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A POLICY ROADMAP ON ADDRESSING

METASTATIC BREAST CANCER

METASTATIC BREAST CANCER POLICY ROADMAP

The policy roadmap is a report developed by a multi-disciplinary Expert Working Group aiming to highlight gaps and best practice in policies around Metastatic Breast Cancer (MBC). It builds on previous work within the breast cancer community to showcase specific and practical policy actions that can be taken across Europe.

You can access the Metastatic Breast Cancer Policy Roadmap at: https://lillypad.eu/

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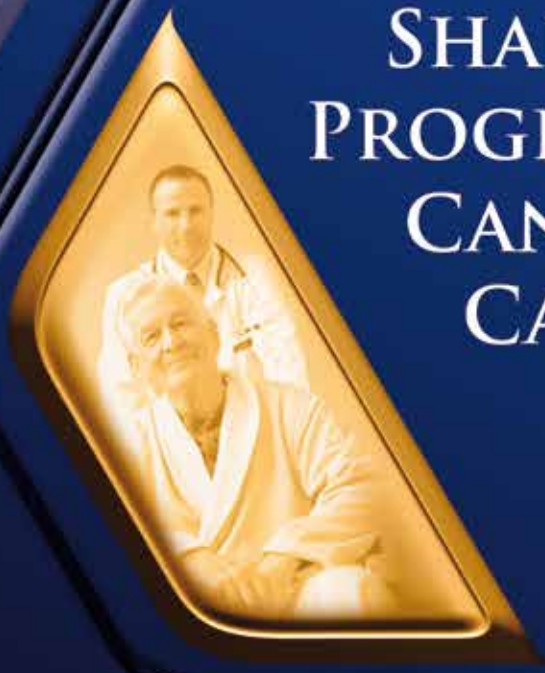
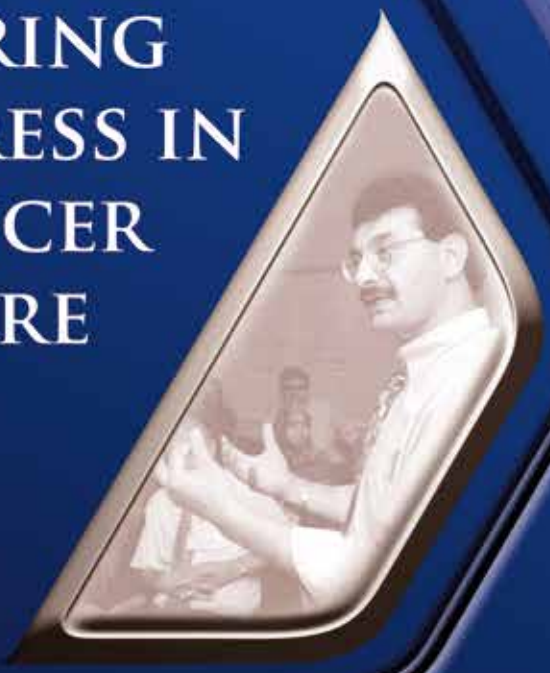
Sharing Progress in Cancer Care





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Winning where it matters

Franco Cavalli, Guest Editor

We're winning the war on cancer on a scientific level but losing it in the real world. That was the conclusion reached by 100 top researchers, clinicians and advocates at the first World Oncology Forum held in 2012.

Developments in precision cancer medicine since then have proved them right. The new generations of high-tech designer drugs that dominate the agenda at oncology conferences are out of reach for the vast majority of cancer patients, including many in Europe.

On June 22nd, as President of the International Conference on Malignant Lymphoma, it will be my privilege to welcome more than 3,500 delegates to Lugano, Switzerland, to share the latest knowledge and experience in treating this group of tumours. The protocols under discussion will reflect the important advances in precision treatments made in recent years: antibody-drug conjugates that transport cytotoxics straight to tumour cells; immune checkpoint inhibitors that are working so well for Hodgkin patients; new treatments targeted at B-cells and B-cell signalling that are proving game changers for patients with chronic lymphocytic leukaemia, acute lymphoblastic leukaemia, and non-Hodgkin lymphoma.

This is what winning the war at a scientific level looks like. Sadly, it is also what the widening disparity looks like between the minority of patients who have access and the many who don't. Many of the delegates to this truly international conference will be left asking how they can access those scientific wins to help their patients win their own battles.

