have access to our full coverage of what’s happening in the world of cancer care.

How to become the best cancer doctor you can be

If your ambition is to excel at the oncology career you have chosen, you have to find your own pathway to success. **Anna Wagstaff** talked to three early-career oncologists who are trying to do just that, and asked them what worked, what didn't, and what tips they have for others who are determined to be the best they can be.



Assia Konsoulova, a medical oncologist at the Burgas cancer centre in Bulgaria, does not specialise primarily in gastrointestinal cancers. So when some patients with locally advanced gastric cancers were assigned to her care, she tried to refer them to specialists who could offer them neoadjuvant therapy, which the evidence indicates could improve their chances.

But neoadjuvant chemotherapy was hardly ever used in Bulgaria for gastric cancers, and no one wanted to do it, because of the greater complexity, the response assessment, and the potential added risk.

So Konsoulova decided she would take on the responsibility, and she managed their care herself. “And I proved that, just as it says in the literature, it works.”

Younger colleagues then followed her lead, she says. “They were motivated, so now I transfer my gastric cancer patients to them, and we work together, and as a result they are now building up their specialist experience.”

What made Konsoulova go the extra mile for these patients when others wouldn't?

Her specialty is breast cancer and neuroendocrine tumours, so it was clearly not superior knowledge. She cares deeply for her patients – but the same can be said for very many medical oncologists in Bulgaria.

What made the difference, in her view, was the experience and confidence in her own capability as a doctor that she had gained through a continuous search to learn and improve, which had included – crucially – spending time gaining hands-on experience in specialist centres abroad.

You've got to make it happen

Konsoulova realised early in her career that if she wanted to be a great cancer doctor she would need to go out and look for the experience and knowledge she needed. “When you start, for every young doctor it is not easy. You get lots of duties, lots of paperwork, night shifts, and then at some point you realise that your dedicated oncological education is not really happening.”

She applied for an EU scholarship to the Jules Bordet Institute in Brussels, and says the experience totally changed her idea about her chosen career. “I understood what oncology is really about – not just prescribing drugs and measuring response. It is care for patients, it is management and organisation, it's a way of thinking.”

It was at the Bordet Institute that Konsoulova got her first experience in the art of medical decision making. “I had a personal supervisor, who would ask me: ‘What would you do in that patient?’ ‘What would you expect in that patient?’ I had the chance to look at patients as their treating oncologist, to discuss with colleagues and then decide on the best options, and argue the case for my decision. And I was taught to always follow patients through to the present, to learn about whether previous management decisions had been right or could have been improved, so that you always learn from experience.”

Konsoulova returned to her post in Bulgaria, where she did her best to implement the new approach she had learnt. Over the next 10 years, she systematically built up her competences by travelling to attend practice-oriented courses

in clinical and medical oncology, as well as more dedicated courses about managing neuroendocrine tumours and breast cancer. Most recently she spent six months at the Champalimaud cancer centre in Lisbon – an international leader in breast cancer – where she also got the chance to further develop competence and skills in clinical research.

“The benefit of that education gets bigger the more you already know. You need a solid background”

“I was writing protocols, learning what was published during the previous month, and immediately discussing its relevance to clinical practice. There were, for instance, Journal Club sessions where, on a rotating principle, we would present what was new and relevant in the field, to really stay updated every single week. All relevant information was considered at the multidisciplinary team discussions and introduced into the patient management.”

While the topic was breast cancer, the approach, the expertise and the confidence related to oncology practice in general. So when Konsoulova returned home again, she felt able to respond to the needs of her patients with gastric cancers, while colleagues specialising in those cancers did not.

“Training is not something that starts and ends. It continues for

Top tip for young oncologists



Of the hundreds of powerpoint slides Hakan Buyukhatipoglu has encountered during his educational journey, this is the one he values the most

life,” says Konsoulova. “Every time I go abroad for a course or a specialisation, I see that I’m getting better, but the benefit you get of that education is getting bigger the more you already know. You need to have a solid background. The improvement is much more significant the more you are advanced with your knowledge.”

Get a good foundation

In neighbouring Turkey, Hakan Buyukhatipoglu, now working as a medical oncologist in Adana, took a similarly proactive approach to his own education and training. His ambition is to work at the frontiers of clinical knowledge, designing and conducting trials in his specialist field of breast cancer.

To that end he has spent years looking for courses and fellowships and other training opportunities, learning from the people around

him, as well as reading, reading and more reading.

Like Konsoulova, he stresses the importance of starting by building a solid background in oncology. For him, this comes down to three essentials: First comes molecular oncology, which he says is not much included in medical oncology training, yet is key to accurate diagnostics and to understanding the rationale behind different treatment approaches. Buyukhatipoglu did a partially grant-funded cancer biology course offered by Harvard, but says there are other good options available in Europe.

Second comes radiology – also not included in medical oncology training. Having some knowledge of how to read and interpret images is important, he says, particularly when you are comparing before and after treatment. “There are a lot of courses available online and at medical schools,” says Buyukhatipoglu, but he chooses to study this alone

– and learns by discussing his cases with radiology colleagues.

The third essential, in his view, is a grounding in clinical trials biostatistics, because oncology guidelines are based on clinical trials and studies. “If you want to draw some conclusions you have to have some knowledge about biostatistics. Why is this study important? How was it done? Is the design correct? How was the patient selection done? Was it randomised? How was it interpreted? This is really important.”

Buyukhatipoglu loves learning and, beyond his own specialism, has spent time learning about pulmonology, radiology, radiation oncology and psychology, and incorporating that knowledge into his practice. But with so much to learn it becomes very important to know how to use your time wisely. The single presentation slide he feels has helped him most is about how young doctors should prioritise their activities.

You’ve got to want it

“I think the life of a doctor, especially from a poorer country, is running around with your handbag, and a small luggage on your shoulder, and then getting educated. You cannot be properly educated until you reach your 40s, and everyone should know it is like this.”

So says Elona Cekani, who did her initial training in Tirana, Albania, but has spent much of the past six years travelling around Europe to build the knowledge and experience she needs to be confident of giving her patients the best possible treatment and care.

As a ‘clinical oncologist’, Cekani needs to master both medical and radiation oncology. And in a country

that is only just beginning to organise cancer care along specialist lines, she needs a good grounding across the major cancers, while also pursuing her specialist interest in lung cancer.

“It is very simple if you have a structure, an institute, a university, that tells you: this is your curriculum, you have to do this, you have to have this exam and then you go and perform everything that you have been told. It is very difficult to go around Europe and look for what you need, and to see what you are missing and look around to see how you can fill the gaps. Especially when you don’t have financial support and you are always hunting grants and fellowships.”

Cekani has invested an immense amount of her time filling out applications, and studying the literature to find gaps where she could propose a research project that might win her a research grant or fellowship in a leading centre.

Good experiences include six months in Madrid doing a Masters degree in advanced technology and radiation therapy. “I was taking part in the decisions, discussing cases and being able to see these patients and visit them with my supervisor, as part of a team.” She learnt “all the basics” involved in radiotherapy, and also trained in stereotactic (multi-directional) radiation therapy – expertise that she says she can use on returning home, as “you can now do it even with a linac”.

The experience also taught her that she needed a better grounding in medical oncology, which led to another good, hands-on experience working as a fellow at IOSI, the Oncology Institute of Southern Switzerland, where she is completing a series of rotations in the main

cancers and in palliative therapy, which she sees as an essential part of her training.

However, successful applications didn’t always turn out as she’d hoped: Cekani had some very mixed experiences with visits to institutes based on watching rather than participating. “I can say that observership periods are generally not useful. When you go to countries that are much more developed than yours, you expect a lot, and you sacrifice a lot to be in these training programmes. Unfortunately I have seen sometimes that people don’t know what to do with us. I couldn’t orient myself very well and there was a lot of empty time, and that is not very useful for a young doctor. When you get the chance for hands-on participation, this is very different.”

The attitude of your supervisor is important, she adds, and she advises potential applicants to get in touch with them before travelling. “Understanding their background, having an interview with them, seeing how eager and passionate they are, can help you a lot. Then you get the first impression of whether you are going to go around corridors in your empty time or whether you are sharing your passion with your supervisor.”

Don’t rely on a mentor

While Cekani feels let down by some of the people who were tasked with supervising her, she has often found great support and mentorship from people with no formal responsibility for her training and from colleagues and teams she was working with. “Getting a proper network around you helps you a lot. Often I have seen people who inspire me to innovate, create, strive for perfection,

practise a lot. ...Working in different structures in different hospitals, you get a sense of what is working and what is not. It’s about never losing your critical sense, and being able to get the best from everyone.”

She had some very mixed experiences with visits to institutes based on watching rather than participating

Cekani makes special mention of the role of online communities as rich sources of discussion and knowledge sharing. This is something she first experienced while in Spain, where she joined a WhatsApp group that included more than 300 doctors.

“Everyone was discussing cases with colleagues all around Europe and the world. It was very helpful, because every time somebody gave you an opinion, they sent the articles they were basing that opinion on. I’ve learnt a lot from them and I’m still trying to practise this kind of learning.”

While social media is not an alternative to multidisciplinary team work, she says, “it is something useful that everyone can do in their own country, even in developing countries.”

Make your own choices

As Scientific Director of the European School of Oncology, Fedro Peccatori’s job is to help young oncologists become the



Anatomy of an oncology education

Assia Konsoulova, Bulgaria

1997–2003	Degree in medicine, Varna Medical University, Bulgaria
2010	EU sponsored clinical unit visit at the Jules Bordet Institute, Brussels (2 months)
2011	Degree in Internal Medicine
2011	ESO First Balkan Masterclass in Oncology, Dubrovnik (5 days)
2013–2014	ESO Breast Cancer Update course, parts I and II, Lisbon/Milan (2 days each)
2014	EORTC-ESMO-ECCO-AACR Methods in Clinical Cancer Research, Flims, Switzerland (1 week)
2015	Degree in Medical Oncology
2015	EXCEMED Masterclass in Molecular Oncology, Prague (2 days)
2015	Advanced Course in Diagnosis and Treatment of Neuroendocrine Tumours, Uppsala, Sweden (4 days)
2016	PhD Medical University – Varna (<i>thesis on Biomarkers for predicting response to anti-angiogenesis treatment in metastatic colorectal cancer</i>)
2017	CECOG (Central European Cooperative Oncology Group) Immunotherapy Academy, Vienna (2 days)
2017	Advanced course in Immunology, Kiel, Germany (4 days)
2017	CECOG fellow at AKH General Hospital, Vienna, Austria (2 months)
2018	ESO Fellow at Champalimaud Clinical Centre, Lisbon (6 months)

best cancer doctors they can be, principally through the courses, fellowships and online teaching offered by the School. He argues that having a great mentor can help guide your understanding of what is important and what isn't. But he cautions that they are a rare commodity, and there are dangers in depending on other people – no matter how eminent or well-intentioned – to tell you how to develop your career.

“You have to understand what is important yourself. So you have to

be proactive, and interact with your mentor and sometimes explain to them what is important to you. You shouldn't just be passive and say, ‘I'll do what the professor told me because he is a very important big professor.’ Everybody at times would like to have someone who acts as a navigator for them. But it's up to you to decide what you need, be that a particular specialism or veering more towards research or whatever excites you.”

Peccatori speaks from experience. He started his career fascinated by

the scientific challenge of cancer, in the days when advances in molecular biology were beginning to reveal the intricacies of the disease. But along the way, his focus on excelling in pathology altered, not because his love of scientific exploration waned, but because he wanted to work with patients. “So I changed my mind and I said, maybe I'll do something more clinical.”

“Every young oncologist must feel their way towards their chosen path, and pursue it as best they can”

Decades later, Peccatori is very pleased he made the decision he did, and shifted his career path from a predominantly scientific focus towards developing knowledge and experience in providing cancer care for women who want to preserve their fertility – a passion he continues to pursue part time at the European Institute of Oncology in Milan.

The decision to opt for a career as a hands-on doctor in his chosen specialist area was the right one for him, he stresses, and it is up to every young oncologist to feel their way towards their own chosen path, and pursue it as best they can – “It's very personal.”

Learn to care

Patients need a doctor with the knowledge to do the best for them. But if that doctor doesn't take the

time and empathy to understand that patient, the pressures they face, their values and priorities, that knowledge won't translate into the best care, says Peccatori. That is why the motto of the European School of Oncology is 'Learning to care', "not 'learning the latest molecular mechanism', not 'learning to treat cancer' – important though that is".

Patients want oncologists to be present for the long term, he says, whether or not the cancer is curable. "The impact of cancer and treatment can last a long time, and doctors need to support their patients and also learn about long-term effects that would otherwise go undocumented.

"We see a lot of excellent oncologists who are not truly great oncologists because they forget how important it is to establish a true relationship with their patients."

This is asking a lot, admits Peccatori, because oncologists work under pressure, "We are human beings, we are distracted, sometimes we are stressed, and tired, and burdened with a high administrative workload."

A big challenge, perhaps is

“Great clinical judgement can only come with practice. It's why ESO encourages young oncologists to travel to get hands-on experience”

Anatomy of an oncology education



Hakan Buyukhatipoglu, Turkey

1994–2001	MD degree, Ankara University School of Medicine, Turkey
2002–2007	Internal Medicine residency, Gaziantep University School of Medicine, Gaziantep, Turkey
2010	MD Anderson Cancer Center, Internal Medicine Observership, Houston, Texas
2012–2015	Medical Oncology fellowship, Gaziantep University School of Medicine, Gaziantep
2013	ESO–ESMO Masterclass in Clinical Oncology, Ermatingen, Switzerland (1 week)
2014	ESO Clinical Training Centres fellowship, European Institute of Oncology, Milan (3 months)
2016	ESO/Ulm University Certificate of Competence in Breast Cancer (1 year)
2015–2016	Harvard University Global Clinical Scholars Training program – methods and conduct of clinical research (1 year, with three 4-day onsite workshops)
2018–continuing	Harvard University High Impact Cancer Research Course – skills to envision, design and lead cancer research projects (1 year, with three 5-day onsite workshops)

the nature of the doctor–patient relationship in oncology. "Cancer puts a very strong burden on the patient – probably more than any other disease – because of the perception of how cancer impacts on your daily life, even if you are cured... You are standing in a position where you have the knowledge, you are healthy, you sometimes have the power to decide whether this drug can be given or not, whether a patient can go on that protocol or not.

"It is difficult to handle well if you are not very keen to understand and take responsibility for this oblique relationship."

It's about wanting to be a great human being, and not just a great

doctor, says Peccatori.

But can that be taught? "Everything can be taught, and everything can be learnt," he says. "We teach by example."

He mentions as an example the ESO–ESMO Masterclass in Clinical Oncology, which lasts five days and starts with a full day on communication skills, where oncologists and cancer nurses learn side by side – "That is so important". It allocates time to discussing real patient cases, submitted in advance by participants, to demonstrate the process of working out the best options and how to convey choices to the patient.

Great clinical judgement, says Peccatori, can only come with practice.



Anatomy of an oncology education

Elona Cekani, Albania

2011–2014	Clinical Oncology residency, Nene Teresa University Hospital Centre, Tirana, Albania
2013	Clinical observership at hepato-biliary department, Hammersmith NHS Hospital/Imperial College, London (3 months)
2013–2014	Clinical observership at the Department of Radiotherapy, Hammersmith and Charing Cross NHS Hospital/Imperial College, London (3 months)
2016–2017	Masters in Advanced Technology in Radiation Therapy, IMOncology, Murcia University, Madrid (6 months)
2017	ESO fellowship at the Department of Radiotherapy at the Oncology Institute of Southern Switzerland (IOSI), Bellinzona (6 months)
2018–2019	ESO/Ulm University Certificate of Advanced Studies in Lung Cancer (1 year)
2018 ongoing	Fellow doctor, Department of Oncology, Oncology Institute of Southern Switzerland (IOSI)

It's one reason why the School is so keen to encourage young oncologists to travel to centres to get hands-on experience.

As one of the young oncologists who took advantage of such opportunities, Assia Konsoulova describes how she learnt the difference between treating patients and caring for them.

In Bulgaria, she says, she felt that the task of the doctor was to see the patient for a certain 'problem' and solve that particular problem.

By contrast, her experience while at the Jules Bordet Institute and the Champalimaud, was that, "the patient is seen as someone with a chronic disease who you will see and care for along the years. So when considering a certain treatment, you discuss the patient – their comorbidity and potential prognosis – you

discuss potential options and evolutions, and the patient's preferences and their expectations."

Multidisciplinary meetings were "exceptionally different" to the discussions she was used to at her home institution, which would rarely last more than a few minutes.

"We as caregivers become a part

She decided staying at her prestigious hospital would not give her the opportunity to be the great doctor she wanted to be

of their life as we treat their disease. We don't simply treat the cancer, but the patient with cancer. This is a really different way of thinking."

No boundaries no barriers

Roger Wilson has been living with cancer almost since Konsoulova started at medical school. He learnt about the damage done by incompetent management when he was first operated on without any of the diagnostic tests required to establish that the lump in his leg was cancerous.

He has played a leading role in initiatives to give patients and advocates a greater voice in decisions affecting care, including at the level of research and the way care is accessed and delivered. He is one of two patient advocates who are on the faculty of the week-long workshop on Methods in Clinical Cancer Research run by EORTC, ESMO, ECCO and the AACR, where he helps participants think about how to incorporate patient perspectives into their trial design.

What does Wilson want from his oncologist? "I expect them to have all the background that they need to address the issues that I am presenting with. I want them to be a doctor. I want them to be caring. I want them to have empathy. I want them to have an understanding that they are not treating a disease they are treating a patient. I want them to be able to work with the other staff – usually a nurse in attendance – with an understanding on both sides that they are working towards a common end."

Wilson knows full well how hard it is to do all of that, particularly

in the current era. “The feeling I have is that chemotherapy and the traditional cytotoxic route was still very disease oriented not patient centred. And as we’ve moved into precision medicine, the science is so mind boggling we are actually moving into a biochemical-centred approach rather than even disease-centred, and the danger is that the patient is absolutely nowhere in this equation.”

He feels for young oncologists who are trying to master the science while keeping a grip on the essentials of being a great doctor. “They are taking on so much already, it is hard to see them coping with anything else.” The key lies in how their more senior colleagues behave, Wilson believes, because young doctors model themselves on what’s in front of them.

With decades of experience as a media producer, manager and company director before becoming a patient, advocate, and teacher, Wilson feels he has become good at picking out which junior oncologists will go on to lead teams and departments that deliver an outstanding service. “They have a sort of buzz about them. No boundaries, no barriers, taking responsibility for getting the best possible answer for the patient, rather than saying: this is my job.”

It’s an important point, not least for the many young oncologists who make an effort to learn new and better ways of working through visiting centres of excellence abroad, but then find it a struggle to put their knowledge and skills to good use when they return to their home institutions.

Konsoulova says that, on returning to her home institution, while many people acknowledged the

value of the time she had spent gaining experience at international centres, others were quite hostile. “They say, ‘OK you were on vacation in Brussels or in Lisbon. Now you have to work more in order to compensate.’”

“Having an open mind is probably the single most important factor in becoming the best cancer doctor you can be”

She found it difficult to introduce a team approach to treatment and care, as there was resistance to anyone addressing problems outside their own immediate area of work. The attitude is “this is your job and this is *not* your job.” In the end, Konsoulova decided that staying at her prestigious university hospital, where her career was well outlined and heading upwards, would not give her the opportunity to be the great doctor she wanted to be.

She left, and moved to work in a large oncological centre where, she says, the management are ambitious to improve, “and are asking how best to do that.”

“I was invited as a specialist, to join a team of specialists and great oncologists. I have the opportunity to work and develop my career, to influence colleagues, the management, the policies, the decision-taking process on a long-term basis. So hopefully this will influ-

ence my career but also influence the decision-taking in the entire institution, which is finally what we are all fighting for.”

Cekani from Albania is also determined to implement new approaches in her home country. To keep her impressions fresh she keeps a diary – a tip she learnt from her father – and writes down first and second impressions, criticisms of herself, of others, and of the institute.

Otherwise, she says human nature is to adapt quickly and forget what drove you to start down a path. “Everything I’ve written down since I’ve started my training is how I can implement this and how I can improve this in Albania.”

She’s aware of the barriers, as team work, specialisation, patient-centred care have not been part of her country’s medical culture. Yet she remains very optimistic. “I’m always in touch with my friends and colleagues... I’m confident the new generation is changing... They are becoming more open minded,” she says.

For Cekani, having an open mind is probably the single most important factor in becoming the best cancer doctor you can be. Her advice to young oncologists is this: “Educate that beautiful mind of yours, and never stop questioning everything, thinking critically about everything, and discuss, discuss, discuss, because medicine is not an absolute science, it is a relative science. Everyone has to make their own decisions, but that must be based on the right training and education and keeping your mind open, because everything is changing so fast.”

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Is precision medicine ignoring people dying of cancer?

While we're pouring resources into learning what keeps cancer cells alive, with the aim of blocking their supply lines, there is next to no interest in the molecular pathways that end up choking the life out of cancer patients, or in the biology behind the longer and better lives that palliative care can offer. **Janet Fricker** talks to some lone voices about why this has to change.

While death itself may always represent the Great Unknown, the biological processes that contribute to making life no longer viable should be amenable to exploration, yet we know very little about them.

Whether dying from cancer, or other conditions like heart failure or chronic obstructive pulmonary disease, a limited field of research suggests there are integrated biochemical systems that result in a final common pathway, leading to the body shutting down and death. But little is understood about the underlying components of these pathways and how they interconnect.

“It’s extraordinary that in over 5,000 years of medicine, the only thing we really know about death is how to describe it,” says Seamus Coyle, a palliative care consultant from the University of Liverpool, UK, who is one of the few investigators undertaking research into the biological processes of death. “The reality is that the fundamental biology of how people actually die represents a complete black hole.”