The World Oncology Forum Taskforce met at the end of 2018 to address the same question. We identified three reasons to be hopeful: efforts to address non-communicable diseases are being taken increasingly seriously by governments and policy makers; the concept of universal health coverage is gaining traction; and global health discussions have moved on from focusing on prevention and treating simple conditions, to include the need to invest in diagnostic infrastructures to promote early and accurate diagnosis.

Yet until they move on further, to include investing in treatments for people who are diagnosed with cancer, we will continue to lose the war in the real world.

In the run up to the 2019 UN High Level Summit on Universal Health Coverage, the WOF Taskforce is compiling evidence on the cost-effectiveness of providing cancer care. We can show that investing in radiotherapy capacity gives an impressive return on investment over 20 years, even in the poorest countries, and that extending the bare essentials of surgical capacity to cover key cancer procedures can be made affordable and quickly lead to savings. As for access to effective new drugs, we can point to evidence from the Global Fund to fight AIDS, Tuberculosis and Malaria, which shows that introducing the principles of transparency, benchmarking and pooled purchasing helps lower prices very significantly, while protecting quality and access to a variety of drugs, diagnostics and other technologies.

The WHO has already taken the important step of adopting ESMO's Magnitude of Clinical Benefit Scale to screen new cancer drugs for inclusion in its Essential Medicines List. We now need to convince governments and policy makers of the economic as well as humanitarian strengths of our case for coordinated action on cancer, as part of the global universal healthcare efforts. Every one of us in the cancer community can help make that happen.

Franco Cavalli is Scientific Director of the Oncology Institute of Southern Switzerland, and founding Editor of *Annals of Oncology*

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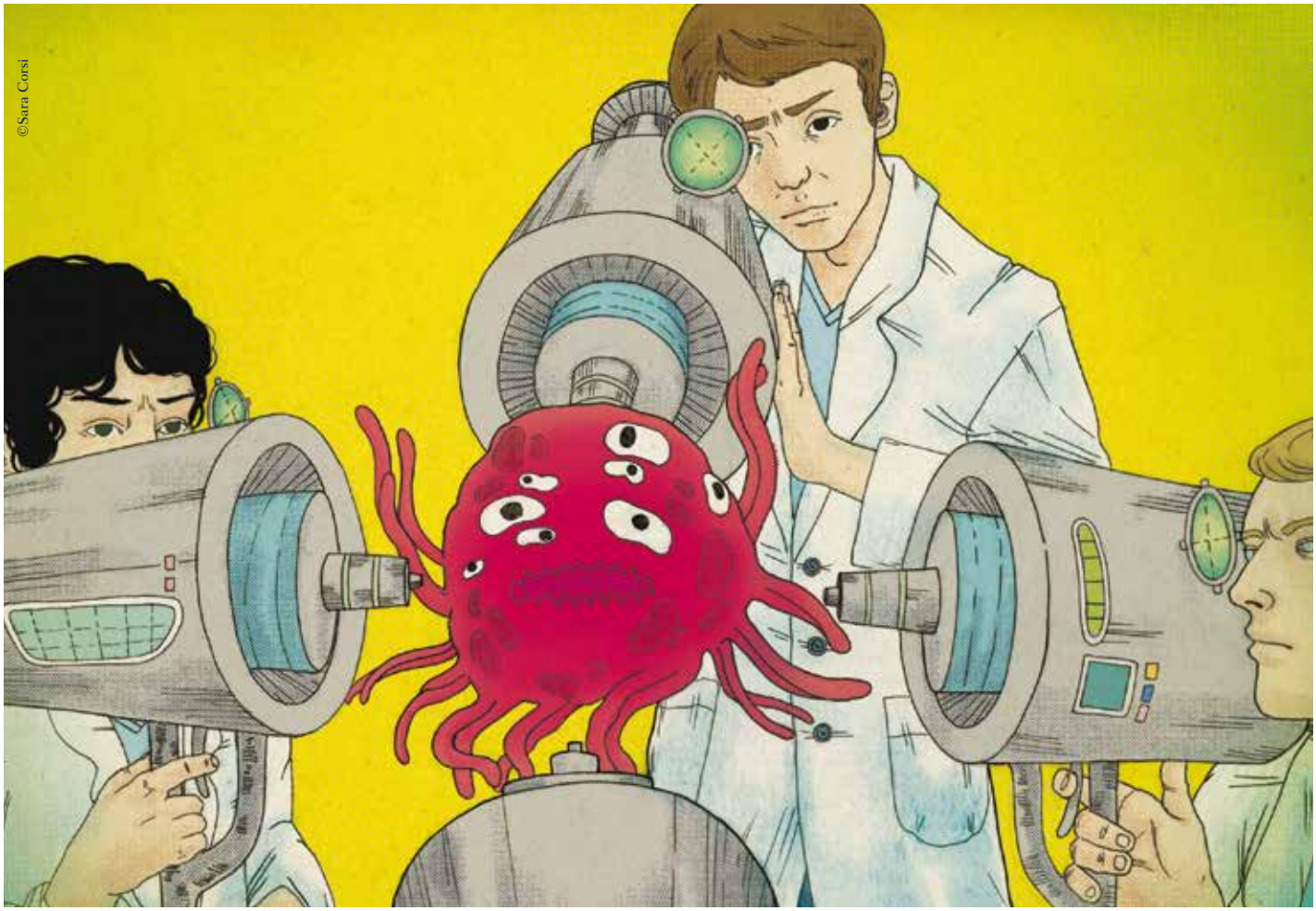

Better care or just more high tech?

Defining the value of new radiotherapy treatments

Many patients are being treated with costly new radiotherapy treatments on the basis of hype rather than evidence that they stand to benefit. For others, lack of evidence is delaying access to new treatments that could make a real difference. **Janet Fricker** reports on efforts to develop a scale to measure the value of locoregional cancer therapies, and asks: could it help us make better use of high-tech interventions?

Over the past few years an impressive array of new technology has become available in radiation oncology. Together with improved diagnostic imaging and better computer algorithms, advanced radiotherapy technologies have evolved treatments from using simple rectangular radiotherapy fields towards techniques such as intensity modulation and stereotactic targeting that focus the beams more precisely on the tumour.

In parallel, the nature of the beams themselves has evolved. In addition to the traditional photon beams delivered by linear accelerators, cyclotrons are now able to deliver beams of much heavier protons and carbon ions. Other innovations include shorter fractionation schedules, motion management and adaptive radiotherapy, novel combinations with systemic drugs, superior image guidance (using MRI as opposed to CT for greater soft tissue resolution), and new immobilisation systems.

"The overall result is that we're better able than ever before to target tumours and spare the surrounding critical organs from toxicity," says Yolande Lievens, chair of the radiation oncology department at Ghent University Hospital, Belgium. But as she acknowledges, none of this high-tech equipment comes cheap, and nor does the additional expertise needed to carry out the imaging, planning and delivery of each treatment.

Convincing health services to introduce these new treatment modalities into everyday clinical practice will require demonstrating that the benefit they deliver is worth the additional cost.

"With so many developments, we need to start to judge value in radiation oncology and define what works best in different clinical scenarios. We want to ensure we aren't using a sledge hammer to crack a walnut and that all these new high-cost technologies deliver real clinical benefits," she says.

Lievens is now leading efforts to develop a framework for assessing the value of radiotherapy and surgical – i.e. 'locoregional' – procedures, in much the same way as ESMO's Magnitude of Clinical Benefit Scale, and its US equivalents (the ASCO Value Framework and the NCCN Evidence Blocks) do for systemic therapies.

A new (as yet unnamed) European group has been set up under the auspices of the European Cancer Organisation (ECCO) umbrella, with Lievens in the chair, tasked with developing a value framework that could be applied across radiation oncology and surgical techniques and across different treatment settings.

If we want to provide the best care…

The rationale for developing such a yardstick is widely accepted, and goes well beyond radiation oncology, as Lievens explains. "Across Europe cancer expenditure is rising exponentially, driven by the growing ageing population, numerous therapeutic advances and expanding choice and consumerism in healthcare."

Cancer care costs health services more than any other disease, with the American Institute of Cancer Research estimating that in 2016 the world budget for oncology treatments was $895 billion. For sustainable health systems, there is growing recognition of the urgent need to define the patient groups who need the most advanced treatment approaches, as compared with those who would do just as well with standard cheaper treatments.