The deficit of knowledge around the science of death was highlighted by Julia Neuberger in her 2013 review of the Liverpool Care Pathway, ‘More Care Less Pathway’. In the review, Neuberger commented that there was no precise scientific way of telling accurately when a patient was in their last few days of life. Her recommendations, which have gone largely unheeded, were for the need to boost research into the biology of dying.

Greater understanding of the biological foundation of death would shed light on patterns of death and identify new approaches for palliating distressing symptoms. It would also introduce more certainty about

how long people have to live, allowing them, their families, and their doctors to better manage their final months, weeks and days of life, and help to prevent futile anticancer treatments that are all too often given to dying patients.

“The fundamental biology of how people actually die represents a complete black hole”

Such knowledge might also help inform how we care for our patients in what has been described as the ‘grey zone’ – the space occupied by long-term survivors of cancer with metastatic disease. Identifying the final pathways could result in new avenues of treatment targeting the molecular events underlying the lethal biology. Having a scientific foundation for understanding the processes of death would also better inform legal and ethical issues at the end of life, such as assisted suicide.

“By understanding so little about the biology of death we don’t know how to optimally care for terminally ill patients,” says Irene Higginson, a palliative care consultant who directs the Cicely Saunders Institute at King’s College, London. The lack of knowledge, she adds, means that we are in effect abandoning the 1.3 million people who die from cancer in Europe each year.

While there is cause for celebration around recent advances in cancer treatments, a statistic that is conveniently forgotten is that 40% of people diagnosed with cancer ultimately die from the disease. Today,

the dying are like new world explorers navigating uncharted waters, with much of their care based on the clinical intuition of palliative specialists rather than having a solid evidence base in rigorous clinical trials. A study undertaken at MD Anderson Cancer Center, Houston, Texas, for example, found that one third of prescriptions given to cancer patients in an acute palliative setting were off-label, signifying the lack of FDA-approved medications for symptom control (*J Pain Symptom Manage* 2017, 54:46–54).

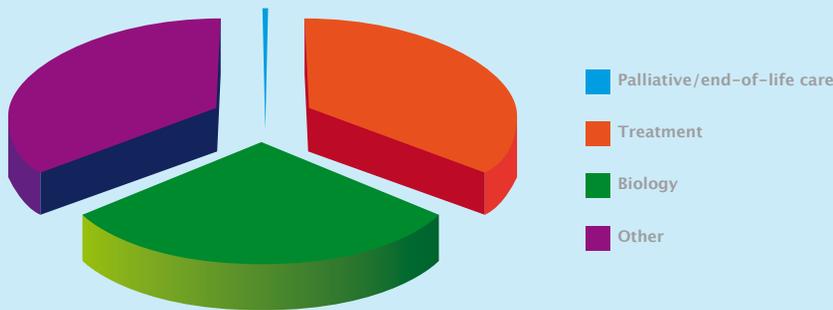
Underpinning the paucity of end-of-life research is the disproportionate amount of research funding spent on oncology versus palliative care. Data by National Cancer Research Institute partners in the UK for 2015–16 found that, of the almost £580 million (circa €630 million) awarded for cancer research, only 0.33% (less than £2 million) was allocated to palliative and end-of-life care (ncri.org.uk/ncri-cancer-researchdatabase, accessed on 14 August, 2018, cited in the *Lancet Oncol* 2018, 19: e588–653).

A similar landscape emerges in the US, with statistics from 2010 showing that palliative care research accounted for only 1% of the National Cancer Institute’s \$5 billion research funding.

Charities, such as Cancer Research UK, for example, have taken strategic decisions not to fund palliative or end-of-life care, and have instead focused on the zeitgeist of precision anticancer medicine. And while the European Commission made EU money available for palliative care research in their Health, Demographic Change and Wellbeing Work Programme, with the 2017 Horizon 2020 call for ‘novel patient-centred approaches for survivorship, palliation and/or end-of-life care’, most of the funding was

The pathways leading to death attract almost no research funding

Cancer Research Funding UK, 2015–16



Source: National Cancer Research Institute. Research spending in cancer 2015–16 in the UK. www.ncri.org.uk/ncri-cancer-researchdatabase. (accessed Aug 14, 2018). Cited in *Lancet Oncol* 2018, 19: e588–653

Forty per cent of patients diagnosed with cancer go on to die from the disease. Yet figures from the UK for 2015–16 show research into palliative/end-of-life care received 0.33% of the £580 million (circa €630 million) total funding for cancer research, and only a small proportion of that goes towards understanding the biology.

US figures show a similar picture, with only 1% of the National Cancer Institute's total appropriation for 2010 of US\$5 billion being awarded to palliative care research (*Lancet* 2012, 379:519).

awarded to organisational work, such as service delivery. “There has been altogether less emphasis on the biology of cancer death, symptom management and how patients live with their cancer,” says Stein Kaasa, who heads the European Palliative Care Research Centre at the University of Oslo, Norway.

Good palliative care prolongs life

“End-of-life research has undoubtedly been the victim of oncology's recent successes in targeted, immune and proton therapies,” says

Kaasa. “There's been a societal shift where the public thinks it's now possible to cure most cancers.” With all the hype surrounding drugs, he adds, it can be all too easy to lose sight of the fact that good palliative care prolongs life.

Evidence for the efficacy of palliative care comes from a landmark study by Jennifer Temel, from Massachusetts General Hospital, in Boston, where 151 patients with metastatic lung cancer were randomised to receive early palliative care and standard oncology treatment or standard oncology treatment alone (*NEJM* 2010, 363:733–42). The study found that

patients who received early palliative care not only experienced a better quality of life, reduced burden of symptoms, and less depression, but their median survival time was also longer (11.6 months for those receiving palliative care versus 8.9 months for standard oncology treatment, $P=0.02$).

Cytokine overproduction activates multiple clinical pathways that result in conditions such as cachexia and hypercoagulability

A second study, undertaken at Memorial Sloan Kettering Cancer Center, New York, randomised 766 patients starting routine chemotherapy for metastatic solid tumours to usual care or electronic patient-reported outcomes (PROs), where subjects reported 12 common symptoms to a web-based platform, triggering email alerts to nurses responsible for their care (*JAMA* 2017, 318:197–98). Results showed that median overall survival was 31.2 months in the PRO group versus 26 months in the usual care group ($P=0.03$).

“The effect sizes of good palliative care of two to five months are comparable to some of the new therapies for lung cancer. But they've additional benefits of having no side effects and being remarkably cost effective,” says Kaasa, who works as both an oncologist and palliative care consultant.

Biological mechanisms of palliative care

One theory of what lies behind the beneficial effects of palliative care is that it could be exerting a fundamental influence on the biochemical processes involved in the final common death pathway. “By supporting patients with palliative care and making them feel less stressed we might be beneficially influencing cytokine levels in their body,” suggests Higginson, who recently failed to secure funding for a study quantifying the effects of palliative care on patient cytokine levels.

Over production of cytokines, says Kenneth Pienta, from John Hopkins University, in Baltimore, Maryland, represents one of the three main clinical categories responsible for death in cancer patients. The other categories are death due to specific organ failure (as occurs, for instance, in patients with brain or liver metastases) and opioid-induced comas that can result in patients with bone metastases requiring higher and higher doses of opioids (as can occur in prostate and breast cancer). In a review written back in 2007, entitled ‘The Lethal Phenotype of Cancer: the Molecular Basis of Death Due to Malignancy’, Pienta wrote that cytokine overproduction activates multiple clinical pathways that result in conditions such as cachexia, which he estimated to be responsible for 20% of cancer deaths, and hypercoagulability, which he estimated to be responsible for 10% of cancer deaths, including those from pulmonary embolism (*CA Cancer J Clin* 2007, 57:225–41).

The concept of a ‘terminal cancer syndrome’ was described in a 1988 paper outlining how patients with all types of advanced cancer are affected by similar systemic manifestations,

including changes in appetite, disturbed sleep, low mood, fatigue, asthenia (loss of strength) and hypercoagulability, which occur regardless of the primary or metastatic site (*Arch Intern Med* 1988, 148:1586–91). This final common pathway, Pienta believes, is mediated by cytokines.

In his review Pienta describes studies that he undertook showing that cytokines, including tumour necrosis factor- α (TNF- α), interleukin-1 (IL-1), as well as IL-6, IL-11 and TGF- β , were upregulated in several cancer types and contributed to the lethal phenotype.

What determines whether patients start to produce these cytokines and embark on their fatal course?

“These analyses suggest that multiple cytokines/combinations of cytokines cause morbidity and mortality for cancer patients and offer multiple avenues for therapeutic development that need to be addressed,” wrote Pienta, adding that no single cytokine or subset was upregulated in all advanced cancers.

Other unanswered questions include whether the harmful cytokines arise from the tumour itself, or the microenvironment surrounding the tumour, or both, and what determines whether patients start to produce these cytokines and embark on their fatal course.

In the intervening 12 years since Pienta’s review was published, it is noteworthy that there have been

few studies exploring the complexity of the final common pathway, and that Pienta himself has moved on to better funded avenues of research, such as studying the tumour micro-environment.

Cachexia

One of the few areas that has received research attention is cachexia, a wasting condition combining loss of skeletal muscle and adipose tissue in patients with late-stage cancer. Here a complex cascade of cytokines act on multiple targets leading to biological responses that culminate in progressive weight loss, anorexia, anaemia, depletion of lipids, and severe loss of skeletal muscle. However, the majority of cachexia trials targeting cytokines have not achieved positive outcomes. “The reason these antibody trials failed is that no one undertook the precision medicine approach of measuring which cytokines were raised in specific patients,” says Pienta, who believes there is widespread variability in cytokine production between individual patients.

Taking a multi-modal intervention approach that does not target specific cytokines, but instead addresses the multifactorial pathophysiology to reduce inflammation, says Kaasa, may prove more successful. The MENAC study, which Kaasa is undertaking with Marie Fallon from the Edinburgh Palliative and Supportive Care Group, in Scotland, is combining omega (n-3) polyunsaturated fatty acid supplements and nonsteroidal anti-inflammatory drugs (NSAIDs) to target inflammation, with a light exercise programme to strengthen muscles (clinicaltrials.gov identifier NCT2330926).

The phase III study, which in April

Taboos and ethics

The low priority placed on end-of-life research has its origins in society's cultural discomfort with death. Medical researchers prefer to focus on prevention and cure, with some oncologists viewing death of their patients as professional failure. Conducting studies on the dying has been controversial, with a traditional view that patients should not be exposed to research at such a sensitive stage in their lives. "From the point of view of clinical studies, end of life is a very challenging area. Patients are often frail, they have multiple physical problems and can experience rapid and unpredictable deterioration," says Marie Fallon, from the Edinburgh Palliative and Supportive Care Group, Scotland. But people who are dying often welcome the opportunity to share their stories, reflect on their experiences, and contribute to knowledge generation, she says. An Australian integrative review of 10 studies concluded that patients with little time left often expressed the view that "it was important that they used that time to do something of enduring value," and that they wanted to help others who may be in a similar position in future (*Palliat Med* 2018, 32:851-60).

2015 started recruiting patients with incurable lung and pancreatic cancer who were at high risk of developing cachexia, is unusual for a palliative care study, in that it involves a number of centres in Norway, Sweden, UK, Canada and Germany. Having multiple centres, each providing access to local funding opportunities such as university grants, has proved key to their success in financing a trial of this size, says Kaasa.

In addition to exploring efficacy of this approach in cachexia, Kaasa hopes their collaborations with basic scientists reviewing blood samples taken from patients enrolled in MENAC will shed more light on the terminal biochemical pathways.

Predictive biomarkers

Seamus Coyle, who is unusual in being a palliative care consultant with a PhD in cell and molecular biology, is taking urine samples from patients in their last few

weeks of life to identify metabolites that can be used as biomarkers to predict how long patients have left. While the study could provide valuable information for patients and their families needing to make plans, Coyle believes it could also provide additional insights into the fundamental biochemical pathways involved in the end of life.

"Knowing the metabolites that change towards the end of life is helping us to identify biochemical pathways that change during the dying process," says Coyle, who received some initial seed funding from the Wellcome Trust health research charity, but then experienced a period of three years of working in his own time before receiving some funding from his own St Helens and Knowsley Hospitals NHS Trust in Liverpool.

At the European Palliative Care Research Centre, recently relocated from Trondheim University Hospital to the University of Oslo, Kaasa is developing plans for addi-

tional multicentre palliative care trials, including testing the efficacy of a ghrelin receptor agonist in cachexia and opioids in neuropathic pain, as well as intervention studies in brain metastasis. "Multicentre studies are essential to recruit the large samples of patients that are needed for external validity of studies," he says.

Making the biology of cancer death a priority

One of the big challenges, according to Kaasa, is the lack of scientists equipped with the skills for basic biological research in the field, which he says is part of a self-perpetuating vicious cycle. "The lack of trained investigators makes it challenging to find suitable referees to review grants and papers, and we've problems identifying enough qualified MDs with end-of-life research experience to hold chairs in palliative care," he says.

A survey by José Miguel Carrasco, from the University of Navarra, in Pamplona, Spain, identified only 50 full professors of palliative care across the 43 (out of 53) WHO European Region countries who responded (*J Pain Symptom Manage* 2015, 50:516-23). "If medical schools don't have chairs of palliative care, there's no one to champion the cause for the undergraduate medical school curricula, yet further reducing the likelihood of having people sufficiently experienced to do research," says Kaasa.

The European survey revealed that 14 countries (33% of those who responded) did not include palliative care in their medical school curricula.

This vicious cycle is exacerbated

by the lack of profile of the research that is actually happening in this field. Irene Higginson, from the Cicely Saunders Institute, points out that, “When investigators try to secure grants, they often hide the term ‘palliative care’, to make the study more appealing to funders.” This can make it hard to identify such studies using PubMed and Google search, which can be confusing enough because of the many and overlapping terminologies that are used, such as palliative care, end-of-life care, supportive care, personalised care, patient-centred care, or psycho-oncology.

“Research on the basic science of death needs to be embedded in a continuum of oncology research”

Kaasa, who chairs the ESMO group for Integrative Oncology and Palliative Care, has ambitions to establish a biannual ESMO conference dedicated to palliative care research in oncology, with a strong emphasis on biological science. “People do present palliative care biological research at ASCO and ESMO, but it just disappears in the big programme,” says Kaasa. The European Association of Palliative Care holds a biannual meeting, he adds, but that conference caters for all areas of medicine, and not just oncology.

“To really develop understanding of the biology of cancer death we need to establish a new forum

A new platform for end-of-life research



France has taken up the challenge of end-of-life research with the establishment, in October 2018, of a national platform, part funded by the French Ministry of Research and French Ministry of Health, to provide an infrastructure to boost palliative care studies.

One of its first steps was to identify relevant investigators, by means of a survey. “As we had little idea who was out there, we used a chain letter approach, where we asked respondents to pass the questionnaire on to anyone else they knew who was working in the field,” explains Elodie Cretin, the director of the Platform, who is a research coordinator for the French Institute of Health and Medical Research (INSERM) at the University of Besançon. “We’re currently analysing around 300 responses and hope to use this information to identify research priorities and to create an online directory that will enable investigators to connect with each other.”

Additional plans for the platform include lobbying charities and government agencies, such as the French National Society for Cancer, for funding, and providing young investigators with training on research methods, how to write papers, and the special ethical considerations that need to be taken into account.

that will attract clinicians and basic scientists from all over the world. It’s by coming together that we can scope the range of research that’s already taking place, and achieve a critical mass of investigators to establish research priorities to advance the field, nurture the next generation of scientists and start to give this vital area of medicine the priority it deserves.”

Marie Fallon, from The Edinburgh Palliative and Supportive Care Group, argues that research on the basic science of death should not be hived off into some specialist niche, but needs to be embedded in a continuum of oncology research. “You can’t just look at patients in the last few weeks of life when they’ve exhausted all

available treatments. You need to understand how the biology evolves throughout the disease trajectory,” she says, adding that if investigators only consider patients who have failed chemotherapy, they are looking at biased samples. “To really understand what is going on, we need to review the whole group and understand the relevance of different patient phenotypes.”

Kaasa agrees: “We need to understand the host’s reaction to the cancer both at the start of the disease trajectory and at the end of life. It’s only with such knowledge that you can start to understand why cancers kill some people and not others.”

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Our Values We recognize the diverse aspects of nursing across Europe and strive for equality for all cancer nurses regardless of gender, race, sexual orientation or disability.

Key activities

EONS organises a range of educational events for European cancer nurses throughout the year, including conferences, masterclasses and workshops. For more information on the EONS12 Nursing track which will take place during the ESMO Congress (27 September-1 October) please visit the EONS website.

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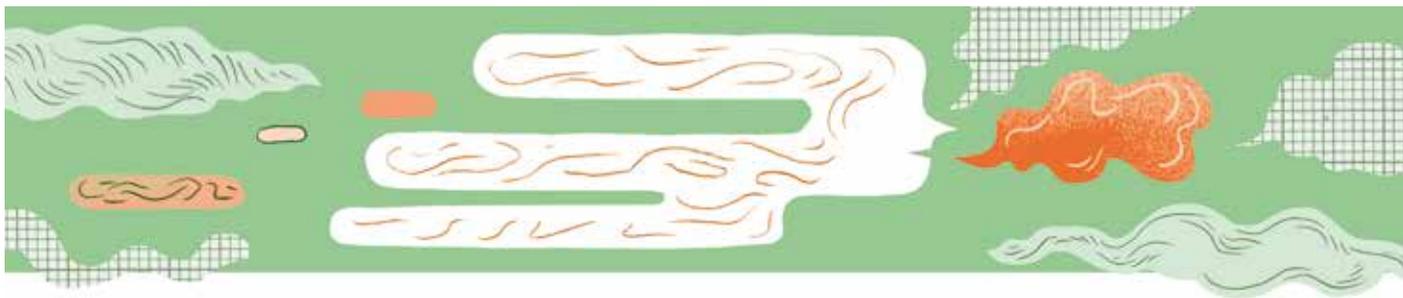
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Maria Nazinkina Del Grande: bridging two worlds

A daughter and granddaughter of Russian heads of radiology, now living and working in southern Switzerland, medical oncologist Maria Nazinkina Del Grande is keen to play a part in bringing her two worlds closer together. She's finding language offers a bridge not just to her native land but to the furthest frontiers of the Russian-speaking world, as **Maria Delaney** reports.

Career choices are often influenced by family. When the intricacies of medical cases had been poured over on a daily basis at the dinner table, Maria Nazinkina's decision to study medicine came as little surprise. As a third generation doctor, a legacy hung over her profession, with her achievements often credited to her parents. In order to carve out her own career, after qualifying as a doctor in St Petersburg, she moved to Switzerland, where she now works as a medical oncologist at the Oncology Institute of Southern Switzerland (IOSI), under her married name of Maria Del Grande.

Del Grande is no stranger to moving. Her family relocated multiple times within Russia during her childhood. She spent the first three years of her life in Novokuznetsk, a Siberian city quite close to the Mongolian border. Her grandmother Zoria L'vovna Brodskaya, herself a leading radiologist, had moved there in 1960 after she'd been advised to leave St Petersburg – more than 4000 km away – because she was Jewish.

After that came several moves between these two distant cities as Maria's mother, Iuliia, pursued her own career in radiology, married a fellow radiologist and started a family,

eventually settling in St Petersburg, where she is now assistant professor in the radiology department of St Petersburg University, as well as carrying on clinical and research work.

The difference with Maria's own travel decisions is that she had more of a choice in her destiny. In spite of living abroad, she hasn't forgotten her roots, and has been developing links with cancer communities in Russia – concentrated in Moscow and St Petersburg – and in Kyrgyzstan – a country geographically much closer to her native city of Novokuznetsk, where Russian is widely spoken. And whether by accident or design, she has also stayed true to the family tradition by marrying leading Swiss radiologist Filippo Del Grande, vice director (medical/scientific) of the recently launched Imaging Institute of Italian Switzerland.

One ambition two realities

Maria Del Grande is positive about the new generation of oncologists in Russia, saying they are very different from the previous generation. Her connection with the NN Petrov National Medical Research Centre of Oncology

in St Petersburg involves a mixture of consultations about patients and educational lectures. “They are very motivated and want to achieve the best results that they can,” she says. One reason for this change is that, while the previous generation didn’t lack ambition, they were cut off from the world due to the Cold War. Though this has changed, Del Grande says that many challenges remain, including a lack of mentors and research structure.

According to the latest data from IARC, the WHO International Agency for Research on Cancer, the most frequent cancer types are the same in Russia and Switzerland – breast, prostate, colorectal and lung. However, the mortality rate is greater in Russia for all of these cancers. Overall, the risk of dying from cancer before the age of 75 years is more than 50% higher in Russia (13.5%) than Switzerland (8.8%).

Knowing both healthcare systems as she does, Del Grande says that patients in Russia have a greater mistrust of doctors and don’t go to them with the early warning signs of cancer. The problem is exacerbated by the lack of a proper family doctor structure. When patients do turn to healthcare, they tend to look for many opinions, often delaying treatment still further. It all contributes to more patients presenting with advanced disease, she says. Lack of any structured palliative care service also contributes to a high suicide rate in patients suffering from poorly treated pain and other burdensome symptoms.

Another big difference between the two countries flagged up by Del Grande is the quality of communication between doctors and patients. Communication training is not included as part of post-graduate oncology education in Russia, so when she first began working in Switzerland, she found this aspect a bit of a culture shock – all the more so because she was working in paediatrics, and interacting with parents who were sometimes extremely anxious and would take their child to the emergency department for “simple problems,” she says, worrying, for example, that a cough might be pneumonia.

This wasn’t the only shock for the enthusiastic young doctor, as she discovered that, “even the students knew more than me about the material and how to work with patients.” Determined to succeed, she worked day and night during her first two years abroad, going home for only six hours sleep. “I was only 23. I don’t have that energy now.”

Taking a break from paediatrics for a year between placements to work in internal medicine, Del Grande found what she was looking for. “I remember the first day in internal medicine – I thought: finally I understand everything. I had no problem with the patients, prescriptions or other medi-



cal personnel. It was so easy and so comfortable.” Following a rotation in rheumatology in Johns Hopkins Hospital, in Baltimore in the US, Del Grande moved into oncology and is now working in a gynaecological oncology team in IOSI.

As part of this, she runs the multidisciplinary meeting twice a week. She finds this structure and the ease of communication between team members and other colleagues makes solving issues for patients very simple. If she has a query, even with a family doctor, she can pick up the phone and talk to them straight away. It’s a big contrast to Russia, she says, where “there is no approach to cure the patient as a team,” and everybody works alone with no direct communication between oncologists and family doctors.

Profile

Balancing clinical and research work

Recently, Del Grande's family life changed with the birth of her son Alberico. She had to return to work after only four months maternity leave, and initially found it very challenging. "I didn't expect that it would be so tough for me. I thought I'd be the perfect mother and the perfect professional." This wasn't helped by baby Alberico refusing to sleep during the night for the first ten months. Between her added responsibilities as a doctor and newly extended family, she says she now has absolutely no time left for her husband.

She also has almost no time left for her research work, which she says is "on pause", apart from some small projects as well as her work with the European School of Oncology (ESO). This is because, in Switzerland, there are no protected research hours outside university hospitals. Del Grande feels this affects the careers of mothers in the hospital, as research publications are necessary for promotion, especially to professorship. She points out that there are no mothers at this level in IOSI, and many careers stagnate at lower levels. She would like the hospital to make it easier for women shouldering childcare responsibilities to be able to do research and progress.

She points to examples of systems that are more researcher friendly in other countries where she has worked. In Italy, they used to finish seeing patients at 2.00 pm, while in the UK they saw patients for two full days, with the other days free from clinical work. "I'm very fortunate, as my husband is trying to help organise some free time for me to do some research," says Del Grande – but she will have to do this research in her free time and not during working hours.

Sharing knowledge

And she has ambitious plans for that free time over the coming two years. She's currently organising a new project together with the radiology department, researching radiological examination combinations, to find out which are most useful for patients. She has a particular interest in exploring the potential of using muscle composition measured by CT scan as a measurable predictor of response to chemotherapy, progression free survival, and other clinically relevant outcomes in ovarian and breast cancers.

In addition, she is going to be the coordinator for all of the ESO Eurasia projects from 2020. The ESO role builds on work she has already done on a cooperative programme

in Kyrgyzstan, supported by ESO and the Swiss Cancer League, which she has coordinated since 2016. Launched by Franco Cavalli, the scientific director of IOSI, and Fedro Peccatori, scientific director of ESO, the SILK project – Setting up digital mammography, breast services Improvements and Learning bridges in Kyrgyzstan – aims to improve breast cancer diagnosis and treatment in this mountainous lower-middle income country, which borders on China to the east, and has Russian as one of its two official languages.

It has already notched up many remarkable achievements, including putting in place a quality-controlled diagnostic system for breast cancer, developing and publishing guidelines adapted to local circumstances and resources, and involving patient advocates. Part of this involved improving the quality of mammography and setting up an immunohistochemistry laboratory that can reliably test tissue samples for ER, PgR, Her-2 and Ki-67 expression. Key elements include a personnel exchange and shared educational programmes between Kyrgyzstan, Switzerland and Italy.

As Del Grande explains, the lab was set up with funding from the Swiss government, but initially the local medical personnel had neither the knowledge nor skills required to use it. "The most important thing is not equipment, but how to work with this equipment. That's why ESO was involved: to improve the education." It's a common pitfall, she adds, having seen this in Russia, where "they have a lot of machines but they don't use them, or don't use them in a proper way." Similar attention was paid to educating and skilling up radiologists in mammography – work that was led by Chris de Wolf, a Swiss medical expert in breast cancer screening.

To ensure sustainability of the services, Cavalli, Peccatori and de Wolf made extensive efforts to involve doctors, patients, patient organisations and the Government.

**“We involved the whole chain
from the patient to government.
This is the point”**

Getting the Minister of Health involved is one of Del Grande's key recommendations when working with middle- or low-income countries. "They are very directorial [in] structure and you will never do anything without the permission of the leaders of the country," she explains, adding that it's a lot easier once they are on board. Not only did the Kyrgyz Minister of Health support the programme, but the

Government decided to invest in two linear accelerators, which she says is a great improvement, as the country currently has only very old cobalt machines. They also restructured the National Oncological Centre, following visits from programme members and with the help of substantial funding from a Canadian company with local mining interests. “It’s amazing the speed that they did it,” remarks Del Grande.

Patient education was delivered as part of the programme. The project team worked with a local NGO, Ergene, and patient groups, who provide education and support. These groups helped by lobbying for changes in the healthcare system that tied in with the programme. Other keys to success, says Del Grande, include having someone on site for the entire duration of the project who leads everything, “because you can’t do it by yourself, if you don’t move”. Projects like this need timescales of years, not months, she says. Good local media coverage was also important in driving funding and support. “We involved the whole chain from the patient to government. This is the point.”

Addressing language barriers

Having a native speaker on the team is also a plus. “I’m the Russian native speaker, and it is very easy for me to connect with the people locally because we have more or less the same background.” Some doctors in Kyrgyzstan are learning English now, enabling them to create a direct connection between specialities there and in Europe, pathologist to pathologist for instance, without having to have Del Grande in the middle. This was not previously possible.

Language is also a problem in Russia, where Del Grande says the majority of doctors don’t speak English. In hospitals she has worked with, she says only about 10–15% of doctors speak the language well. There’s an absolute lack of language education, she adds, as in university they don’t read medical information in English, but have it translated into Russian.

“I find that makes no sense. You have to push the person to learn the language and open their mind.” This lack of language skills creates an unhelpful reliance on the few who are confident in English to act as liaisons between colleagues in Russia and other countries. Del Grande says this also has an impact on research, as medical knowledge is not easily accessible. “You shouldn’t reinvent the bicycle,” she comments.

Her Russian accent when speaking Italian in her adopted home region of southern Switzerland has the locals con-



Coming from a similar background and sharing a language means Del Grande can play a pivotal role in promoting efforts by the European School of Oncology (ESO), and others, to work with the cancer community in Kyrgyzstan. She is pictured here with a patient and with ESO’s Scientific Director, Fedro Peccatori, at one of the breast cancer consultations they attended during their most recent visit to the National Centre of Oncology and Haematology in Bishkek, Kyrgyzstan, as part of the SILK project to improve breast cancer diagnosis and treatment in the country.

fused – most patients assume she’s from the German part of the country, she says. She’s much happier about her communication with patients than when she first arrived, and has grown used to Swiss culture. “We understand each other very well and they’re happy to be [treated] by me.” Being useful, she feels, is “the most beautiful thing” about working in oncology.

Looking ahead, she is optimistic about the progress that genetics and precision medicine can achieve, and remarks that, when she was away from clinic recently for a year, on her return she found that the first line of treatment had changed in every field. “I saw the patients that were treated differently, how they changed.”

As for her links with Russia, she wants to achieve more results there with not only the ESO Eurasia Masterclasses in Clinical Oncology, but also on-site visits, with reviews and audits. She wants to create centres of excellence that will “have the opportunity to educate other doctors, and show others how they can improve their work”. It’s all spurred on by her desire “to give back something valid to my country” – an ambition she will pursue with the ESO Eurasia projects in the coming year.

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EUROPEAN ACCREDITATION AND DESIGNATION PROGRAMME FOR CANCER CENTRES



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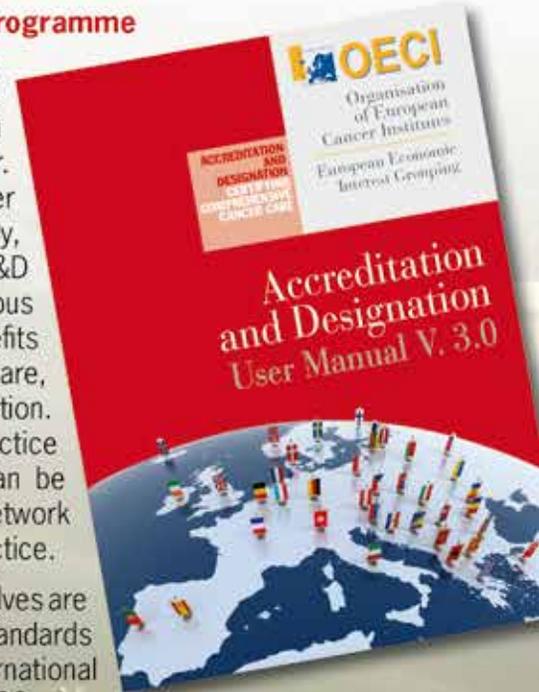
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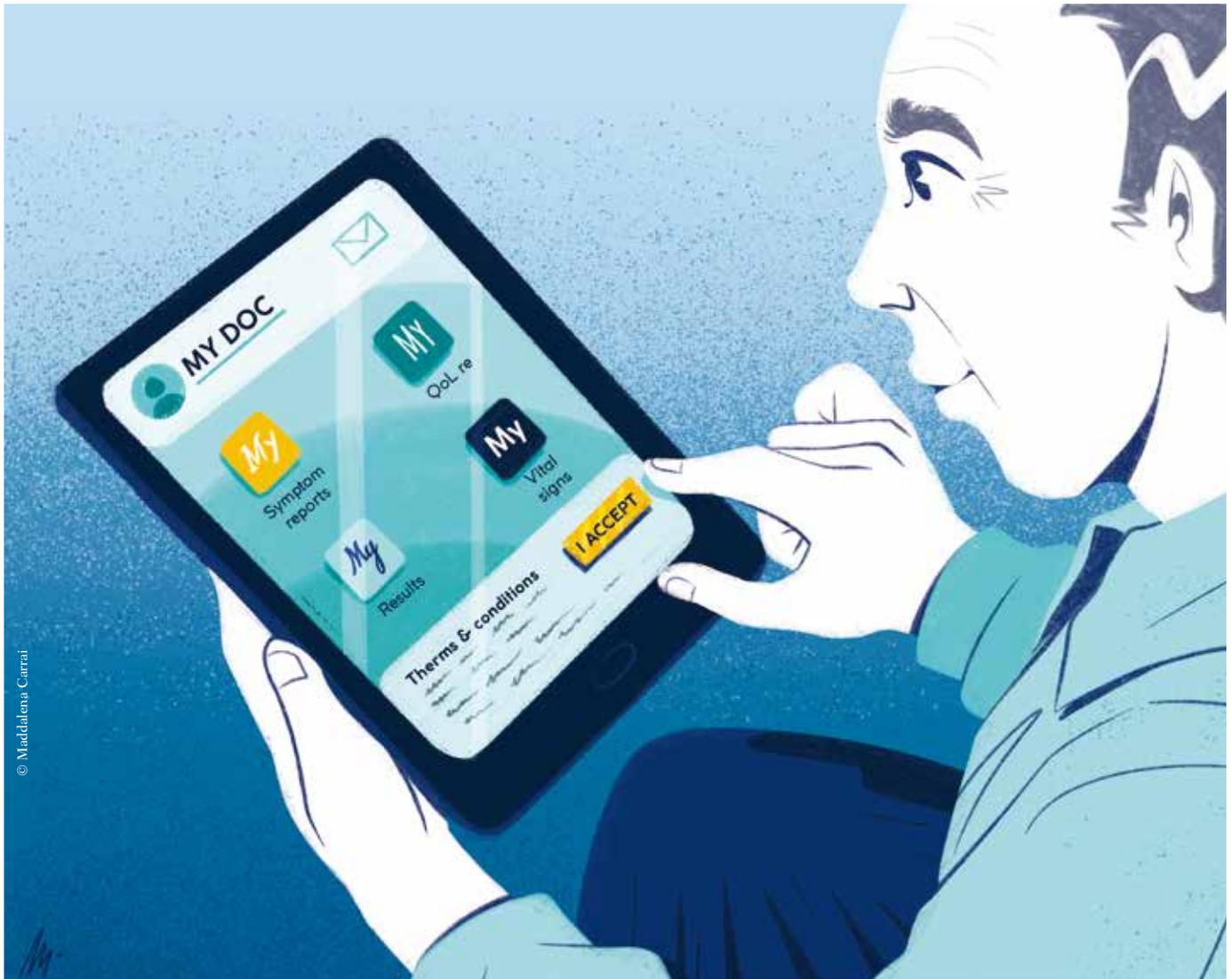
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If your Cancer Centre is interested in applying to the A&D Programme, please find the application form and all the needed information at: <https://www.oeci.eu/Accreditation/>



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The future is digital – but is it safe?

Joined-up patient-centred care requires sharing of data between patients, oncologists, hospitals, labs, GPs, nurses and even social care. But as apps designed to gather and share this data proliferate, so does the risk that the data ends up in the wrong hands, and possibly in identifiable form, as **Peter McIntyre** reports.

Following treatment for prostate cancer in 2015, Eric Hounslow from Hampshire in England joined a “supported self-management” study at University Hospital Southampton for follow-up care.

It was his second cancer. Six years earlier he had undergone surgery for an unrelated kidney cancer and experienced a traditional follow up of regular tests and anxious waits for results. Today there is virtually no waiting. He uses the internet to access the results of PSA tests almost as soon as they are done.

“It’s an extremely tense time, because so much rests on what they’re going to tell you,” he says. You’re praying for good news, but waiting a week or more to find out. Now I can give my blood at 9.00am and access the results myself later that day, saving me from all that stress every six months.

“I can access my appointments, medical details, personal information and surgery reports from anywhere in the world. I can also communicate with my surgical team quickly and easily. As someone who has experienced both systems, I’d recommend this scheme to anyone.”

Eric Hounslow, now 72, is just one example of the way that patients are gaining autonomy in follow-up care. Health professionals are increasingly able to use real-time data to monitor and support people in the community living with conditions as varied as diabetes, dementia and cancer. Patients with long-term complex conditions can give immediate feedback on how the treatments impact on their quality of life.

The potential is exciting, but there are also dangers, and a need for patients to keep their data safe – especially with the increasing use of

apps on mobile phones.

By 2018 there were more than 318,000 health-related apps downloadable from online stores worldwide, with more than 200 being added every day. Most are lifestyle apps: counting steps, monitoring heart rates or sleep patterns, or other proxies for ‘wellness’.

On average each app requested four ‘dangerous’ permissions, such as reading other accounts and noting when the user is engaged in a call

However, about 15% of health apps give patients advice on medication, allow patients to provide feedback, or are designed for health professionals.

They will increasingly be used for two-way traffic – a patient uploads health data to a physician or to a hospital and is then able to download reports or some of their medical records.

The proliferation of apps designed to share this sort of personal medical data is giving rise to concerns. When researchers tested 24 serious health apps they found that, unknown to the user, 19 were sending sensitive information to a remote server (*BMJ* 2019, 364:1920). On average each app requested four ‘dangerous’ permissions, such as reading other accounts on the device and noting when the user is engaged in a call.

Although data from devices are anonymised, the phone can be uniquely identified, and when two databases are combined anonymity can be stripped away.

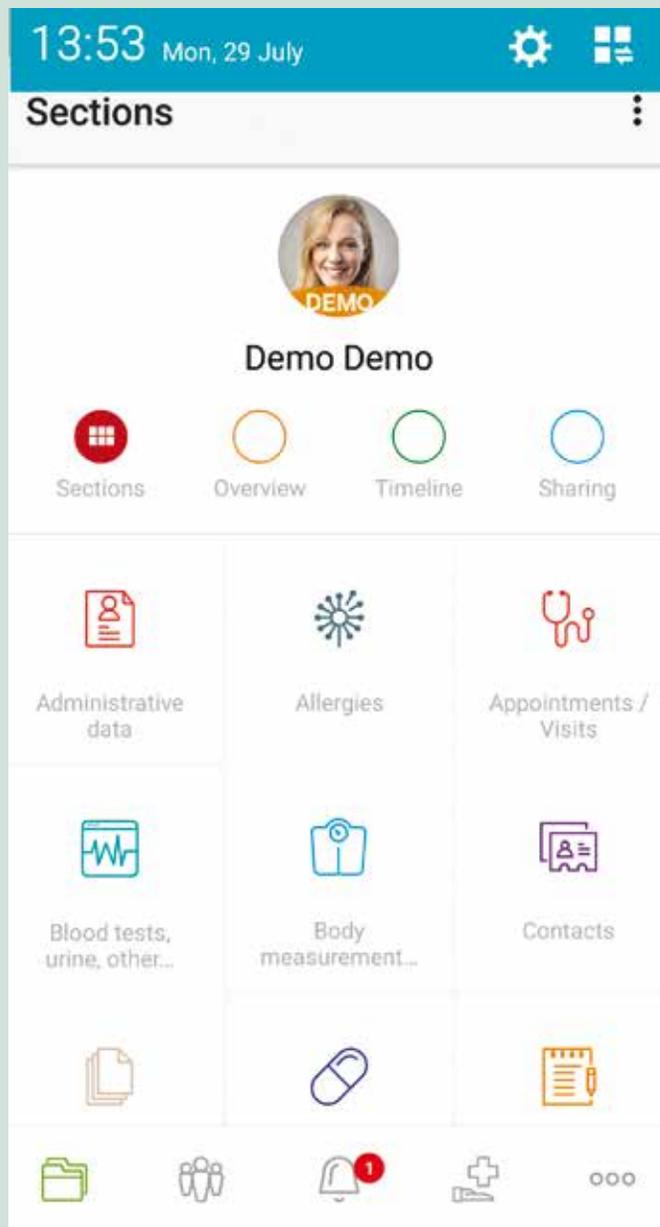
More than 20 years ago, Massachusetts Governor William Weld approved the release of hospital insurance data, reassuring the public that it had been anonymised. Until Latanya Sweeney – now a Harvard Professor, but in 1996 a bright research student – cross-referenced the anonymous data against the electoral register (which includes gender, age and birth date) and sent the shocked Governor his personal health records, including diagnosis and prescriptions.

Today’s risks may be no less startling. The authors of the 2019 *BMJ* paper point out that people often download apps without understanding that they are giving permission to collect information on user activity, target advertising and share information with business affiliates. “The lack of transparency, inadequate efforts to secure users’ consent, and dominance of companies who use these data for the purposes of marketing, suggests that this practice is not for the benefit of the consumer.”

One of the researchers, Ralph Holz, a lecturer in networks and security at the University of Sydney, says that finding ways for patients to protect their data is one of the burning questions of the day. “Even if you are transparent at one point in time and everyone knows what is going to happen with your data, that is not necessarily going to guarantee that the regulation does not change or the company does not change ownership or move to another jurisdiction.

“My hope does not rest with technology. My hope rests with forward-looking policy making and hopefully

When the drive for faster health data became personal...



For Vincent Keunen, getting better and faster cancer treatment and research about cancer is personal. In March 2007 he learned he had chronic myeloid leukaemia (CML). Three months later his ten-year-old son Pierre was diagnosed with Ewing sarcoma.

Vincent Keunen found his way onto a Glivec trial and, 12 years later, now describes his cancer as “a detail” in his life.

His son was not so lucky. Pierre lost his leg and went through two years of intensive treatment. The cancer still affects his life and requires regular check-ups.

Vincent Keunen was a software engineer and businessman with 25 years of experience. He had already developed software widely used in his home country of Belgium to exchange information between hospitals and family doctors.

But he felt helpless and frustrated.

“Glivec is super-efficient and has almost no side effects. CML was deadly before Glivec, with a few months – maximum two years – survival. So it went from a death sentence to no worse than a cold really. At some point I asked how can I contribute to develop new drugs like that, which are so efficient and super-targeted to the disease?” In his vision, he saw cancer patients pooling experiences to help researchers speed up the search for effective treatments. In real life he saw his son undergoing numerous treatments in different centres that were not properly joined up. “Doctors don’t exchange data, they don’t have time for that. IT systems don’t talk to each other as well as they should. If you go from one hospital to another that is difficult. If you go from one country to another – well ...”

He also noted that, when his son had his annual check-up, some tests are repeated several times, when the technology exists for medical staff to monitor things like blood pressure and side effects continuously and remotely.

also with ways for consumers to find redress in case their data has been used in ways that they did not agree to. The big question being how can they even prove how their data has been used unless it is some kind of public leak and someone discloses business practices.”

Hospital data sharing systems

Few European hospitals allow patients to access hospital records – but they are making moves to become more connected, aided by developments in the US. As part

of ‘Obamacare’, US hospitals were compelled to introduce an interface (API) to exchange data with the outside world if they wanted to receive insurance money. The US standardised on a protocol called Fast Healthcare Interoperability Resources (FHIR), and that is now

He began to work on a smartphone app - now downloadable as Andaman7 - that would make it easy to share data between patients, healthcare professionals and researchers.

“What drove me to develop Andaman7 initially was the goal of giving patients a way to easily collect data from all sources in a way that is easy for them to use.”

“Security by design means that the data does not reside on any server. It is only saved on your smartphone”

He designed it for the phone because that is what everyone carries. At the same time, Keunen recognised that people are wary about allowing personal data to be held in the cloud. The software is designed therefore to hold everything only on the phone, even if the user decides to share with a family member or health professional.