In a position paper calling for public policy debate on access to cancer innovations, Matti Aapro, President-Elect of ECCO, argued that 'newer' may not necessarily equate to 'better', and that 'older' alternatives, and 'simple' interventions may deliver the greatest impact on improving patient care (*EJC* 2017, 82:193–202).

"We need to apply more scrutiny to the way we deliver care today, be ready to remove or discontinue practices or interventions that are inefficient, and be forward-thinking to prioritise innovations that may deliver the best outcomes possible for patients with the resources at hand."

His point is echoed by Ajay Aggarwal, a clinical oncologist specialising in prostate cancer at London's Guy's and St Thomas' Hospital, who is working with Lievens on the value framework. "Access just because a treatment is new is not something we should be striving for. We need to have shown clearly that access to new treatments will bring meaningful improvements in the quality and length of life, and can reduce the toxicity and financial burden to patients associated with treatment."

Adapting the medical oncology benefit scales

The ESMO Magnitude of Clinical Benefit Scale (ESMO-MCBS) was developed to provide a 'rational, structured and consistent' approach for ranking relative benefits of drug treatments in solid tumours, to help with priority setting and decision making in the face of large numbers of new and costly cancer treatments coming onto the market.

As Elisabeth de Vries, chair of

Advances in radiation oncology

Traditionally, external beam radiation therapy (EBRT) uses a linear accelerator (LINAC) to deliver photons (high-energy X-rays) to tumours. More recent advances include improved image guidance and computer algorithms, allowing radiotherapy to evolve from simple treatment fields towards highly conformal radiotherapy techniques, such as intensity-modulated radiotherapy (IMRT), and stereotactic radiotherapy (SRT).

- IMRT enables dose to be shaped to tumours by modulating (controlling) the intensity of the radiation beam, allowing different doses of radiation to be given across the target. CT scans map tumours in 3D, with computers controlling machines fitted with a multi-leaf collimator, composed of thin lead leaves, to shape radiation beams precisely to tumours.
- Stereotactic radiotherapy (SRT) uses 3D coordinate systems and/or advanced imaging to locate small tumour targets. It was originally delivered with brands including CyberKnife and Gamma Knife, but it is now most frequently delivered with standard LINACs. It was used first for brain and spinal cord tumours, but development of stereotactic body radiation therapy (SBRT) allowed the principle to be transferred to other indications such as lung, liver, pancreas and prostate cancers.

Such conformal approaches have improved outcomes by escalating dose to targets and minimising toxicity to normal tissue and critical organs. Treatments can be delivered in one to five treatment sessions compared to typically five to eight weeks for standard external beam radiation therapy. More detail on these advances can be found in a review by SS Ahmad and colleagues (*BMJ* 2012, 345:e7765).

Conformal radiotherapy techniques can be adapted to deliver heavier particles such as protons and carbon ions, produced by particle accelerators (cyclotrons), as alternatives to photons.

- Proton beams (charged nuclei of hydrogen atoms) have a peak of dose deposition at a sharply defined point (the 'Bragg peak') allowing for a much lower dose to nearby critical organs. Proton therapy is most widely used for treating tumours located close to vital organs that would be unacceptably damaged by X-rays, or in paediatric oncology where late side effects are of major concern. According to the Particle Therapy Co-Operative Group, around 80 proton beam facilities exist worldwide, with around 30 now operating in Europe.
- Carbon-ion radiotherapy (CIRT) uses charged carbon nuclei particles, which have a larger mass and greater charge than protons, yielding even sharper dose distributions. Another advantage is that its efficacy is unaffected by the low oxygen levels occurring in tumours, so it is more effective in radioresistent tumours. Although CIRT has been used since 1994 to treat cancer in Japan, it has only recently been available in Europe, with facilities now operating in Vienna, Heidelberg, Marburg, and Pavia. The lack of centres has made phase III trials difficult. Photons, protons, and carbon ions all kill cells in different ways, making it important to establish the different tumour types where each is most effective.

the ESMO-MCBS working group, explains, that exercise too was about delivering the best possible outcomes with limited resources: "In cancer there's a profound problem with numerous new drug treatments, but only finite amounts of money, making it necessary to discriminate drugs that really make a difference to patients," she says.