“We follow the GDPR principles of privacy by default and security by design. Privacy by default here means that if you put data directly into Andaman7 it won't be shared with anybody by default. Security by design means that the data does not reside on any server. It is only saved on your smartphone. It is a lot more difficult to hack your phone than to hack a server in the cloud. And even if it was hacked, the pirates would only have access to one record. Not a big deal.”

Keunen is also offering the platform to allow pharmaceutical companies to collect real world data from patients on the effects and side effects of treatment.

Currently the Andaman7 app has only been downloaded by about 23,000 patients worldwide, but it is being used and validated in a number of specific projects.

- At the Central University Hospital (CHU) of Liège in Belgium 3,000 patients are using the software to access their medical records - every time they have

a hospital visit they automatically receive a report on their phone.

- The Lithuanian National Cancer Patients Association (POLA) is using the software to build a patient-driven registry.
- The EORTC is using Andaman7 to digitise a quality of life questionnaire - currently in two countries and eventually in ten. Patients will have the choice of filling in the questionnaire on their phones or on paper.
- It is being used by a pharmaceutical company to develop a cohort of patients for a clinical trial and by another company to feed data back to patients who have taken part in a trial.

Laboratoires Réunis in Luxembourg, with centres in Belgium, France and Germany, is allowing patients to use Andaman7 to directly download pdf reports on the results of blood or urine tests. Patients will eventually be able to track changes graphically, using the international LOINC standard (a universal standard for identifying medical laboratory and clinical observations).

Keunen believes that being able to access records and input data will improve health literacy, especially for patients with complex conditions like cancer. But he is frustrated at the slow rate at which hospital electronic health records are being opened up to accept patient input.

“Almost no hospital is ready to take in patient data. They need to extend their software, because it is only used by doctors, nurses and health professionals, and you don't even know if it is the doctor or the nurse who entered the data.

“Patients want to be empowered and to know more. If a patient is 45 years old and has had a rare disease for the past 15 years, this guy has been talking to the best specialists and has had lots of hours researching this problem and knows more about this disease than 99% of doctors.”

increasingly being taken up in other English-speaking countries and in Europe.

However, clinicians and researchers face major challenges when comparing data collected in different systems. To address this, ASCO published in June 2019 an mCODE

initiative - short for Minimal Common Oncology Data Elements.

Richard Schilsky, ASCO Chief Medical Officer, told *Cancer World*: “More than 15 million of individuals with cancer have their data in some sort of electronic health record, but they are prioritised in

different ways and the different systems collect data in many formats, making them incompatible with one another. This affects the opportunities for the patients, because their doctors are unable to compare the cases and their outcomes. It also affects the opportunity for research,

Systems & Services

especially in the drug domain. We could collect a lot of information on side effects after the official trial ended, if we were able to dig into a large number of electronic health records.”

The NHS is now encouraging hospitals to develop their own data sharing systems, which are presumed to have greater local support

Pooling data from many sources opens opportunities to draw treatment lessons from big data but, despite the GDPR data protection regulation, it may lack public trust. The UK NHS suffered a spectacular rebuff a decade ago when the Government decided to pool information from patient records, drugs companies, insurers and others in a new, centralised NHS patient records database. It foundered on lack of trust by family doctors, who were expected to upload patient records, after it became clear that anonymised data would be shared with private companies. The Care.data initiative was put on hold in 2004 and scrapped two years later.

The NHS changed tack and is now encouraging hospital trusts and regions to develop their own data sharing systems, which are presumed to have greater local support. An NHS map of these personal health record schemes shows that

cancer services and patients are in the forefront of attempts to improve care.

The Movember Foundation supports the TrueNTH UK self-management and follow-up study led by Southampton University that, amongst other things, allows 2,675 men previously diagnosed with prostate cancer to use an app to access PSA results online, via the NHS-hosted My Medical Records system.

Despite initial concerns that patients saw results before clinicians had assessed them, men were not adversely affected even when test results were abnormal.

There were only slight improvements in outcomes, but high satisfaction levels from patients. And although direct healthcare costs were higher, because the approach includes workshops and support workers, the overall cost was lower because men used fewer health services, and the programme met NICE cost-effectiveness adoption criteria.

This study identified a need to embed patient reported outcome measures (PROMs) in an IT system where patients can be monitored remotely.

Prostate Cancer UK and the Movember Foundation are now calling on all UK health trusts to adopt the programme. Heather Blake, Director of Support and Influencing from Prostate Cancer UK described the approach as “a win-win for cash strapped NHS Trusts”.

In another example, the Leeds PPM+ platform connects more than 35 systems across health and social care and has accumulated integrated care records for 2.8 million patients. It began with cancer services in 2003 and broadened out as it proved its worth. Today it links

hospital and GP records with hospices, social care and mental health services, allowing clinical and care staff across the region to access vital information about a person's care. It delivers more than 50 million pieces of information every month and is accessed every 3.8 seconds. And in this system patients are able to hold their own electronic records.

As such schemes spread, the NHS has produced a Code of Conduct for those developing apps. This includes the right of patients to opt out of information being used for anything other than individual care and treatment, the need to be fair, transparent and accountable, and the need to ‘bake-in’ data protection in business practices as well as in software.

However, giving patients the ability to access and input data while keeping them safe from exploitation poses significant challenges, as the European Haematology Association (EHA) is finding, with the development of its electronic monitoring app HM-PRO.

Data security is a concern, and for the time being HM-PRO does not save data or send information from the phone to a server

The aim is to develop a tool that captures patient experiences and makes a measurable difference to clinician decision taking, says Esther Oliva, a haematologist at the

Grande Ospedale Metropolitano Bianchi Melacrino Morelli in Calabria, Italy, who co-chairs the EHA Scientific Working Group on Quality of Life and Symptoms. HM-PRO is already being used in the global Acute Leukaemia Advocacy Network (ALAN) survey to gather information on treatment, experiences and quality of life. It has been translated cross-culturally for use in Europe, China, Korea, Japan and Israel, and will be available in 15 languages within three years.

Significantly, in a study that compared paper and electronic versions of HM-PRO, 87% of patients (average age 63) preferred using the electronic version, which can be downloaded as an app onto their phones. However, data security is a concern for the EHA Scientific Working Group and for the time being HM-PRO does not save data or send information from the phone to a server.

Esther Oliva said that while this clearly protects privacy, the app only becomes fully useful when it connects patients with their clinical teams. “At the moment it is a surrogate for a potential app that might be able to be used in clinical practice, but it requires development to protect patient data. The app should communicate with the server of the health department or hospital, and that is what we are planning to work on.”

One of the HM-PRO developers Sam Salek, Professor of Pharmacoeconomics at the University of Hertfordshire, England, and co-chair of the EHA Scientific Working Group, has a vision where patients use the app to submit reports on quality of life and side effects of treatment into a secure repository, and an algorithm alerts

health staff if something appears to be wrong. They use their phones to fill in questionnaires before each outpatient consultation, which can be seen by the clinician in advance and used for joint decision making.

“On the one hand these things have made our lives easier. On the other it has opened a floodgate in terms of abuse of our personal information”

“Use of an app in that sort of fashion to me is really a dream come true – absolutely revolutionary.

“As healthcare professionals we don’t have very much access to what the patient knows. We know the clinical diagnosis and a bit about the treatment but not the non-medical factors which are the patient’s expertise. The patient’s full engagement is absolutely vital.”

Salek does not fear that patient data will leak from hospital systems protected with firewalls, or from trials where data is encrypted and anonymised. “I don’t think that any of the data of patients taking part in any clinical trial or any sort of observational study or real world data use is abused.”

He agrees, however, that despite GDPR many commercial phone apps are not secure. “When we accept their cookies as we access the website, then they can trace all

our activities on the internet. We are dealing with a double-edged sword. On the one hand these things have made our lives easier. On the other hand it has opened a floodgate in terms of abuse of our personal information and theft of our identity.”

Sophie Wintrich, chief executive of the MDS UK Patient Support Group, for patients with myelodysplastic syndrome, collaborated in the development of HM-PRO, because she could see it was being developed entirely with patient interests at heart. But she has noticed an increase in older patients using phones and tablets to access information about their condition, and wonders how aware they are about possible leaks from other apps.

“People with a disease are vulnerable because they are desperate for contact with other patients, and desperate for information for assistance, and they may overlook the fact that not all of the sharing platforms that are available provide you with the safety that they should.

“You have platforms where patients are invited to put in their details about their quality of life but also their co-morbidities or some personal data, and they are not fully transparent in terms of who funds the tool and what happens to the personal data.

“You also hear of situations where data of patients has been sold to insurance companies or to pharma companies. Smart phones in the hands of people who do not necessarily read the terms and conditions is potentially quite dangerous. There is no proper informed consent unless information is fully transparent.”

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NETs – Why this master of disguise needs careful handling

Rare, hard to recognise, with primaries occurring at many different sites and associated with a wide variety of symptoms, tumours of the neuroendocrine system (NETs) are often detected too late to cure, and can be a cruel burden to live with. **Sophie Fessl** hears from patients and experts about why specialist NET services are so important.

“When you hear hoof beats, do not only think of horses, but also zebras.” With this slogan, patient advocates are trying to raise awareness of one of the more uncommon cancer types – neuroendocrine tumours. “Doctors are taught that, usually, a more common disease – a horse – is the reason for a patient’s symptoms, rather than an uncommon disease – a zebra. But that is how rare diseases get overlooked. We are asking doctors to specifically consider zebras,” says Teodora Kolarova, Executive Director of the International Neuroendocrine Cancer Alliance (INCA), an umbrella organisation of 26 NET patient advocacy and research groups spread across six continents.

With only 7 in 100,000 people diagnosed a year with a neuroendocrine tumour, misdiagnosis and late diagnosis are big issues for patients with NETs. But that is often only the start of their problems, because these tumours occur at a wide range of sites (see box p 38) and their treatments are associated with a variety of burdensome symptoms and treatment side effect that require specialist management, which is often lacking due to the rarity of this cancer type.

“I’ve read your file, and I don’t know much about NETs. Will you tell me what your experience is?” is what Sally Jenkins, from south Wales in the UK, was asked when she first received her diagnosis, a few years ago. “Patients at diagnosis would be seen in an endocrinology clinic, by different people, none of whom knew anything about NETs,” says Jenkins, who went on to successfully campaign for the establishment of a specialist NET service for Wales.

The NET ‘experience’ is often at the heart of the late diagnosis problem. Depending on the tumour’s location and behaviour, it often mimics common conditions that physicians and clinicians are more used to encountering. Abdominal pain can be mistaken for irritable bowel syndrome, hot flushes for menopause, and breathing problems for asthma. Because of this, NETs are sometimes referred to as the ‘forgotten cancer’, and a global survey conducted by INCA and Novartis in 2014 found a mean patient-reported time from first symptoms to diagnosis of 52 months (*J Glob Oncol* 2017, 3:43–53).

Sabine Wagner lived with gastrointestinal problems on and off for several years until a diagnosis of NET was finally given in May 2012. “I was admitted as an emergency patient because of my acute abdominal pain. I told the emergency doctor about my problems and that I felt like I was pregnant as my abdomen was so swollen by ascites. When the doctor did the ultrasound, she said that it was no wonder I had lost so much weight recently – there were metastases on my liver. Only six weeks earlier, I had been

discharged as healthy from a different hospital.”

By the time a diagnosis of NET is given, many patients will have metastases, precluding curative treatment. In many cases, NETs are slow growing; however, they can be aggressive and resistant to therapy. Survival outcomes also depend on the primary site of the tumour, which most often is in the gastrointestinal tract, lungs or pancreas.

“I’ve read your file. I don’t know much about NETs. Will you tell me what your experience is?”

“NETs need to be recognised,” says Jenkins. “Not necessarily by GPs, but once patients are referred to a gastroenterologist, surgeon or oncologist, they should be able to recognise that the symptoms are probably from a neuroendocrine tumour – and then refer the patient to a specialist team. But this doesn’t necessarily happen.” She was initially referred to a surgeon, who did not realise she had a neuroendocrine tumour, says Jenkins, until she nearly died as an emergency patient. “For me, it is all about awareness among the medical community.”

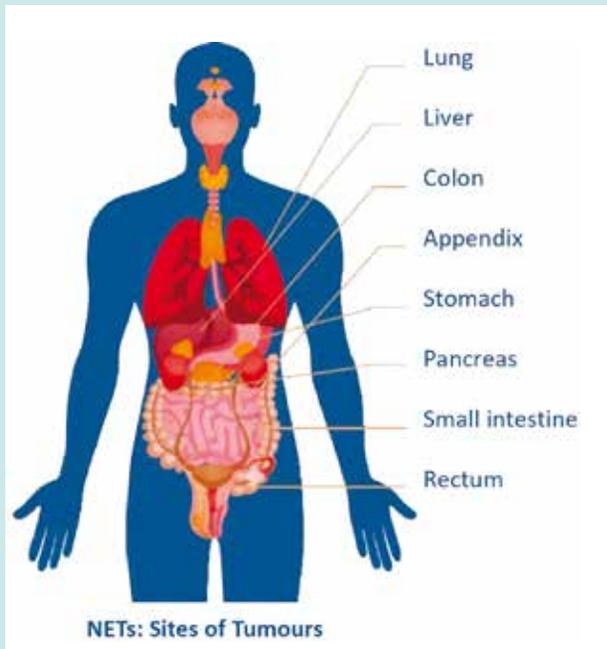
“No two patients with NETs are the same,” she adds, “because the disease is so heterogeneous. This makes supporting NET patients very difficult, and healthcare professionals need a lot of knowledge to do so.”

Living with a chronic cancer

For patients with well-differentiated, slow-growing tumours, NETs often turn into a ‘chronic disease’ – a cancer they live with for many years. This does not make NETs a ‘good cancer’, however, says Nikie Jervis, former NET nurse specialist and now Patient Support Manager at the NET Patient Foundation in the UK. “No cancer is a good cancer. Just because it may not be imminently life-threatening does not mean it is good. Patients have to live with no cure, often experiencing lifelong symptoms, with acute phases that can occur at any moment. They are not in remission, but living with cancer day in, day out. Their fear is not so much recurrence as progression, and the uncertainty of not knowing when this may happen.”

These lifelong symptoms can have a significant impact on quality of life, depending on the patient, their tumour and the care they receive. Mohid Khan, consultant in gastroenterology and neuroendocrine tumours at the University

NETs – the Nearly Everywhere Tumour



Neuroendocrine tumours (NETs) arise from specialised neuroendocrine cells, either from glands containing neuroendocrine cells or, more commonly, from neuroendocrine cells scattered throughout the body (diffuse neuroendocrine system). These cells can sometimes produce and release hormones into the bloodstream. Most NETs are slow growing. Survival varies from a few years to decades, even with widespread metastases, including in the liver. The most common sites for primary neuroendocrine tumours are shown in the

figure, but they can also be located on ovaries, the adrenal gland (and paraganglia), the thymus gland, the thyroid gland and others.

Because they affect such a wide variety of organs, specialist NET services require a broad range of specialists, including specialists in: gastroenterology, gastrointestinal and hepatobiliary surgery, endocrinology, medical and/or clinical oncology, radiation oncology, nuclear medicine, cardiology, thoracic medicine/surgery, gynaecology, as well as NET nurse specialist, nutritionist/dietician, psycho-oncology and palliative care.

The quality of care for NETs patients is currently being held back by very patchy access to specialist physicians, surgeons, multidisciplinary teams and nurses, says Mohid Khan, consultant in gastroenterology and neuroendocrine tumours at the University Hospital of Wales, in Cardiff.

Access to specialist treatments and equipment can also be a problem in some cases, he adds. Gallium PET scanning, for instance, is difficult to access for many patients, but only in a small proportion of patients does it result in changing management. Likewise, peptide receptor radionuclide therapy is indicated in only a very small proportion of patients with metastatic NETs, but access is a problem in some areas of Europe.

Information about consensus guidelines for managing NETs and about accredited NET Centres of Excellence can be found on the website of the European Neuroendocrine Tumors Society www.enets.org

Hospital of Wales, conducted a patient-reported outcomes (PROMs) survey asking about the impact of NETs on quality of life, as part of an effort to improve the NET service by listening to patients. Top of the list, he says, were gastrointestinal symptoms, such as diarrhoea, bloating and abdominal pain. “Lethargy and fatigue also scored quite highly,” he adds. “The NET medical community’s clinical knowledge in these areas is low.”

Some of the problems that affect patients’ quality of life may also affect the care they are able to access. Sabine Wagner, who lives in Stuttgart, says she would have to travel three hours to reach the next accredited NET centre of excellence. “Despite treatment, I need to go to the toilet three to five times a day. How am I meant to travel? This is a challenge.”

Then there is the psychological impact, which can be immense, says Jenkins. “We live with uncertainty. We are given a death sentence, and know how we will probably die, but not when. This needs to be recognised.” Jervis adds that the long-term, chronic character of NETs can lead to problems in the social sphere. “Because NET patients don’t always look sick, there is less sympathy, it is assumed that things are OK. This is a huge issue, a hidden issue. But patients don’t necessarily want sympathy, they want better awareness and understanding of what they are experiencing – some acknowledgement that they’re not alone, unsupported, in this.”

Jenkins sought support by going to support groups for patients with other types of cancer, including a colorectal

Sabine Wagner – diagnosed with neuroendocrine tumour in 2012, living in Germany

“In March 2012, I was seen in a small hospital for my severe symptoms. I had abdominal pain and had lost weight massively. Nothing showed up on the ultrasound, and the ward physician recommended a biopsy of the small intestine. But the senior physician declined, saying it would go away – I should eat chicken and potatoes only. Six weeks later, I was diagnosed with a neuroendocrine tumour.

I was overwhelmed. If I had been diagnosed with breast cancer or cervical cancer, I could have understood the diagnosis better. But NET? There is no reference frame for this.

My tumour progressed in 2014 and I received peptide receptor radionuclide therapy, which stopped the progression.

Since 2015, I'm again taking somatostatin analogues. When I once couldn't receive my monthly injection promptly because of bureaucratic problems, I felt worse than I had for many years. Now I know again that I'm ill.

In the first two years after my diagnosis, I didn't want to know that much about my disease. But through Netzwerk NETS [a self-help organisation], I help newly diagnosed patients by also giving them more background about the disease. In Germany, we do not have nurse specialists for NETs, but it would be desirable. There is case management in some clinics, but if not, you receive no information about follow-ups and have to organise your own scan appointments. Also, the case management does not answer questions you may have.”



cancer support group. “But I didn't fit into the stereotype of a cancer patient: immediate death is not probable, but I will also never get over the disease. However, that is what the counsellor there was used to dealing with, and so they were not able to give me any help other than being sympathetic. I am now seeing a clinical psychologist, and it was a learning process for her as well. NET patients need specialist support in all areas.”

Multidisciplinary specialist care is essential

The global survey of patients with NETs conducted by INCA and Novartis showed that patients in the US who visit specialist centres felt more satisfied with treatment than those who were cared for in other settings (*Pancreas* 2017, 46:639–47). This is backed up by an analysis of the SEER database, which showed that the median overall survival in patients with distant metastatic disease was higher in patients cared for in specialised NETs centres (*JCO* 2008, 26:3063–72). To promote centralised care, the European Neuroendocrine Tumor Society (ENETS) established criteria for the certification of NET centres of excellence. Since 2009, 50 such centres have been accredited worldwide (enets.org/coe_map.html).

Sally Jenkins experienced what a big difference specialist

care can make. “When I was diagnosed, NET patients in south Wales were dealt with by a group of well-intentioned endocrinologists who didn't have expertise about what patients with NETs needed.” A survey conducted by the NET Patient Foundation, commissioned by Wales Health Specialised Services Committee (NHS Wales), found an overall satisfaction score of just 18%. This was later followed by consultant Mohid Khan's PROMs assessment, which demonstrated a high burden of unaddressed gastrointestinal symptoms even in those patients who had lived with a NET for years without specialist care.

“We raised awareness with the Welsh government that our treatment did not meet the criteria that patients with cancer in Wales should expect – including access to specialist care,” says Jenkins. “This led to the funding for a specialist NET service.” The service is now gastroenterology-led, with Khan as the clinical lead, and oversees the treatment of all patients diagnosed with NETs in south Wales. “Patients with stable disease previously often led a miserable life with diarrhoea and other symptoms. But now, with the gastroenterology-led service, these symptoms are managed very well, as all relevant issues are being addressed,” (see p 41).

The objective of this turnaround is clear, says Khan. “We want to give patients a decent quality of life and confidence in their disease management as part of value-based healthcare. We remeasured patients' burden of symptoms and have

Quality of Life



Mark McDonnell – diagnosed with a neuroendocrine tumour in 2011, living in Ireland

“ I was diagnosed by accident. In an ultrasound, doctors saw clouds on the liver, which the hospital then confirmed as tumours. Initially, I was diagnosed in a private hospital, which did not have great expertise on NETs. I received a call from my consultant, telling me I have a neuroendocrine tumour. I got off the phone and my wife asked me: ‘Is that cancer?’ I replied: ‘I don’t really know.’

Initially, my oncologist recommended to take a wait and see approach, which I agreed with, as I had no symptoms. But she urged me to get a second opinion from a NET specialist in another Dublin hospital. I thank her to this day that she did this, as the specialist saw my scans and decided we should take a proactive approach including surgery and treatment with somatostatin analogues.

It took me a full year trying to recover from surgery, both physically and psychologically. After taking somatostatin analogues, I got all the symptoms of NETs, including flushing, sweating, diarrhoea, which caused a lot of problems and led to me retiring from work. My doctor was very dismissive of these symptoms, and he really didn’t acknowledge that they were coming from the medication. But when the NET specialist returned from a stint working abroad, we revised this approach and decided that I should stop taking SSAs [somatostatin analogues].