Under the MCBS system, systemic therapies are judged on a range of factors including overall survival, progression free survival, hazard ratios, long-term survival, response rates, prognosis, quality of life and toxicity. For curative settings, the therapies are graded A, B, or C, with grades A and B representing a substantial level of clinical benefit; while for the non-curative setting, the scale is graded 5,4,3,2,1, with grades 5 and 4 representing substantial levels of clinical benefit.

The question being asked by

Lievens and her colleagues is: how can this scale be 'nuanced' to reflect the specificities of locoregional treatments – both in radiation and surgical oncology. Their initial conclusions, published earlier this year (*Lancet Oncol* 2019, 20:e112–23), indicate that such an exercise could be possible – but will take a lot of time and effort.

End points

One of the first differences the review authors identified between systemic and radiation oncology treatments was relevant trial endpoints. Aggarwal, a co-author of the paper, explains that, while both approaches consider overall survival, in radiotherapy far greater emphasis is placed on local control, organ preservation and acute and late toxicity, which are not weighted in the current value frameworks. Progression free survival is considered of far less importance in this setting.

"Local control represents organ function aspects like the ability to swallow in oesophageal cancer or control urination in bladder cancer. These are the outcomes which really affect patient wellbeing," says Aggarwal. He also points to the need to take into consideration the late clinical effects on organs beyond the cancer, such as rectal bleeding and chronic diarrhoea, that can result after radiation oncology for prostate cancer.

A clear distinction in radiation oncology trials needs to be made between acute toxic effects (that occur within three months of treatment), and late (chronic) toxic effects (that occur months or even years after treatment). "With more patients cured with radiotherapy than systemic treatments, the issue of survivorship quality becomes much more pertinent," he points out.

Progress in technology or outcomes?

For radiotherapy trials, it will be important "to focus on innovations that represent real changes in the treatment process that could advance our ability to control the cancer or reduce toxicity," such as new fractionation schedules or the addition of systemic drugs to standard radiotherapy, stresses Aggarwal.

He contrasts these with "incremental innovations that are likely to achieve similar outcomes to established technology, but to do so more efficiently."

Types of evidence

Different levels of evidence beyond formal randomised controlled trials might be considered for radiation oncology, they suggest, such as model-based studies and real world evidence.

Cai Grau, a radiation oncologist at Denmark's Aarhus University, who has done a lot of health economics work with the European radiation oncology society ESTRO, is another co-author of the study. He explains that modelling – exploring how therapy doses affect patients according to their individual anatomy – can be performed to predict benefits without the need for randomised trials. The approach can also be used to 'enrich' trial populations, he says. "The principle is more or less the same as testing for biomarkers before enrolling patients in targeted therapy trials. Modelling allows you to perform studies in specific cohorts of patients where you know there is likely to be benefit."

The study also suggests that registries can be used to explore the intervention in real world populations, allowing consideration of patients who do not meet the stringent criteria of clinical trials. Aggarwal takes pains to caution, however, that the quality of the data is only as good as the registry infrastructure.

"Registries in radiation oncology need to have near complete coverage of the relevant population, with low levels of missing data, and ensure that endpoints in addition to survival can be captured, such as adverse events from treatment as well as markers of disease progression or relapse." This needs considerable methodological input and time, stresses Aggarwal, who challenges the "often heard assumption that any available patient-level real world data is relevant and can be used to inform practices of care."

Greater emphasis is placed on local control and organ preservation, which are not weighted in current value frameworks

"Using a combination of modelling and real life data you can get a feedback loop to define the types of clinical questions that you want to pose in a trial," says Aggarwal.

Then there is the issue of accounting for the expertise of the provider. Radiation oncology is more dependent on healthcare provider expertise than systemic treatments, says Lievens. "Consequently, any benchmarking of value will need to take into consideration the quality of delivery."

The patient perspective

New tools will be needed to identify the aspects of care that matter to patients, such as shorter and less

invasive treatment schedules, and the ability to return quickly to normality and work. This may be trickier than it looks. As the review acknowledges, patient values are not a 'one size fits all', but are influenced by external factors such as social, religious and cultural environments as well as patient-specific factors, such as gender, education, and personal finances.