Eight years down the road from diagnosis, do I see a long-term future? Maybe. I know it will be problematic, but now I think about it in terms of years. I have changed my lifestyle around eating and drinking, as I know that I need to stay healthy.”

achieved a significant difference in QoL compared to previously, which is reflected by the positive feedback demonstrated in a repeat patient experience survey.” In addition to providing centralised specialist care, Khan believes that the new service has also raised awareness of NETs among the medical community in the region, reflected in a reduction in the median time to diagnosis, which has decreased from nine months in the old service to four months in the new service. “We give individual feedback on cases, but in addition, gastroenterologists and surgeons are educated about NETs and become more aware of the disease in south Wales.”

Patients and patient advocates emphasise that all NET patients have to be seen by a specialist to receive best care. “Hanging on to a patient because it is an interesting case is not good medicine,” argues Jervis. “Care should be patient-

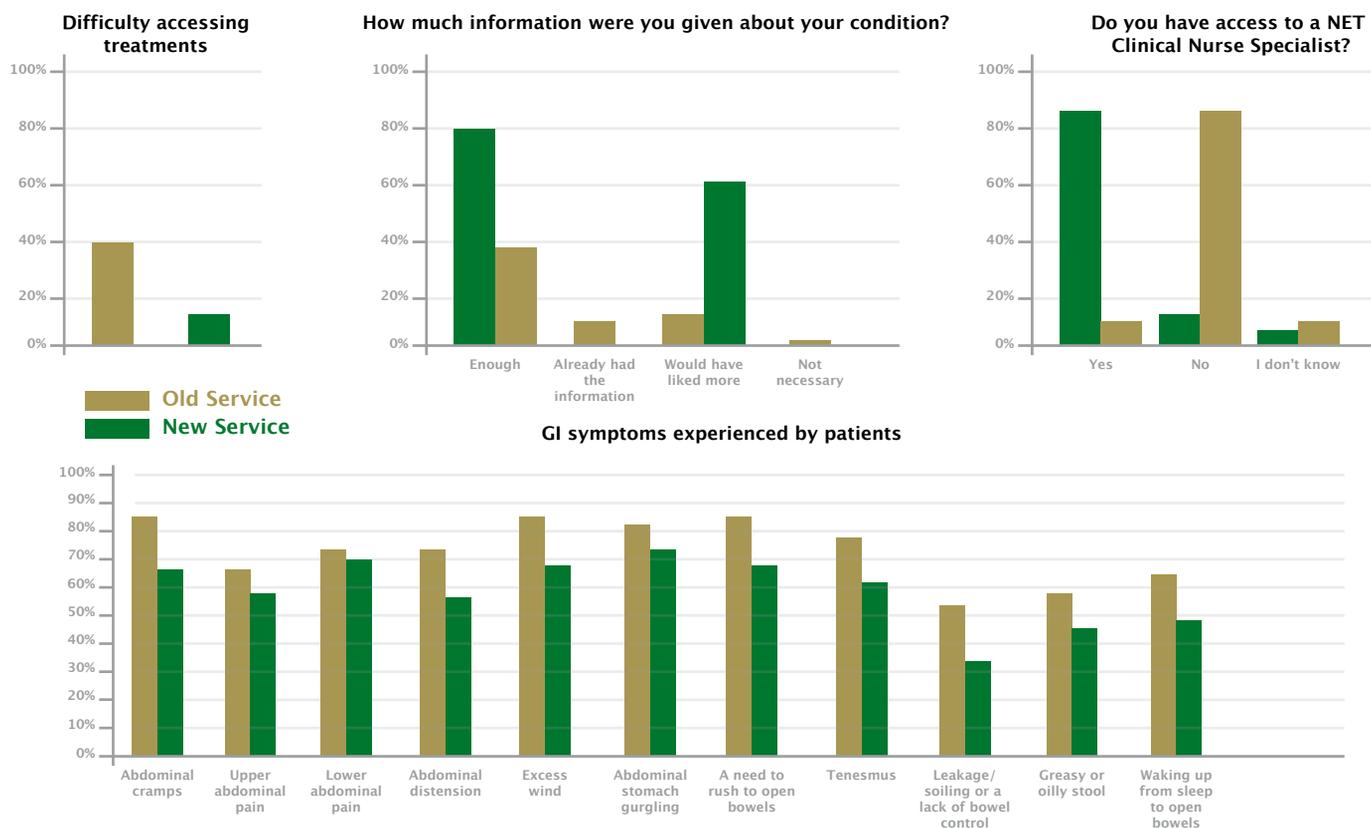
“When they have a patient with a NET, they just give somatostatin analogues, even if it may not really help”

centred. All patients with neuroendocrine cancer should be referred to a specialist centre for review – an expert opinion – and then triaged. Any treatment that can only be given at a specialist centre should be done there. But if the recommended treatment can be safely and effectively delivered locally then, yes, with good communication and collaboration, care should be given locally.”

Mark McDonnell, who was diagnosed with a NET in 2011, and is Chairperson of the Irish NET Patient Network, is campaigning for such a model of care in Ireland. “We are pushing the message that patients need to see a NET specialist. Patients cannot accept to be handled solely by an oncologist without specialist NET knowledge. If a patient is not treated at a centre of excellence, he or she needs at least to be seen by a NET specialist, or their care should be overseen by a NET multidisciplinary team. Unfortunately, that doesn’t always happen.”

Vera Megdanova, a doctor in Bulgaria who completed her medical oncology training last year, is seeking to improve care for NET patients in her home country. An ENETS fellowship will allow her to do fellowship training at centres of excellence in Dublin and Manchester. The current situation is dire, she says: “Patients with NETs are treated everywhere and by everyone. All doctors know

Transforming the NET service in south Wales: measures of success



Source: M Khan et al. (2019) Turning it around: The South Wales Neuroendocrine Cancer Service, developing a patient-centred service through co-production <http://patientexperiencenetwork.org/wp-content/uploads/2013/11/WINNER-Turning-it-around-Cardiff-and-ValeUHB-Developing-a-patient-centred-service-for-NET-cancer-across-South-Wales.pdf>

The radical improvement in NET care in south Wales, led by consultant gastroenterologist Mohid Khan, won Cardiff & Vale University Health Board the UK Patient Experience 2019 Award for 'Turning it Around'. The service was commissioned across seven National Health Service boards or trusts, covering 16 hospitals in south Wales. In designing the service, Khan used quality-of-life assessments and patient-reported outcome measures, including the EORTC QLQ-GINET21 and gastrointestinal symptom rating scales (GSRs). The GI symptom scores were significantly lower in the new service ($P=0.006$ for GINET21 and $P=0.004$ for GSRs), and the reduction was felt across all symptom categories. Overall patient satisfaction with the service improved from 18% to 99%. "At the heart of it, our turnaround came from listening to patients. We involved patients throughout the process through stakeholder meetings and by going to patient group meetings," says Khan.

The service for NET patients now works collaboratively across the region. Any patient diagnosed with a NET in south Wales is referred to the NET service, regardless of geography or organisational boundary. Scan and laboratory reports and other documents are accessible electronically to the specialists, through a national Wales Clinical Portal, who give initial advice and guidance to the referring hospital before the multidisciplinary team meeting, and request additional tests or scans. The referring doctor/nurse also provides initial feedback to the patient. "After the MDT, we confirm the diagnosis and bring the patient to the clinic to provide ongoing management. Any aspects of care that can be done locally are done there, e.g. basic tests and imaging, but we still see most patients centrally, on a regular basis, if needs be through a phone consultation." Critically, the MDT brings together specialists from different areas of expertise to cover the very varied needs of NET patients.

Quality of Life

about somatostatin analogues, so when they have a patient with a NET, they just give somatostatin analogues, even if it may not really help. We have no specialist NET centres in Bulgaria and few specialists interested in that area.” As elsewhere, patients frequently turn to the internet for more information. “Sometimes, patients know more about their disease than the doctor.”

Wanda Geilvoet, a NET specialist nurse practitioner in Rotterdam, describes her role as ‘the bridge between cure and care’

Economic challenges also hamper efforts to help NET patients. “In most places, it is difficult to give a diagnosis, as patients have to pay for immunohistochemistry themselves. Tumour markers in NETs are also not covered by health insurance.” According to Megdanova, Gallium-DOTATATE PET/CT – highly effective in detecting NETs with high levels of somatostatin receptor 2 – should soon be available in the capital Sofia. So should peptide receptor radionuclide therapy – a molecular targeted therapy used in a small proportion of patients with NETs, which binds to somatostatin receptors and delivers high doses of radiation. Coverage of the imaging or treatment by health insurance, however, is so far unclear. “The money problem is exhausting,” says Megdanova. We want to help patients, but it can be very frustrating as it takes such an effort in money and time to give the right diagnosis and treatment.” As EU citizens, Bulgarian patients are often sent to be treated in other countries – once a diagnosis is finally given.

Nurse specialists provide vital information and support

Mohid Khan attributes the success of the south Wales NET service in part to the recruitment and training of two clinical nurse specialists with expertise in caring for patients with NETs. “The clinical nurse specialist provides crucial support at the time of diagnosis, and coordinates care at the start and throughout the pathway. In a nurse-led clinic, the nurse specialist carries out simple procedures, clinical review including holistic assessment, signposting, education and simple management under supervision of a doctor. For example, a nurse specialist gives the first injection of soma-

tostatin analogues and then provides follow-up and virtual consultations on how patients are doing,” he says.

Importantly, dedicated nurse specialists may fill a major gap identified in the global survey on unmet needs of NET patients, which was carried out by the advocacy group INCA in 2017 – namely the need for high-quality information.

Wanda Geilvoet, chair of the ENETs nurse group (enets.org/net_nurse_group.html) and a NET specialist nurse practitioner at the Erasmus Medical Center in Rotterdam, describes her role as “the bridge between cure and care”.

“I’m the main contact person for patients and their families when they have questions, both about medical and non-medical issues. I do triage when patients are referred to our hospital – this avoids duplicating diagnostic tests, and patients have a point of contact before their first outpatient visit. I’m also the care coordinator for new patients, and they know that they can call me if necessary.”

Geilvoet also screens patients to assess their need for psychosocial support or whether they need to see a physiotherapist or a dietician. She’s in contact with the home nurses about somatostatin analogue injections, and sees patients in the outpatient clinic and during follow-up. As a prescribing nurse, she prescribes medications to treat side effects, as well as ordering CT scans or additional lab tests. “I think it is a must for hospitals treating patients with NETs to have someone specialised to deal with all non-medical aspects around NETs,” she says.

Kolarova, from INCA, agrees. “Specialist nurses make a huge difference as they can give information, follow up and stay in touch with patients,” but she adds that, unfortunately, “in many systems this role is not recognised.” One reason for this may be linked to one of the more surprising results from INCA’s 2017 survey, which showed that almost 90% of the health professionals who responded felt they were able to meet patients’ information needs about treatment options at diagnosis, while only 36% of patients indicated that all their information needs were met (bit.ly/NETs-UnmetNeeds).

As it happens, 36% is very close to the proportion of NET patients in south Wales who reported their information needs were met before care of NET patients in the region was reorganised. Under the new NET specialist service, that figure has risen to 80%, while the overall patient satisfaction score has risen from 18% to 99% – rock hard evidence, for anyone who has yet to be convinced, of the benefits of establishing a specialist service to care for patients with this rare, very varied disease which, without expert care and support, can put such a burden on quality of life.

To comment on or share this article go to bit.ly/CW87-Managing-NETs



The 2020s: Europe's potential decade of leadership on cancer

I am confident that 2019 is going to be remembered as an exciting year in the history of our international efforts against cancer, not least because of the start of the new EU Cancer Mission.

At ECCO we were thrilled to hear the news that the esteemed Professor Harald zur Hausen has been appointed to chair this Mission. His pioneering research on cancer of the cervix, and discovery of the role of papilloma viruses, were rightly acknowledged with the award of the Nobel Prize in Physiology or Medicine 2008. He is the kind of visionary expert required to galvanise and oversee the coordination effort ahead. As mentioned in my last *Cancer World* editorial, as well as in the recent special edition of the *Tumori Journal* on this subject, at a political level the EU Cancer Mission should also have a secondary aim of re-inspiring citizens with an understanding of the exciting milestones we can achieve when combining efforts across countries towards precise goals.

In the field of cancer we are now fortunate to have a range of achievable targets that could be pursued officially across all health systems, including, but not limited to:

- the European Cancer Concord 70:35 vision of achieving 70% long-term survival for cancer patients by 2035; and
- the European Society of Paediatric Oncology (SIOP Europe) proposed goal of halving the deaths and halving the burden of childhood cancer by 2030.

I would propose the EU Cancer Mission (and a potential accompanying EU Cancer Masterplan) should set a number of ambitious though precise goals, such as, but not limited to, those above.

One other area where a precise goal can be set and pursued is to fully join forces with the World Health Organization in its campaign to eliminate cervical cancer. Europe can, and should, give international leadership on this.

For this reason I am delighted that ECCO, with its member societies (ESGO, EONS, ESOP, IPOS and others), has been teaming up with a large network of interested organisations and experts to put forward a precise resolution for the EU on the elimination of HPV-related cancer and diseases.

This will be voted on at the ECCO 2019 European Cancer Summit, and will be accompanied by a recommended Action Plan, and additional detailed papers by ECCO and ESGO thereafter. We hope, by this facilitation and network building effort, to play our part in invigorating an exciting decade of progress fighting cancer in Europe.

Such a period of focused collaboration towards major milestones will energise all of us working in the field to go further and faster. In addition, it will help restore popular belief in the promise of international cooperation. Stimulating and leading a decade of tangible progress on cancer would represent the European Union at its very best. ECCO and its members will all fulfil our role to support this.

The ECCO 2019 European Cancer Summit draft resolution on HPV elimination will be voted on at the concluding session of the Summit's first day, Thursday 12th September, in Brussels
eccosummit.eu



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Obesity and cancer

Obesity is overtaking tobacco as the leading preventable cause of cancer. Oncologists have an important role to play in informing patients and directing them towards assistance in making lifestyle changes. **Antonio Di Meglio** reviews the links between obesity and cancer, the implications of weight gain after diagnosis and treatment, and strategies to help patients lower their weight-related risk.



This grandround was first presented by Antonio Di Meglio, from the Gustave Roussy Institute, Villejuif, France, as a live webcast for the European School of Oncology. It was edited by Susan Mayor. The webcast of this and other e-sessions can be accessed at e-eso.net.

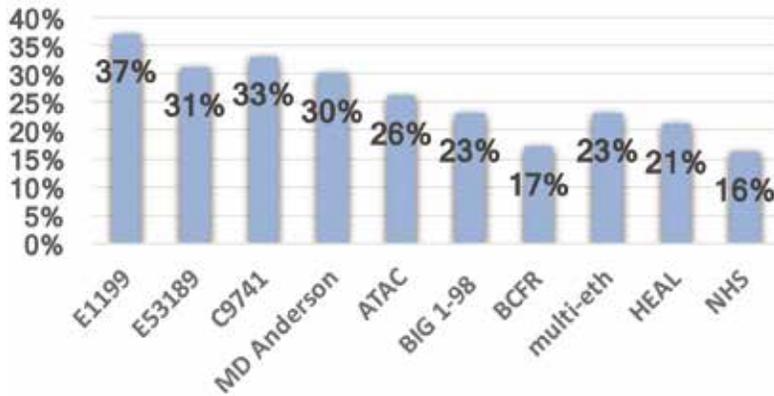
Obesity has a major impact on cancer. The proportion of cancers attributable to obesity is increasing so much that obesity is now overtaking tobacco as the leading preventable cause of cancer, with recent figures from the US showing that it accounts for 4% of cancers in men and 7% of cancers in women (*Cancer Detect Prev* 2008, 32:90–99; *Lancet* 2011, 378:815–25). Several studies have shown high rates of obe-

sity in cancer patients at the point of diagnosis, as defined by a body mass index (BMI) of 30 kg/m² and higher. For example, the French national CANTO cohort, which included more than 12,000 patients diagnosed with early breast cancer between 2012 and 2018, showed that the prevalence of obesity at the time of diagnosis was 19.2%, and this increased to 20.3% at one year after diagnosis and to 20.9% at two years (*Ann Oncol* 2018, 29 Suppl 8).

The link between obesity and cancer

There are many aspects to consider in the link between obesity and cancer. The first relates to the biological substrate of cancer in obese individuals. People who are obese have expanded and reprogrammed metabolically active adipose tissue with an increase in several mediators, including pre-adipocytes, inflammatory cells, cytokines and other

Prevalence of obesity at diagnosis in breast cancer patients across studies



Source: Courtesy of Antonio Di Meglio; data sources include *JCO* (2015) 33:2353–60; *JCO* 2003, 21:1431–9; *Lancet Oncol* 2008, 9:45–53; *N Engl J Med* 2005, 353:2747–57

inflammatory markers. The adipose tissue interacts with an altered systemic physiology, with an increase in circulating levels of insulin and glucose. This interplay has a direct impact on cancer cells, through enhancing signalling pathways in addition to a direct metabolic effect. In addition, the interplay has also many indirect effects on the tumour microenvironment (see figure p 48).

Second, obesity is an established risk factor for cancer. A recent analysis (*Int J Cancer* 2018, 143:1595–603) showed a strong positive association between BMI and several types of cancer, including endometrial cancer, oesophageal adenocarcinoma, postmenopausal breast cancer and kidney cancer (see figure p 49).

In contrast, there seemed to be an inverse relationship between BMI and risk of oral cavity cancer, lung cancer and premenopausal breast cancer. The relationship between obesity and cancer is also sex specific, with a higher risk of colorectal cancer among obese males and increased risk of brain and kidney cancer among obese females.

Third, obesity is also a prognostic factor for many cancers. Data linking obesity to poor outcomes are strongest in breast, colorectal and prostate cancer. There is also compelling evidence starting to emerge for other cancers, including childhood leukaemia.

Two meta-analyses (*Ann Oncol* 2014, 25:1901–14; *Breast Cancer Res Treat* 2012, 134:769–81) showed a significant relationship between obesity and poor outcomes in women with early breast cancer.

There are mixed data on obesity in colon cancer. Some studies have shown that very obese patients (BMI > 35 kg/m²) have increased risk of colon cancer recurrence, total mortality and colon cancer-related mortality (*JNCI* 2006, 98:1647–54). However, a meta-analysis of adjuvant chemotherapy trials in colon cancer found that the association between increased BMI and poorer outcomes was sex specific (*Cancer* 2013, 119:1528–36), with a significant prognostic effect of BMI in men for both disease-free and overall survival, but not in women.

There is also evidence that patients with prostate cancer who are obese may have poorer outcomes, and that obesity is associated with the development of more biologically aggressive and more advanced prostate cancer (*Cancer Epidemiol Biomarkers Prev* 2006, 15:1977–83).

Finally, a study in children and adolescents with acute lymphoblastic leukaemia has shown obese patients had worse outcomes than those who were not obese (*JCO* 2007, 25:2063–69).

Fourth, obesity increases the risk of second cancers. Together with other modifiable lifestyle factors, obesity has been shown to be associated with a higher risk of a second primary breast cancer. One study demonstrated a 40% higher risk of developing contralateral breast cancer in women who were obese at diagnosis of oestrogen-receptor positive breast cancer (*JCO* 27:5312–18).

In another study, which accounted for use of screening, access to treatment, type of treatment, use of adjuvant therapy, and tumour characteristics, there was a more than two-fold increased risk of recurrence among obese patients compared with normal-weight patients with breast cancer (*Cancer Causes Control* 2013, 24:305–12).

Impact on cancer diagnosis and treatment

Another way that obesity impacts cancer is through its effect on diagnosis and the delivery of treatment and its toxicity in cancer patients. Obese individuals may delay seeking medical care and may be less likely than the non-obese to participate in screening programmes (*J Gen Intern*

Med 2009, 24:665–77; *J Obesity* 2011, doi:10.1155/2011/218250). The accuracy of diagnostics may also be reduced in obese patients, as shown in studies reporting haemodilution of tumour biomarkers and impaired quality of imaging among obese cancer patients (*J Urol* 2009, 181:567–73; *Crit Rev Oncol Hematol* 2013, 85:193–205).

In terms of treatment, there can be technical difficulties in the delivery of radiation therapy and surgical management in obese patients (*Radiother Oncol* 2009, 91:114–19).

In addition, studies have shown higher rates of thromboembolism in obese patients receiving chemotherapy (*JCO* 2006, 24:484–90), and a study in patients undergoing major abdominal cancer surgery found that higher BMI was associated with increased rates of post-surgical complications and wound infections (*Ann Surg Oncol* 2008, 15:2164–72).

Implications of weight gain after cancer diagnosis and treatment

Weight gain after cancer is another very important problem. Many cancer survivors gain weight after being diagnosed with cancer, particularly those treated with chemotherapy and women who transition to post-menopausal status as a result of cancer treatment.

On average these patients gain 2–5 kg, but weight gain can be as high as 10 kg in the first two years after cancer diagnosis.

Sarcopenic obesity is also particularly common in cancer patients, consisting in loss of muscle mass and concomitant gain of adipose

tissue. It can occur in patients treated with chemotherapy, but also with androgen deprivation therapy for prostate cancer.

In an analysis using data from the French national CANTO cohort, among more than 4,500 patients with early breast cancer diagnosed between 2012 and 2015, one in four gained substantial weight (at least 5% of baseline weight) two years after diagnosis, with an average increase of 6–7 kg (*Ann Onc* 2018, 29 Suppl 8:620–21).

Many factors were associated with a higher likelihood of gaining weight by two years post-diagnosis, including treatment with chemotherapy, younger age at diagnosis, lower physical activity levels and gaining weight within one year following diagnosis.

Weight gain after being diagnosed with breast cancer may be associated worse breast cancer outcomes, but studies have shown inconsistent results. A higher risk of breast cancer recurrence among women who gained more than 2.0 kg/m² after diagnosis was reported (*JCO* 2005, 23:1370–78), although other studies showed similar rates of breast cancer recurrence among women who gained weight and those who maintained their baseline weight (*Breast Cancer Res Treat* 2006, 99:47–57).

Obesity and post-diagnosis weight changes also have important implications in terms of quality of life of cancer patients.

An analysis of obese patients with early breast cancer among the CANTO cohort showed that gaining at least 5% of baseline weight between diagnosis and completion of primary treatment was associated with the highest rates of severely impaired patient-reported

The link between obesity and cancer



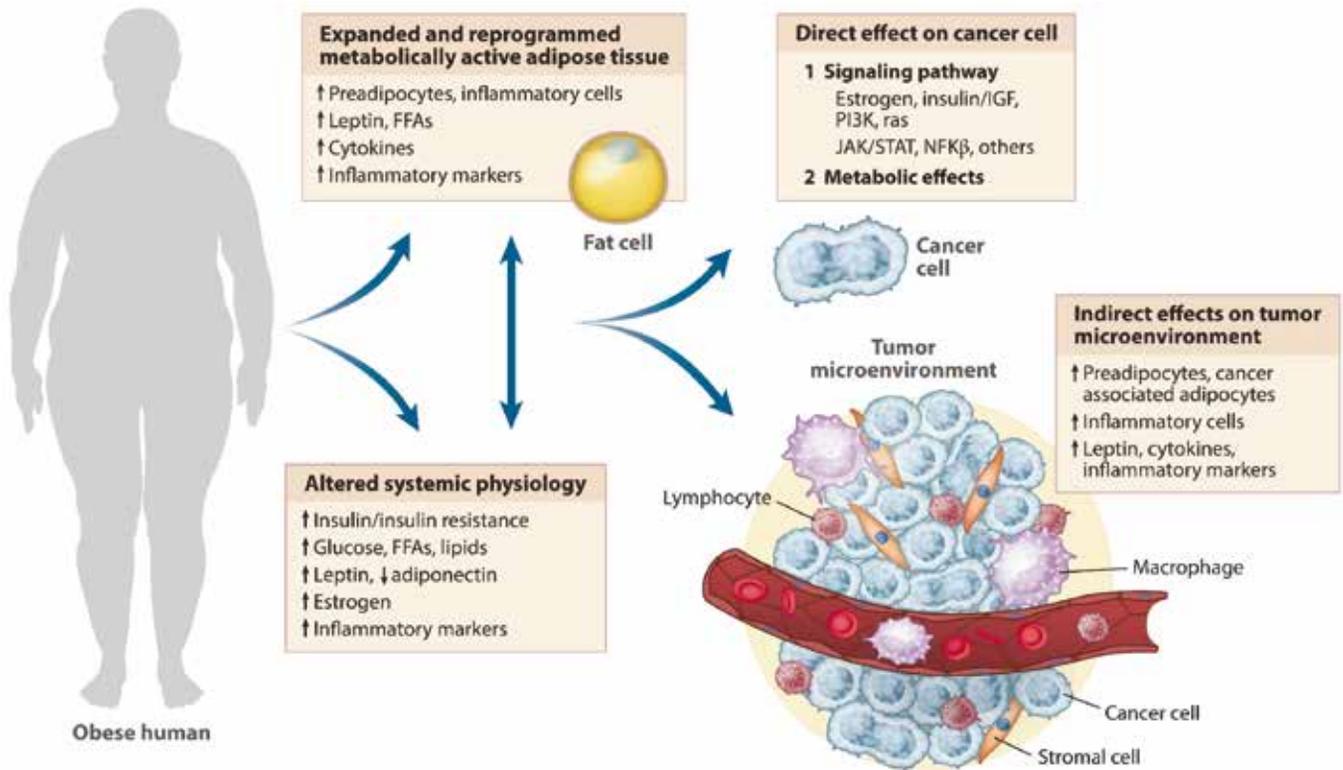
functions and worse symptoms. Conversely, losing at least 5% of baseline weight was associated with a significantly reduced risk of severe dysfunction or reduced quality of life at one year after diagnosis (*Ann Onc* 2018, 29 Suppl 8:620–21).

Strategies to promote weight loss or prevent weight gain in cancer survivors

There is now increased awareness of the availability and benefit of strategies to promote weight loss or prevent weight gain in cancer survivors. Studies with these strategies, and particularly those that include calorie restriction, increased physical activity and behavioural counselling, have consistently demonstrated that weight loss of 5–7% of body weight may reduce the incidence of other diseases, particularly diabetes and cardiovascular disease, and improve several general and cancer-specific outcomes.

ASCO published a key position statement on obesity and cancer a

Underlying biological mechanisms



People who are obese have expanded and reprogrammed metabolically active adipose tissue with an increase in several mediators for cancer

FFA - free fatty acids, IGF -insulin-like growth factor

Source: PJ Goodwin and V Stambolic (2015) *Annu Rev Med* 66:281-296. Reproduced with permission of Annual Reviews

few years ago (*JCO* 2014, 32:3568-74). It has also released a guide for oncology providers on obesity and cancer that provides guidance on selecting weight loss treatments for cancer survivors (bit.ly/ASCO_Obesity-Cancer).

According to this guide, the use of lifestyle therapy based on diet, physical activity and behavioural therapy should be recommended to support weight loss in all cancer survivors who have a BMI that is greater than 30 kg/m², as well as in those whose BMI is between 25 and 30 kg/m², if they suffer from two or more comorbidities.

Further strategies to facilitate weight loss are also reviewed in this ASCO guide, including pharmacotherapy for patients who have not lost 1 lb (0.45 kg) per week after six months of lifestyle therapy, and bariatric surgery only in selected patients who particularly struggle to lose weight. Lifestyle strategies for prevention of further weight gain are always indicated in any patient with a BMI of more than 25 kg/m².

Lifestyle interventions to facilitate weight loss have been tested in multiple settings in oncology care.

The Lifestyle Intervention Study for Adjuvant Treatment of Early

Breast Cancer (LISA) is the largest weight loss intervention study in cancer (*JCO* 2014, 32:2231-39). It included breast cancer patients treated with adjuvant letrozole and with a BMI > 24 kg/m². They were randomised to a control arm or a two-year telephone-based intervention with individualised goals of 10% weight loss, a calorie restriction of 500-1,000 fewer calories per day, and 150-200 minutes of moderate-intensity physical activity per week. Even though accrual to the trial was interrupted because of funding issues, results showed significantly greater mean weight

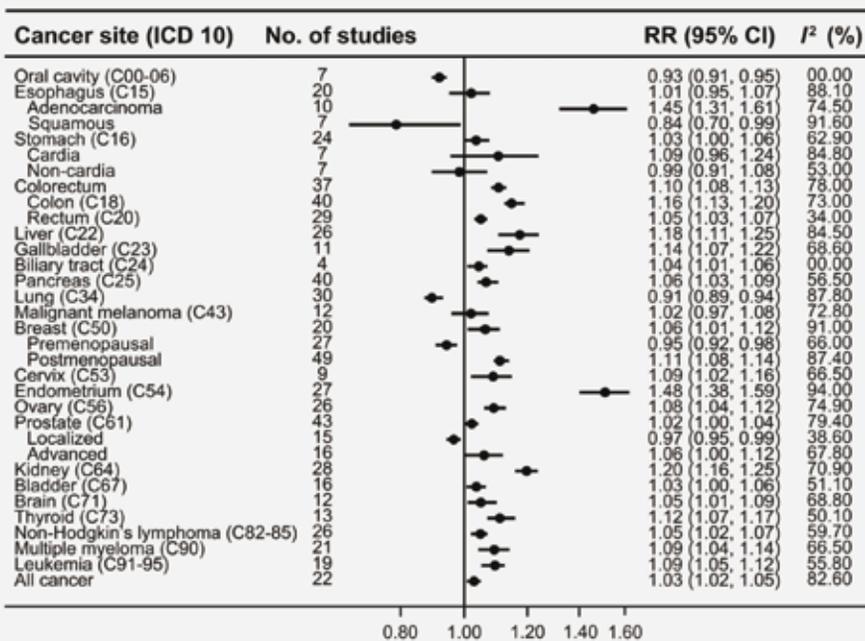
loss among patients in the intervention group compared to the control group (-3.1 kg vs -0.3 kg at two years).

Another trial, the Active After Cancer Trial (AACT), in survivors of breast and colorectal cancer who were not physically active at the time of diagnosis, showed that a 16-week telephone-based exercise intervention improved physical performance and physical functioning compared to a control arm (*Breast Cancer Res Treat* 2012, 132:205–13). This study also confirmed the feasibility of using cooperative clinical trials systems for conducting lifestyle interventional research.

Lifestyle interventions are now deemed to be safe and feasible in cancer populations, and several studies have shown benefits in different types of cancer. Results have shown a positive impact on quality of life and favourable changes in cancer biomarkers. Lifestyle interventions also hold the promise to improve cancer outcomes, but this is still an open question that ongoing trials are trying to address. One such trial is the Breast Cancer Weight Loss (BWEL) study (*NPJ Breast Cancer* 2017, 3:37), which is randomising 3,136 participants with a BMI of 27 kg/m² or higher to two arms: a health education control arm versus health education plus two years of supervised weight loss programme based on caloric restriction and increased physical activity, delivered remotely by a personalised lifestyle coach. The primary endpoint of BWEL is evaluating the impact of weight loss on breast cancer invasive-disease-free survival.

In addition, one of the important questions that we should ask ourselves when conducting research

Multiple studies show an association between obesity and cancer



A systematic review and quantitative meta-analysis of cohort studies reporting body mass index (BMI) and the risk of 23 cancer types revealed the following associations:

- Positive association of increasing BMI with cancers occurring in a wide range of sites.
- Strong positive associations between BMI and
 - endometrial cancer (RR: 1.48)
 - oesophageal adenocarcinoma (RR: 1.45)
 - postmenopausal breast cancer (RR: 1.11)
 - kidney cancer (RR: 1.20);
- Significant inverse associations between BMI and
 - oral cavity cancer (RR: 0.93)
 - lung cancer (RR: 0.91)
 - premenopausal breast cancer (RR: 0.95)
 - localised prostate cancer (RR: 0.97)
- A male-specific association between BMI and
 - colorectal cancer
- A female-specific association between BMI and
 - brain cancer
 - kidney cancer

RR- relative risk

Source: J Min, F Wang, S Liu et al. (2018) *Int J Cancer* 143:1595–603. Republished with permission from John Wiley and Sons

testing lifestyle interventions in cancer survivors, and also in analysing the impact of obesity on cancer, is whether cancer survivors behave differently to the general population. Research suggests they are no more likely to engage in healthy behaviours, including regular physical activity or consuming at least five servings of fruit or vegetables per day, than adults without a history of cancer (*Cancer Prev Res (Phila)* 2011, 4:522–29; *JCO* 2008, 26:3958–64; *Cancer Epidemiol Biomarkers Prev* 2009, 18:87–95; *JAMA* 2005, 293:2479–86).

Overall, studies have shown that the prevalence of inactive patients among cancer survivors is very high.

ASCO guidelines on weight management and physical activity

Nevertheless, cancer organisations such as ASCO are working to raise awareness about the importance of cancer as a ‘teachable moment’ for patients. This views cancer as “a naturally occurring life transition or health event that has the potential to motivate individuals to adopt risk-reducing or health protecting behaviours” (*JCO* 2005, 23:5814–30).

Several studies support the notion that most cancer survivors are interested in health promotion programmes, with a preference for home-based formats. Many cancer survivors report dietary changes or stopping smoking after being diagnosed with cancer.

However, there are barriers and limitations to using cancer as a teachable moment. Factors reducing the likelihood of healthy lifestyle adoption include: male sex and

older age, lower education, or living in urban areas.

Physicians, and particularly oncologists, can make a real difference because they are the most powerful catalysts for promoting behavioural change in cancer patients. Nevertheless, a study showed that only 20% of oncology care physicians provided assistance for lifestyle changes (*JCO* 2005, 23:5814–30), because of competing concerns, uncertainty regarding the type and most appropriate health behaviour messages to give, and issues regarding insurance coverage and reimbursement of lifestyle interventions. The ASCO obesity initiative is trying to address these concerns.

The ASCO Position Statement on Obesity and Cancer (*JCO* 2014, 32:3568–74) proposes a practical approach to weight management in cancer patients and survivors based on assessment of BMI, giving advice and referring to local resources. First, physicians should always assess BMI, as a simple measure that does not require any special equipment. Second, health professionals should advise patients on weight management in a neutral manner, including BMI as part of reviews and discussing exercise habits and weight issues. Particularly, it is important to acknowledge the challenges and struggles that patients may face in trying to lose weight. Finally, it is crucial to identify local resources, particularly dietitians and nutritionists, who have specific training in the oncology setting and can provide tailored support for individual patients.

There are also guidelines from the American College of Sports Medicine that provide guidance to cancer survivors on physical activ-

ity (*Med Sci Sports Exerc* 2010, 42:1409–26). They suggest that adults aged 18 to 64 should engage in at least 150 minutes of moderate-intensity physical activity per week, or 75 minutes of vigorous physical activity per week, or an equivalent combination. Moderate activities include biking on level ground, general gardening, tennis or walking briskly, while vigorous activities include fast cycling, hiking uphill, race walking or jogging and fast swimming or swimming laps.

Summing up

Obesity has reached epidemic levels worldwide, with more than one in three adults in the US categorised as obese, and these figures are very consistent in the rest of the Western world. Obesity is now becoming the leading preventable cause of cancer, with a prevalence of up to 40% in cancer patients.

There is a strong link between obesity and cancer, and compelling evidence exists that obesity acts as a risk factor and prognostic factor in cancer and that it can negatively impact treatment toxicity and quality of life and pose an important financial burden in cancer care.

There is also a major problem with weight gain after cancer, with a substantial proportion of patients gaining weight after their cancer diagnosis and treatment.

In the contemporary scenario of cancer survivorship, it is essential that weight control and weight loss strategies based on lifestyle interventions become part of standard oncology care.

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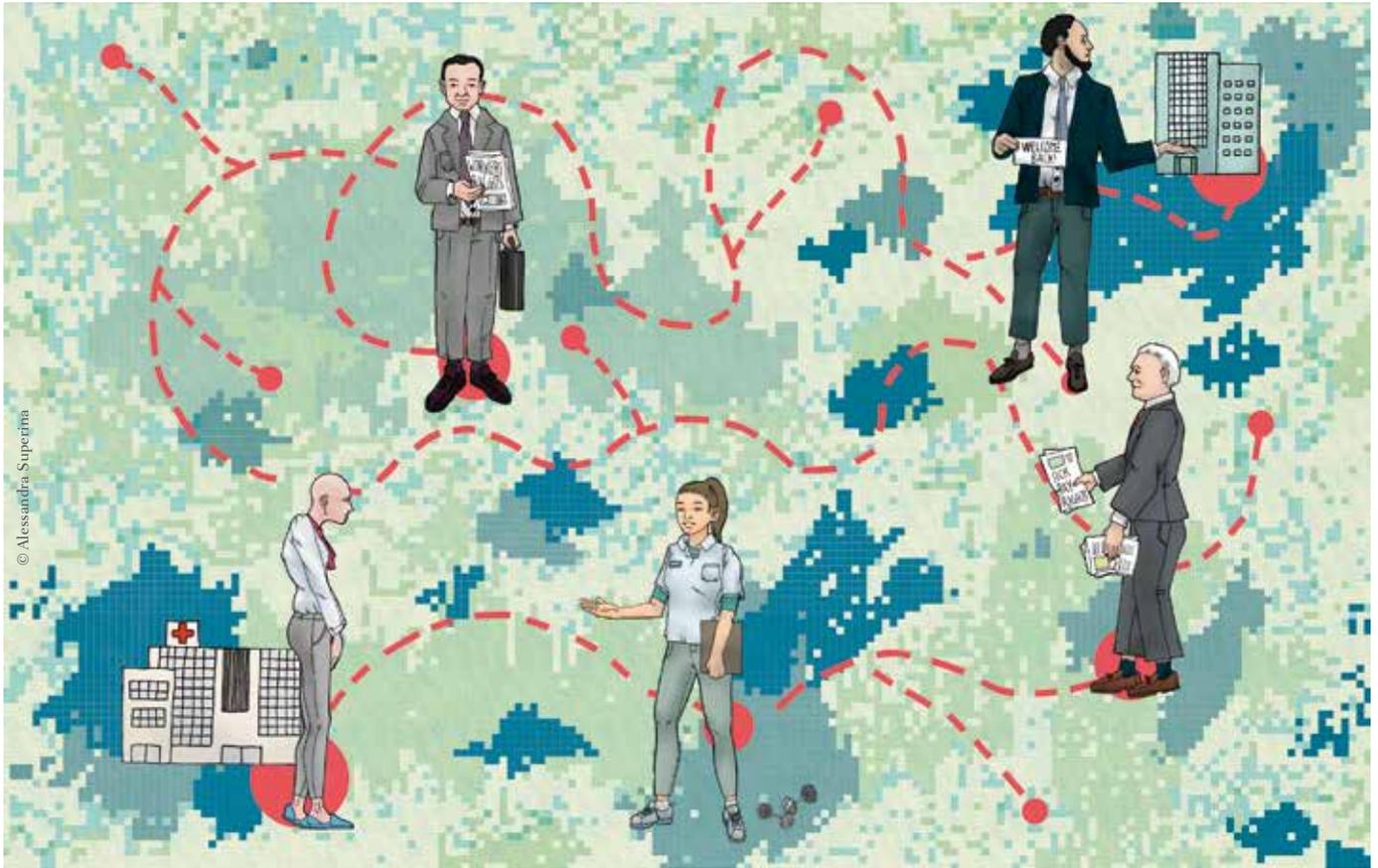


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Surviving in the workplace

Why it's so hard and how we can make it easier

Working lives can be an important part of who we are, and many of us also need to work for financial reasons. Yet cancer survivors often have to struggle to get their working lives back on track. Rights, attitudes and policies could all make a big difference, but so can expectations, preparation and advice. **Marc Beishon** explores what can be done better to help patients achieve their desired 'back to work' endpoint.

There has been an important trend in the cancer advocacy movement in the past few years: a number of cancer survivors who have encountered problems in returning to work have set up or contributed to organisations to help others with work issues. It's a sign of growing concern about the problem, as many more people of working age are living with cancer and/or the effects of having undergone treatment, due to the combination of cancer becoming a more survivable disease and the age of retirement rising.

Most governments have responded slowly – if at all – with policies that can reduce the difficulties, and many still fail to see the societal picture in terms of the impact of chronic diseases and disability on the economy and society.

Take Isabelle Lebrocqy, a cancer survivor in the Netherlands who has set up Opuce, a social enterprise for cancer survivors that helps find suitable work for job seekers who have recovered from their illness. She lost her own job, working as a manager in the services sector, in 2011, after treatment for colon cancer. “I couldn't hide that I had cancer – it was an emergency and I had to have surgery – but I was only away for about four months. But I got a text message from the human resources director when I was about to return that said I couldn't.”

This led Lebrocqy to investigate whether she was alone, and she discovered that while Dutch employment law is very generous for full time employees with job security – employers have to pay two years of salary if someone is ill – a lot of people on contracts can fall through gaps. “I did a survey that was completed by about a thousand people that indicated that one in four cancer

patients in the Netherlands lose their jobs when they get cancer, and other patient organisations have reported a similar figure. It's spurred us to talk to employers and the Dutch government to improve matters.”

“Healthcare professionals must bear some responsibility for not preparing patients better for survivorship, including work”

The number of people who end up leaving their employment after cancer is much higher than 25% – probably 50% or more, as a paper on barriers and facilitators for return to work from the Netherlands notes (*Eur J Cancer Care (Engl)* 2017, 26:e12420). That's because there are many who find they cannot perform well enough in their roles, and although an employer may be supportive, they can feel inadequate and leave anyway.

Attitudes in the workplace

That's what happened to Magali Mertens, who was diagnosed with a salivary gland tumour while working as a communications officer for a non-profit organisation in Belgium. “I loved my job,” she says. “I went back to work about 10 months after my first surgery, but I just didn't expect effects such as memory loss and fatigue such a long time after. No one told me a lot

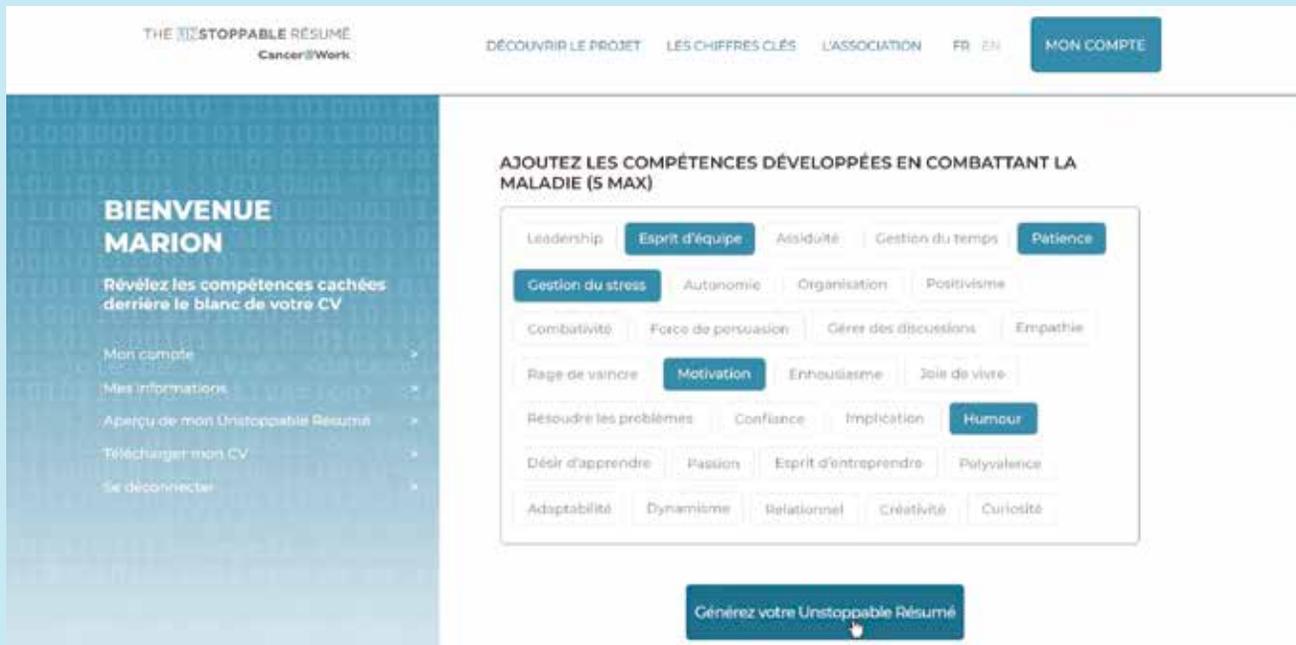
of patients experience such effects. At first, I had a lot of empathy and attention at work, but after a year my manager said I should ‘get a hold of myself’ – but she didn't know what I was experiencing. I felt guilty and left. I'm still in contact with her and she does know now that fatigue, especially, is still normal after a year.”

Mertens met a coach – someone who showed her how to become more empowered after cancer. She then trained to become a coach herself, and started her own organisation in Belgium, Travail & Cancer, to work, as Lebrocqy does, with employees and employers on integration plans in the workplace.

Healthcare professionals must bear some responsibility for not preparing patients better for survivorship issues, including work, says Liz O'Riordan, who has sat on both sides of the table – as a breast cancer surgeon in the UK National Health Service (NHS) and then a breast cancer patient herself. “As doctors, we are so busy explaining diagnoses and treatments that a lot of life problems for patients are just not on our radar,” she says. Talking of her own experience as a patient, she says that she was initially off work for 18 months, and then tried to negotiate a phased return to work, not working full time at first, as she just did not have her previous energy. “But I was only offered one month for a phased return – and I just didn't know my rights, that I was entitled to more time.”

Her hospital did though keep her stand-in surgeon on, but as she says: “I was very aware that if I couldn't make it work I would have to retire. As a super-specialised surgeon I couldn't think realistically about retraining, say as a GP, as that would take years.” A recurrence of the cancer then forced retirement. In the meantime, however,

A CV service that works for cancer survivors



The “unstoppable résumé” is a CV generating service developed by the French organisation Cancer@Work (canceratwork.com), together with LinkedIn, to help survivors trying to re-enter the jobs market. It helps people create a work résumé that ‘tricks’ the digital CV scanning software used by a large proportion of companies, which automatically sifts out people with gaps in their employment history. By using invisible (white) text it fills the gap while also offering users the opportunity to add in up to five positive work and life skills that they feel they have developed while undergoing treatment for cancer. Cancer@Work also

offers interview coaching and it works with a growing number of employers to provide advice and education to human resources departments and offer a job ‘dating agency’ aimed specifically at cancer survivors. At a wider societal level, the organisation works to challenge attitudes and assumptions about what cancer survivors can offer at work.

Cancer@Work was set up and developed in the context of a strong national policy supporting the rights of cancer patients to stay in work or return to work after treatment – an issue that was highlighted in the 2009–2013 French national cancer plan.

O’Riordan had met Barbara Wilson, who runs the UK group Working With Cancer, who helped her cope with both the physical and psychological aspects of survivorship. She has since joined Wilson’s team as an advocate, with workplace issues as part of her interests.

O’Riordan appreciates how important work can be as an escape route for people to feel normal and maintain a sense of purpose both after cancer and during treatment. A case in point:

when working as a surgeon, she was treating a young woman with learning disabilities. “I told her that she needed chemotherapy and that people don’t usually work during the treatment she was to receive, but she burst into tears and I couldn’t work out why. Then one of the nurses told me that work got her out of the house and gave her purpose – and I had told her she can’t work.”

The opportunity to continue life as normal is emphasised by all three

advocates, with work often a central part of activity, although it can also be a financial necessity. While fatigue is a common long-lasting effect of cancer treatment, even among those who are considered cured, there are many other effects, which may depend on the type of cancer and its treatment, and which can also influence how colleagues in the workplace view someone who has returned.

As O’Riordan notes, many women who have had breast cancer will have

had surgery and radiotherapy but no chemotherapy, so will not lose their hair, which is a stereotypical view that people often have about cancer treatment. “So they mostly look normal to others, but can be experiencing low energy, stress and also psychological problems. People with other cancers may need more obvious accommodations, such those who have had a colostomy after colorectal cancer.” She mentions too a nurse who had breast cancer but had to wear an arm sleeve to counter the effects of lymphoedema – but NHS policy is ‘bare arms’.

It may never be possible to get back to what was ‘normal’ before, and there is often no linear path of improvement, but good and bad periods (and people with metastatic disease may be moving in and out of treatment cycles over some time). What people who have had, or still have, cancer want is choice about how and whether to work given uncertainties, and they need employers who have information about the nature of cancer and its long-lasting effects.

As O’Riordan stresses, they also need healthcare and social care professionals who can provide information about long-term effects and rights, in addition to the more immediate treatment-related issues. “I would like to see people told about the rights available to them in any country when they start a job,” she says. “When you’re diagnosed you’re caught up with your treatment, as I was, and I knew next to nothing about my rights or those of others when I was working as a surgeon.”

A point made by both Lebrocqy and Mertens is about the type of work involved. It can be much easier to make accommodation for someone returning to an office role than those with jobs that involve manual tasks

such as truck driving and delivering mail. They may not have the physical capabilities to continue in these jobs and are more likely to be made redundant. This challenges society and employers to help people retrain and find new types of job, says Lebrocqy, whose organisation acts as a ‘matchmaker’ for finding suitable roles – which can take months.

Another point made by both advocates is that people returning to work after cancer can have a different outlook on life, having had a serious illness. They can be determined to live life to the full (but possibly try too hard) and can give much back to an organisation in terms of ‘soft skills’ of a positive outlook, and time and stress management, which is where coaching is valuable.

While legal recourse to return to work varies around Europe, there is nothing to stop organisations implementing good practice, and Lebrocqy highlights electronics giant Philips in the Netherlands as an exemplar. The company runs an employment scheme that includes placing people with occupational disabilities, and which since 2013 has accommodated cancer survivors.

Towards a European strategy

The European Cancer Patient Coalition (ECPC) has a new director, Antonella Cardone, with a particular interest in work issues, as she moved there from running the Fit for Work Global Alliance, led by the UK’s Work Foundation. She says one of the biggest problems is still the stigma of cancer, and the view that patients are often just not expected to return to work. But in recent years some countries have established best

practice backed by legislation that allows people to work part time for extended periods, for example. There is no pan-European strategy, however, which is why ECPC included a call for one in a manifesto issued ahead of the 2019 elections to the European Parliament. Workers with cancer should be protected from dismissal and there is a need to better understand the living conditions of cancer survivors who return to work.

It may never be possible to get back to what was ‘normal’ before, and there is often no linear path of improvement, but good and bad periods

“There is no pan-European strategy on survivorship, not just about work, and there is huge disparity among countries,” says Cardone. In some eastern European countries, survivors get very little protection, if any, while countries such as France, Italy and the UK have extensive rights. “But if countries invest in protection there can be great economic gain in both the employment and welfare sectors, as people stay on at work rather than retiring early, taking pensions and putting extra burdens on welfare systems.” People forced into inactivity often develop comorbidities, she points out, and with the rising retirement age, taking increasing numbers of people out of the workforce can have a double impact of lower productivity and

higher health and social care costs.

“We know that healthcare spending is becoming increasingly unsustainable in Europe, so we need to find ways of balancing this with return on investment in other sectors. But a big obstacle is the ‘silos’ that ministries often work in,” she says, and she argues for much greater cooperation between departments responsible for health, labour, economy and welfare, in particular. The economic impact of other conditions, such as musculoskeletal disorders, have been studied more than cancer, she adds. The ECPC manifesto calls for urgent action to address this knowledge gap – along with other survivorship issues such research on late effects, social rights (eg access to financial services), and implementation of the EU’s Work–Life Balance Directive, which includes more rights for carers, who are a critical and largely unpaid workforce.

A number of members of the European Parliament have taken an interest in survivorship issues. Among them is Lieve Wierinck, a Belgian MEP who hosted a meeting on the topic with the Advanced Breast Cancer (ABC) Global Alliance, in 2018, entitled ‘I have cancer but I want to work – working rights of cancer patients’ (see also bit.ly/ABC_I-want-to-work). Wierinck has herself been treated for colorectal cancer, including six months of chemotherapy. She said that quality of life is strongly impacted by cancer, and that she was happy to go to work for the distraction of focusing on something else. It is crucial to address disparities and harmonise standards for all Europeans she said, and she has since promoted the idea of a European cancer plan.

Wierinck emphasised that financial support is crucial to enabling flexibility for employers that find it hard to support unpredictable patterns of

absence for cancer patients. What would help – and break down ‘silos’ – is replacement income from the welfare budget that switches in on days when an employee cannot work.

A report from the European Parliament, on pathways for the reintegration of workers recovering from injury and illness, now includes amendments on cancer, and in 2018, a group of MEPs led by Rory Palmer (UK), launched the European *Dying to Work* campaign (dyingtowork.co.uk), which aims to protect terminally ill workers from dismissal. As it stands, there are no specific protections for terminally ill employees. The campaign, which originated in the UK, “notes with concern the cases of the unfair dismissal or treatment of terminally ill employees. We are calling for the introduction of EU legislation to safeguard the rights of employees by identifying terminal illness as a protected characteristic.”

“What would help is replacement income from the welfare budget that switches in on days when an employee cannot work”

Karen Benn, Deputy CEO and head of policy and public affairs at Europa Donna, the European Breast Cancer Coalition, says the EU’s Employment Equality Framework Directive 2000 is the legislative framework that should protect people with both early and advanced cancer from discrimination. This directive prohib-

its discrimination on the grounds of disability, sexual orientation, religion or age, and cancer can be considered to be a disability. But it is a directive and not a regulation, and while it must go onto the statutes of the EU member states, each country has the flexibility to define what constitutes disability, and whether cancer fits their definition. The directive requires employers to make “reasonable accommodation” for the working environment for all employees, but must not cause the employer “disproportionate burden”.

Some states, such as the Nordic countries, Netherlands, Ireland, France, Belgium and the UK, do give cancer patients the option to register as disabled and benefit from this legislation for their working rights, among other things. In Italy and France people can also register as disabled for a certain period of time and then ‘unregister’ themselves – as not everyone wants to be defined as disabled for the rest of their lives. However, in many European countries, formal protection is either non-existent or legally ambiguous, and there is no data on how many cancer patients return to work or how easy they find it to do so.

There are also big disparities in how countries help people return to work after long-term illness. The Scandinavian countries are good, says Benn, offering every cancer survivor a return to work plan. There is an opportunity for national cancer plans to address employment as part of survivorship; this is already happening in the UK and France, and has been proposed in the European multistakeholder reports which resulted from the EU joint action projects such as the CanCon Joint Action (see opposite). But even in the more advanced countries, there is little provision for the growing numbers of people who

It's about policies and plans

The European Guide on Quality Improvement in Comprehensive Cancer Control, developed by the CanCon European Joint Action, calls for national cancer plans to include policies to support cancer patients from diagnosis to return to work (bit.ly/CanCon_Guide).

It also advocates for a pan-European strategy to tackle the differences between workers with cancer in different countries and to prevent discrimination, and argues for generation of more evidence to better understand the living conditions of cancer survivors who return to work. It offers detailed policy recommendations for quality improvement in cancer after-care at the community level and in cancer survivorship and rehabilitation.

In its manifesto issued before the European Parliament elections in 2019, the European Cancer Patient Coalition called for member states to implement the CanCon recommendations (ecpc.org/ECPC-Elections-Manifesto-2019.pdf). They also called for adequate funds for research on survivorship to generate data

on late effects, as well as on the impact and cost-effectiveness of supportive care, rehabilitation, and palliative and psychosocial interventions.

The European Agency for Safety and Health at Work (OSHA) has produced a report and advice for employers on reintegrating workers with cancer in the workplace. The report, 'Rehabilitation and return to work after cancer: instruments and practices', identifies good practice in countries such as the Denmark, Belgium, the Netherlands and the UK, and includes case studies and focus group reports, and also a literature review of the health and economic impacts, and interventions (bit.ly/OSHA_RtW-BestPractice).

France has taken a lead in developing and implementing policies supporting patients who want to work during and/or after cancer. This issue was highlighted in the 2009–2013 French national cancer plan, which made resources available for initiatives and projects, and created conditions for the development of organisations such as Cancer@Work (see p 54).

are self-employed or who work on short-term or 'zero hours' contracts (where employees are essentially 'on call').

In eastern Europe, as an article in *Cancer World* recently detailed (Spring 2019), the focus is still on hospital-based services, and much less on outpatient and survivorship programmes. For example, a recent paper on return to work policies for cancer survivors in Romania reports that while there is a strong focus on compensation, with paid sick leave and access to pension and disability benefits, "for several components of return to work, only the general principles are stated, e.g., the need for work adjustments or the importance of stakeholders' communication, yet the procedures to put these general principles into practice are not specified... the law reflects the low awareness of cancer survivorship as related to work issues," (*Disabil Rehabil* 2019, 24:1–8).

In another paper, the authors say that employers need information and guidelines for assisting employees with cancer, and "better channels of communication and collaboration with health professionals are essential for more adequate support for the long-term consequences of cancer. A detailed return to work policy is required to tackle the inconsistencies in the support offered, and this policy must also rethink how diagnosis disclosure takes place in Romanian organisations," (*J Occup Rehabil* 2019, July 11).

At European level, a number of other organisations are looking at cancer and work. Foremost is EU-OSHA, the European Agency for Safety and Health at Work, which has produced a report and advice for employers on reintegrating workers with cancer in the workplace (see above).

Eurofound, the EU agency for the Improvement of Living and Working

Conditions, has looked at cancer in the workplace. EPF, the European Patients' Forum, has also focused on patients' rights in the workplace and protecting those living with chronic illness from workplace discrimination. There are also reports by the Economist Intelligence Unit, 'Cancer in the workplace' and 'The road to a better normal: Breast cancer patients and survivors in the EU workforce', both of which contain detail on obstacles and strategies to overcome them.

So there is much information about what 'good' looks like in employment practice for cancer survivors and a growing clinical literature base on the physical and psychological effects that survivors experience. What's missing is data on how many people are affected around Europe – and the joined-up strategies that can help them.

To comment on or share this article go to bit.ly/CW87-Cancer-and-Work



How ESSO Young Surgeons are promoting surgical oncology training

An invitation to ESSO from a section of the Russian Association of Oncologists to present a joint session at their annual 'White Nights' Oncology Congress offered a welcome opportunity to look at the differences in surgical training between Russia and Europe, and highlight what ESSO offers in terms of training and support, especially for young surgeons.

The session, which took place in St Petersburg in June, was chaired by Dr Aisha Isaeva, who works at the PA Hertsen Moscow Oncology Research Center, and is the national representative for Russia in EYSAC – the ESSO Young Surgeons Alumni Club.

The joint White Nights session offered ESSO the chance to contribute to a better understanding of structured training of young surgeons, which is a major problem in many countries. Surgical training is often not supported or rewarded, which makes it dependent on personal relations rather than part of a training mentality.

Andreas Brandl, a young oncology surgeon from the Champalimaud Centre in Lisbon, Portugal, spoke at the joint session as member of the EYSAC steering committee with responsibility for education.

"It was great to see how passionate and motivated young Russian surgeons were to co-operate, and to share with them my experiences and my own path within surgical oncology," said Brandl, adding that he particularly valued the chance to explain what ESSO can offer in terms of fellowship opportunities, quality training courses and EYSAC membership.

The experience of the White Nights joint session, with EYSAC Russian representative Dr Aisha Isaeva in the chair, shows

that the national representative programme – which was launched in 2018, with the aim of strengthening cooperation among European countries – is starting to produce real cooperative results. "We have also been contacted by other national representatives to attend similar talks, so I think the future is very bright for this programme. The more EYSAC members can collaborate and share information and experiences, the better," said Brandl.

His advice for future aspiring EYSAC or young surgical oncologist members wanting to get involved in similar cooperative initiatives is: "Work hard, invest in your profession and career, and in national and international societies. Collaboration in knowledge is a beautiful thing, and the more we can collaborate in knowledge about cancer care the better outcomes we will reach in our patients as surgical oncologists, young surgeons, and surgeons in training."

For more information on how to apply to be a national representative or join EYSAC, please contact the ESSO secretariat.

ESSO hosts two structured surgical training programmes. The European School of Peritoneal Surface Oncology (ESPSO) is a joint venture between ESSO and the Peritoneal Surface Oncology Group International (PSOGI). The European School of Soft Tissue Sarcoma Surgery is a joint venture between ESSO and CTOS (the Connective Tissue Oncology Society). These two schools provide excellent curricula consisting of an advanced two-year training period including clinical training and involvement in scientific projects in reference centres.

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The body after treatment

Do we do enough to protect our patients' self-image?

Studies indicate that a significant proportion of patients live to regret saying 'yes' to cancer treatments because of the impact on how they look, function or feel. **Simon Crompton** talks to patients and physicians about how oncologists and surgeons can minimise the number of their patients who end up feeling that way.

It was only once she had arrived at hospital, donned her surgical gown, and begun her pre-operative check that Joanna Moorhead acknowledged to herself and her surgeon what she had known all along. The surgery wasn't going to go ahead. A mastectomy was not for her.

She'd been told a few weeks before that she had a 10-cm-long grade 2 invasive tumour. But the diagnosing surgeon had barely met her eye, and straight away started talking about mastectomy and reconstruction.

He seemed more keen to talk about surgery dates than to help her make sense of the news. Joanna, a journalist who wrote about her experiences for *The Observer* newspaper in the UK, knew the surgeon was not right for her. So she consulted another one, who talked, listened, and in the end agreed with Joanna. There were alternatives to mastectomy, and she could remove the tumour with a good margin.

"My breasts seemed such an important part of me," says Joanna. "My big fear was that I'd be diminished by a mastectomy, that I'd never feel comfortable with myself again. I denied those feelings until the morning of the operation, when there was nowhere to hide."

For others in the same circumstances, mastectomy might have been the correct decision. Sometimes making treatment choices for any kind of cancer isn't just a matter of long-term disease outcome or even quality of life. It's about making a choice that fits your personality – what's important to you, what you do, how you see your body.

How well do clinicians help patients through this process, taking conversations beyond cool analysis of risk and benefit? Not very, according to Kari Tikkinen, consultant urologist and adjunct professor of clinical epidemiology at the University of Helsinki and Helsinki University Hospital.

"We should do shared decision-making better," says Tikkinen, who has studied how men make choices in prostate cancer. "We not only need to provide evidence-based information, but also to let the patient talk and then really listen. Many clinicians will say they do this already, but they don't. They do it too quickly. You can't get the big picture of patient values, expectations and preferences in a short appointment."

The research would seem to back him up. A study looking at breast cancer survivors found that almost 43% regretted some aspect of their treatment five years later – most often relating to primary surgery (*PsychoOncol* 2011, 20:506–16). Another study, looking at attitudes among long-term survivors of localised prostate can-

cer, found that 15 years after treatment, 15% of men regretted deciding on surgery for prostate cancer, and almost 17% regretted deciding on radiotherapy. Reasons for regret were dominated by sexual function problems (*JCO* 2017, 35:2306–14).

For some people, the most troublesome implications of treatment are about long-term effects on who they are and what their new body says about them. If these issues of self-image haven't been addressed before decision-making, the real implications of treatment often only hit people once it's too late.

A 2013 survey of 600 women who had been treated for breast cancer found that almost nine out of ten felt the disease and its treatment had had a negative impact on how they felt about their bodies, and only one in four felt they had been prepared for what was to come (bit.ly/BC_Self-Image).

Joanna Moorhead feels she had a close escape. She might never have had the courage to acknowledge her feelings and call off surgery at the last minute if, after the shock of diagnosis, she hadn't taken time to research all her options and find a surgeon she could talk to.

"I needed to get my head around the fact that I had cancer. Many of us have this deep-rooted feeling that cancer means we're going to die, but I had to expunge that and recognise that early stage breast cancer is probably not something I'm going to die of."

"My big fear was that I'd be diminished by a mastectomy, that I'd never feel comfortable with myself again"

Joanna says a few short discussions with her new surgeon, Fiona, went a long way. "Fiona and I talked about how one size does not fit all. The risks I was happy to take would have been totally unpalatable to others. Good clinicians understand that there is no one way, but that it all comes down to how each individual accepts risk. My philosophy is that the best way to live life is to take risks, but I wouldn't impose that on anyone else. It's really about understanding someone's inside track."

"It might sound ambitious for surgeons to get to know their patients," she says, "but I think they should all be competent at listening. If I could choose one skill in a surgeon it would be intuition every time."

Getting Personal

Getting it wrong

Women who choose mastectomy also have big decisions to make about reconstruction. But this too can feel rushed. Studies have shown that lack of discussion and information around reconstruction can lead to regret about decisions.

A recent study shows that those who choose reconstruction tend to overestimate how good and attractive it will make them feel, whereas those who decide against reconstruction can be pleasantly surprised at their well-being afterwards (*JAMA Surg* 2018, 153:e176112).

These findings mirror those of Laure Andrillon, a French journalist who investigated the experiences of women who had not had reconstruction for an article in the online magazine *Slate* (bit.ly/Beautiful-with-one-breast). The article went on to win a Cancer World Journalism Award.

In France, she says, it is assumed that women will want reconstruction and it is discussed at the first possible opportunity. “There’s an assumption that reconstruction is part of the treatment, which is in some ways good,” she says. “But it means some of them feel puzzled, guilty or alone if they don’t take that option... Talking to women who had not had reconstruction, they were quite surprised to find that it could be a positive experience.”

The way that options had been presented implied that reconstruction would bring a much better result for them psychologically. “The phrasing used is very important. Just the way physicians talk about the options shouldn’t imply that some are better than others.”

The wisdom of personal experience

Before making decisions, women need to have a realistic picture of what they might look like – and feel like – after removal or reconstruction. Some breast surgeons have taken this need very seriously. When he was Director of the Breast Surgery Unit at the Maugeri Foundation in Pavia, Italy, breast surgeon Alberto Costa built up a group of ten women who had undergone different breast procedures who agreed to meet patients who were considering similar surgery.

“I’ve always been convinced that any explanation by a doctor or nurse – no matter how accurate – is not like contact with a person who has been through the same operation,” says Costa. “You need to see and physically feel what it means.”

“The women were available and accepted that there is no other way to understand what a reconstructed breast is. And this was really beautiful. We left these women in a room in peace, and the patient always came out saying now everything is clear. It was done through seeing and feeling.”

“You need to see and physically feel what it means... there is no other way to understand what a reconstructed breast is”

Such a service, he says, is easily organised by a surgeon or breast nurse. Breast cancer patient organisations can also help. The problem today is time. A system of 20-minute appointments doesn’t permit such flexibility or in-depth exploration, he fears.

Some French doctors, says Andrillon, also organise meetings with former patients. Others have books of photographs of women after surgery to help them understand how the body will look, and how they respond emotionally to that. “For the women I talked to, they see images as a very very important part of the decision,” she says.

Despite systems encouraging early decisions, there is actually plenty of time for women to make their mind up about what happens after cancer removal. “Many doctors have explained to me that usually it’s better to delay reconstruction anyway, so that women have time to think about it, read information, and discover their new body,” she says.

A hurried decision is rarely needed

Similar problems apply in prostate cancer, where clinicians and clinic systems often put unnecessary time pressure on patients. “At diagnosis, in at least 90% of cases it’s not an urgent situation and it doesn’t matter if you make the treatment decision today or next month,” says Kari Tikkinen.

There’s plenty of evidence that radical treatments such as prostatectomy and radiotherapy deserve unhurried consideration of personal implications: they can leave men with incontinence, bowel problems, impotence and a profoundly changed sense of self.

A 2017 review of studies concluded that men experience

psychological and social changes after prostatectomy and that their perceptions of their masculinity are affected (*Int J Nurs Stud* 2017, 74:162–71). Men often described prostate surgery as “life-changing”, and although they recognised the trade-off between survival and postoperative complications, long-term effects such as erectile dysfunction often caused them more distress than the potential return of the disease itself.

Former patients have spoken of their regret. One who had his prostate removed soon after a cancer diagnosis said: “In hindsight, there are questions I wish I had asked. I should have spoken up before the surgery and discussed what I was feeling afterwards too.”

The problem, says Tikkinen, is not that radical curative options are wrong but that they are wrong for some people. And surgeons – and oncologists too – aren’t always suited to assessing this.

They tend to think in terms of abstract facts about survival and quality of life, but patients are often more interested in how everything fits in with their detailed personal agenda. “We tend to think about mortality, incontinence or erection, and actually patients think about whether they can do something – whether they can travel to a wedding that’s coming up, for example, or when they will be catheter free – which we might think of as quite secondary.”

Surgeons, oncologists and other specialists also tend to dictate decision-making by guiding patients towards their own specialty – even if it’s subconsciously. Studies have indicated that whether a prostate patient is referred first to an oncologist or a urologist has a major influence on their treatment decision. “We are all biased towards what we do,” says Tikkinen.

The answer, he says, is to be systematic in treatment decision-making, taking patients carefully through all the options, their risks and benefits, but also allowing them time and space to think and speak. He is an advocate of ‘encounter patient decision aids’ – tools such as infographics and bullet points that allow the clinician to go through vital information with the patient in a structured, considered way. For example, Tikkinen uses pictograms to show risks and benefits of different procedures.

Allow time for thorough discussion

A review of evidence conducted by Tikkinen and his team indicated that such aids help reduce regret about decisions made. But they need to be blended with time

for discussion, and exploration of the patient’s outlook and values.

“I always ask questions like: ‘Are you the sort of person who likes to get rid of all kinds of risk?, or ‘Are you the sort of person who’s happy seeing what happens in life?’ They can give an indication, for example, of whether they are suited to active surveillance rather than active treatment.

“It can be challenging. You need time. In most systems you have around 20 minutes, but I’d say that a cancer decision-making appointment usually takes 45 minutes. That leaves me behind schedule but it’s crucial and you have to give it.”

The issues apply to every cancer, because the physical changes that come with any radical treatments inevitably change people’s sense of self. In colorectal cancer, for example, a stoma may be indicated for some patients – but this needs sensitive discussion. According to Stefan Gijssels, Executive Director of Digestive Cancers Europe and himself a colon cancer survivor, some older patients decide not to go through with stoma surgery even though that choice may have a significant impact on their life expectancy. “They don’t want to go through the burden of surgery or living with a stoma for the last years of their life,” he says. “This is a choice they should have, an alternative that should be discussed and offered.”

“In most systems you have around 20 minutes, but I’d say that a cancer decision-making appointment usually takes 45 minutes”

For anyone who needs a stoma as a result of gut surgery, there are difficult implications. Some may cope better than others. “Obviously it creates problems in terms of practical day-to-day life, sexual intimacy, self-image. I think these are manageable concerns once people have made their choice, often together with their partner. It’s also good to listen and discuss with other patients who have gone through it.

“I know of people who are quite satisfied after a stoma operation – for them it is better than they had anticipated. But you don’t tend to hear much from the

Getting Personal

“You don’t tend to hear much from the ones who find it difficult because they don’t like to go into a public environment”

ones who find it difficult, because those who are suffering don’t like to go into a public environment much.”

Gijssels believes that people are far more likely to be able to face life with a stoma if they are given plenty of time to talk to family, friends, surgeons, oncologists and even psycho-oncologists before the surgery. Many hospitals work with patient organisations so that people can find out first-hand from other patients about what it’s like to live with a stoma.

“The important question to ask, which is often forgotten by oncologists, is: ‘What do you expect from life?’ I know that’s really a philosophical question, but it’s about assessing what quality of life means. What do you like? How do you want to continue to live after surgery?”

What do patients want and expect?

Dora Constantinides from Nicosia, Cyprus, who had a colostomy when she was diagnosed with colorectal cancer at the age of 42, believes a lot has to do with a person’s outlook on life. “Cancer can act as a catalyst and bring out the best or worst in us.” Support from family and access to the right healthcare at the right time are also important.

At diagnosis, Dora was young, and very physically active with a young family, so she knew her sense of self would change. But talking to a doctor and stoma nurse about what life might be like after the operation helped her enormously. “They were considerate to ask where I would like my stoma to be, and asked me how I wore my pants and where it would be convenient if I went swimming.”

Dora stresses the importance of patients knowing the positive and negative impacts of both temporary and permanent stomas. Doctors and former patients are a valuable source of information on both options, she said.

“From the beginning, my health professional team’s open communication and understanding facilitated the

difficult journey to recovery and rehabilitation. They gave me an opportunity to make a choice, and every choice they gave was important – to feel you have a degree of control in your pathway. This kind of consideration helped me to accept my colostomy and come to terms with my new image.”

Dora went on to become a municipal councillor for Nicosia, representing the newly formed Green Party. She continues to live a busy and active life. She still swims and cycles, and is Head of Awareness at the Cyprus Association of Cancer Patients and Friends.

“There were changes of course, physically and psychologically. People always used to tell me what a nice figure I had and how beautiful I was, and I was an athlete. So it was a big change, but I felt okay after the initial shock of diagnosis – I’d been lucky enough to enjoy all that before, and I now felt there was more to me than the outside. I would look at myself as I was, and I accepted it. It’s a new part of me. Sharing everything with my family made the transition smoother.”

“It’s not the decision aids or the information package that matter. You have to listen to the patient and what’s useful for them”

Patient accounts are clear about what helps them accommodate the effects of their treatment into their daily lives. They are clear on what helps them make treatment decisions that suit their outlook on life and their sense of self. The question is, are clinicians and their organisations able to learn from those clear messages, and accommodate them into daily practice? Can hospital systems adapt to provide the time and access needed?

“We should be doing better shared decision-making,” says Tikkinen. “We are all so busy now everywhere in the world, and there’s an argument we need to rethink our clinical practice and give more time to help with decision-making. In the end, what really makes a difference is not the decision aids, it’s not the information package that matters. It’s the discussion in the office. You have to listen to the patient and what’s useful for them.”

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REDUCING INEQUALITIES IN CHILDHOOD CANCER CARE

The substantial inequalities in access to the best available care, expertise and research innovation for children and young people with cancer remains a critical issue across Europe. These inequalities contribute to 20% differences in survival rates when comparing north and western Europe with central and eastern Europe. There is a fundamental need to ensure childhood cancer centres meet a specific standard level of expertise and are continuously updating their best practice. Europe needs to recognise that paediatric cancer remains an urgent health and socio-economic issue. More than 35,000 children and young people are diagnosed in Europe each year, and despite improvements in cure rates over the recent decades, cancer remains Europe's leading cause of death in children aged over 1 year old. It is also a substantial cause of morbidity and socio-economic costs, with half of the survivors – who now number around half a million in Europe – suffering long-term side effects that negatively impact on their health and wellbeing.

The European Society for Paediatric Oncology (SIOPE Europe) has a well-defined European policy agenda for paediatric cancer (siope.eu/strategy), which has gathered substantial support in successive European Parliament election manifestos. Equal access to the best available care and research for all patients across Europe is a fundamental pillar of this agenda. Our community is already driving important initiatives to reduce the stark inequalities in paediatric cancer research, treatment and care. This is exemplified by the work of the European Reference Network on Paediatric Cancer (ERN PaedCan), supported by the EU Health Programme, which is aiming to reduce inequalities in childhood cancer survival by providing high-quality, accessible and cost-effective cross-border healthcare to European children and adolescents with cancer, regardless of where they live in Europe.

SIOPE Europe has also contributed to the Joint Action on

Rare Cancers (JARC). Funded by the EU Health Programme, JARC is addressing the lack of systematic inclusion of rare cancers – including paediatric malignancies – in National Cancer Plans across Europe, and is ensuring the appropriate implementation and sustainability of European Reference Networks.

There is now cause for optimism for the future of cancer research in Europe, with the announcement of a mission area dedicated to cancer under the EU Framework Programme 'Horizon Europe'. The incoming President of the European Commission, Ursula von der Leyen, recently highlighted plans for a 'European plan to fight cancer', and dedicated members of the newly constituted European Parliament are ready for further engagement in the fight against the disease.

As a collection of rare diseases, it is clear that cross-border, collaborative research underpins all progress in childhood cancer, and a focused research effort at the EU level holds great potential to unlock and accelerate therapeutic progress. SIOPE Europe looks forward to collaborating with all stakeholders to ensure the imperatives for childhood cancer patients – namely, equal access to the best treatment, care and innovative research – are at the forefront of this dynamic landscape. The ultimate aim is for all childhood cancer patients in Europe to have equal access to the best available standards of treatment and care, no matter what their country of origin or residence may be.

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COURSES AND SEMINARS

Real world evidence

Why we patients need it, and how we can get it



Roger Wilson is a leading voice in cancer patient advocacy. He has been living with a recurrent sarcoma for 20 years, and is a co-founder of Sarcoma Patients Euronet. He is on the faculty of the EORTC/ESMO/ECCO/AACR Methods in Clinical Cancer Research workshop, and has a particular interest in the use of patient reported outcomes in research, clinical decision making and treatment availability.

Patients and advocates welcome the dawn of precision medicine. But we want more certainty about the benefits and the risks. So far these new drugs have been used by very few patients in small phase II trials, and the long-term data we have are mixed. There is no statistical certainty: there is single-case or small-group benefit, but only assumptions about overall efficacy. Nonetheless registration follows.

Attitudes towards the balance between faster access and greater certainty may differ between patient activists and between patients and experienced advocates. Having been both patient and advocate over the years, I try to balance the viewpoints.

It is important not to be fooled by surrogate endpoints such as Progression Free Survival. They are not about survival, but about delaying the certainty of progression. There is a rational case that Overall Survival and Quality of Survival are the only measures that make any sense for decision-making about standards of treatment. This implies that more rigorous evidence than is offered by phase II studies is needed. Hence the call for real world evidence.

However, as a patient advocate, I see no standard methodologies, no funding, no independence emerging in this area. This is not good for patients. The call for real world evidence is a headline answer to the loss of rigour, and like most headlines it is simplistic. It is not clear how clinically relevant evidence can be gathered and analysed in a manner that ensures completeness, quality, and freedom from bias.

The patient advocate should not accept second best, and we must stand up and say so. This rigour is what we have become used to and it is what we still need. Precision medicine may be providing a tumour response in a small number

of patients, but is it a high quality of treatment? We just do not know.

The key element is the quality of survival. Assessing quality of life is an evolving area of research, moving from all-encompassing Quality-of-Life models towards targeted patient reported outcomes (PROs), developed with patient input, measured long term, with data gathered using new technologies. This helps us look at specific aspects of survival, including side effects, on a longitudinal and long-term basis. Putting this alongside Overall Survival, with both measures derived in a rigorous manner, can give us the real world evidence we need.

Yes, we want any patient who believes that a particular treatment would benefit them, and whose clinicians agree, to have access to that treatment as soon as possible. But at the same time we think that a treatment should only be made available if it has robust evidence that it offers holistic benefits to patients in the target patient group.

There is a fine boundary between these two stances, which is brought into sharp focus by the issue of payment. A payer will usually hold a position balanced between the scale of cost and the degree of benefit that the evidence shows can be expected. A healthcare system, hospital, or insurer will have analysts and health economists to advise them. They can refuse funding even when a treatment is licensed.

A patient who is funding treatment from their own resources or those of supporters may not be so sophisticated. Extending mortgages, cashing in pension funds, reaching out through crowd funding – we hear about all these financial routes to treatment. Suddenly there is a lottery – where is the boundary between degrees of evidential certainty and financial exploitation?

Comment

Clinicians sit in the middle of this, keen to support their patients but reluctant to see them spend money on what may be undeliverable expectations.

To try and get back some certainties, a group of leading cancer societies, led by the European Organisation for

Research and Treatment of Cancer (EORTC) and supported by many organisations including the European Society for Medical Oncology (ESMO), is proposing a move to put standards into appraising the real world clinical use of new treatments through 'treatment optimisation'. Their

A proposed model for integrating real world evidence into the evaluation of new drugs

Step 1: Market access

A pharmaceutical company Runoutofink Laboratories Ltd submits its experimental anticancer drug canigetanib to the regulatory authorities for marketing approval, which is given on the basis of:

- Two phase II studies both demonstrating improved progression free survival (PFS) of 3 months in a genetically defined subset of patients with cancer xyz. The studies show that the drug was well tolerated.

Step 2: Reimbursement decision

The Ruritanian Health Technology Assessment (HTA) programme agrees funding terms with Runoutofink Laboratories Ltd for a 3-year period subject to a study of real world evidence.

Step 3: Real world evidence study

A real world evidence study is:

- Conducted by an independent academic research group, according to a protocol agreed between the researchers, Runoutofink Laboratories Ltd and the Ruritanian HTA body,
- Funded by a national fund, the Ruritanian Oncology Agent Research agency (ROAR), set up jointly between the healthcare system and the pharma industry. The healthcare system funds the treatment. Runoutofink Laboratories Ltd supplies the drug under usual market terms, but only to doctors who have adopted the protocol.

The protocol requires that:

- Any doctor wishing to prescribe the drug does so under the terms of the protocol and data gathering standards,
- Every patient provided with canigetanib accepts that their data will be part of the study
- Patients are asked to provide their own reports of outcomes using a smartphone or internet access (via voucher code).

The protocol:

- Determines a standard follow-up with details of data to be gathered and standards to be applied,
- Gives scope for tighter follow-up and emergency action at the clinician's discretion,
- Indicates side-effect reporting and treatment, including dose reduction.

The key data point at patient death is confirmed by the national registry.

Step 4: The real world evidence tells us more information

The real world study gathers data from several thousand patients with cancer xyz and shows:

- A 6-week overall survival benefit compared with historical data extracted from the Ruritanian national registry.
- PFS in the study is shorter than in the trials, explained by the fact that the trial cohort was younger than the average patient.
- Side effects are generally well tolerated, but reports of grade 3 adverse events are more frequent – again a factor of trial population.
- Dose reduction has been shown to reduce these side effects with no discernable difference in tumour response or duration of response. However longer-term side effects appeared after 12 months on continuous treatment, even on reduced dose, which patients reported affected their quality of life,
- Patients on average withdrew from treatment 5 months before dying and they experienced an improvement in side effects and quality of life for a period after withdrawal.

Step 5: Results are fed back into the system to inform further research and adjust pricing

- Research: ROAR withdraws the real world protocol. A phase III randomised clinical trial comparing a reduced dose with standard dose canigetanib is designed and put in motion, funded by ROAR. It has an overall survival primary endpoint. ROAR is considering academic proposals for phase II studies of combinations with other therapies.
- Reimbursement: After 3 years the Ruritanian HTA body gives a further period of approval to canigetanib, but the healthcare system reduces funding for the full dose of the drug after its HTA health economics analysis takes the 'real world' response and previously unknown side effects issues into account.

We await the results of the dose reduction study.

proposal would employ methods proven in clinical research to develop robust evidence. In addition, such studies could allow structured testing of the best ways of using the new technology, including identifying minimum effective dose – a move that could save on costs.

Medicine is not a lottery and should not become one, but it is in danger of doing so. Real world evidence is an obvious thing to be doing, and many patients will wonder why it is not already being done. The question then becomes how to gather real world evidence in our clinical systems to a standard of completeness and rigour that compares with what we are used to? Various stakeholders in the world of precision medicine have come at this challenge in different ways, but no clear sense of how to do it emerges.

The people with the most to gain are patients, but we have had no meaningful voice. Even though the views of patients and of experienced patient advocates sometimes differ, one set of priorities comes through clearly: we must not deny access to those who may benefit when a new drug is approved, but we must build certainty that the safety and efficacy characteristics of that treatment are real in the longer term and, crucially, that the quality of life of patients taking that treatment reflects benefit.

Where is the problem? Perhaps surprisingly to some, patients generally expect that some kind of ‘virtuous’ feedback loop happens in medicine. They find it a shock when they discover that no such feedback loop exists.

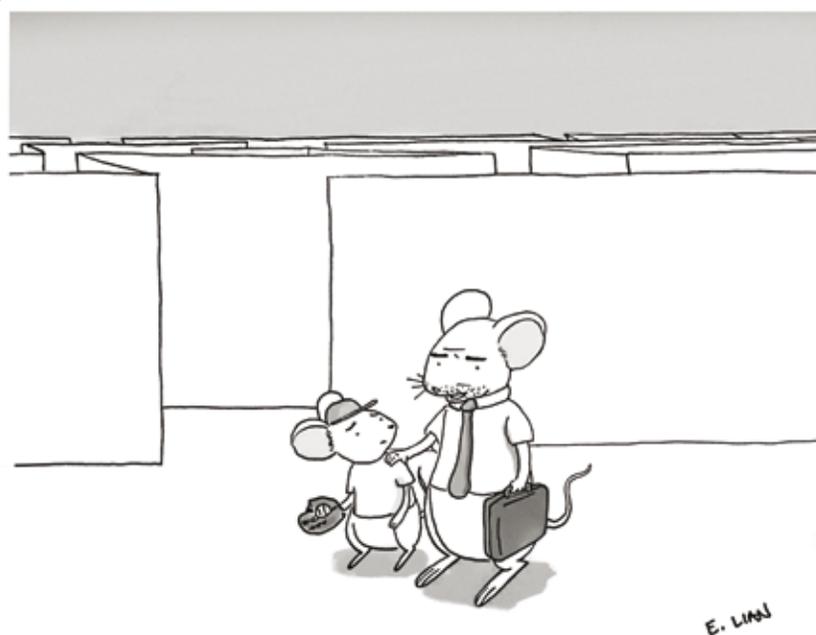
The opposite page shows a suggested model of how such a thing could be brought about, using an imaginary scenario played out in Ruritania – an imaginary, relatively wealthy, western European state.

For me this scenario constructs a model that has the opportunity to deliver rigour, independence, absence of bias and completeness of data. It respects pharma innovation, serves the needs of healthcare systems, and above all identifies the value in terms that patients want.

The key that unlocks it is ‘ROAR’, the independent but funded Ruritanian Oncology Agent Research agency. The scenario illustrated in the model opposite certainly begs a whole range of further questions – it is an imaginary scenario after all. But is it really too much to ask all the stakeholders to come together and reach some form of agreement that can bring rigour and certainty back into the equation that patients are forever balancing? I will happily chair the meeting.

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For a laugh



“Sorry, kiddo. Your old man has to work so you can go to the best drug trials in the country.”

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