"Trials need to focus on innovations that represent real changes that could advance our ability to control the cancer or reduce toxicity"

"It's important for scales to distinguish living longer with better quality of life from living longer with worse quality of life," says Bettina Ryll, founder of the Melanoma Patient Network Europe, who has been providing patient input for the ESMO-MCBS scale. "There is a need to measure what matters to patients and this varies between individuals. For example, not being able to walk far would have an entirely different dimension for a marathon runner compared to a couch potato." Tools, she adds, should be able to take into consideration potential trade-offs, for instance between short-term severe toxicity and low-grade but long-term toxicity.

Values are not static, cautions Kathy Oliver, founding director and chair of the International Brain Tumour Alliance, who contributed the patient advocacy perspective to the *Lancet Oncology* study. "They alter as the patient's journey unfolds and he or she travels through illness, treatment, survivorship, and potentially end of life. During some of these stages, non-interventional support may be of huge value to patients, this includes access to patient organisations, support groups, clinical nurse specialists, rehabilitation and palliative care. But these types of support are rarely acknowledged as being of importance in value frameworks." Added to this, says Oliver, cancers can be very different from each other, with varying side effects, symptoms and outcomes. "Short prognosis conditions may call for different value scales than longer-term conditions, taking into account trade-offs between benefit and risk and extended survival versus quality of life."

Value for money

The group believe that it will be important to include economic endpoints to define more explicitly the financial costs of new innovations. This is something the ESMO-MCBS was careful not to do, partly because costs vary so much across Europe.

de Vries, who chairs its working group, says excluding cost considerations also "gives freedom to think what the scale really means for patients". She adds, however, that ESMO does now see the value of addressing financial aspects, and is exploring whether it might be possible to incorporate the ESMO-MCBS in a geographically based reimbursement model.

Ending hype-driven decision making

The hope is that having a single scale by which to judge the value of new technologies used in locoregional cancer treatments will help ensure decisions on investment and deployment of new technologies are taken on the basis of evidence not hype.

Aggarwal points to the experience with the introduction of DaVinci robotic surgery systems as an example of the latter. When in 2006 the UK's National Health Service allowed greater choice over where patients received treatment, many men with prostate cancer opted to attend robotic centres. Resulting market forces led to a rise in the number of centres offering robotic surgery from 18% (12 centres) at the beginning of 2010 to 71% (39 centres) at the end of 2014 (*Lancet Oncol* 2017, 18: 1445–53), with nearly 90% of all centres offering robotic surgery for prostate cancer.

"The growth was despite a scarcity of evidence for superiority of robotic surgery with respect to both functional and oncological outcomes, and the procedure costing far more than conventional open surgery," says Aggarwal. "It's human nature to assume that the latest innovations are better, and should replace older more established treatments," he adds – which is exactly why robust quality performance measures, are so badly needed.

In the United States, such 'human assumptions' have been used to market proton therapy for a variety of cancer indications. Men with prostate cancer have been a target, because they are a large market, and because one of the 'unique selling points' of proton therapy is that protons deliver most of their dose at a particular point rather than along their entire beam trajectory, which offers the potential for protecting organs on the far side of the target.

However, unlike the many other options for treating prostate cancer, the evidence base for proton therapy is small and conflicting. One of the few studies comparing conventional with proton beam therapy for prostate cancer found that gastrointestinal

problems were in fact worse in the group receiving proton beams (*Eur Urol* 2011, 60:908–16). In addition, many men who opted for proton treatment would not have required any treatment at all beyond 'watchful waiting', because their disease was unlikely to progress in a clinically meaningful way during their lifetimes.

And this uncertain benefit does not come cheap. A new proton beam therapy service at The Christie Cancer Centre in Manchester, UK, cost around €145 million to develop. Little wonder then that, in the absence of any restraints, US healthcare providers who invested in this technology were driven to aggressive marketing to pay off the loans.

For Cai Grau, however, the inappropriate use of expensive high-tech treatments is only one side of the problem. Perhaps a greater concern for him is that public health services, where academic research is located, have been reluctant to invest in such expensive technologies when the commercial sector already has more than enough capacity to treat the limited number of patients for which there is evidence of benefit. But the commercial providers, who now carry out the lion's share of proton therapy procedures, have minimal interest in performing the trials that are so badly needed to generate evidence on whether new technologies like this really do deliver better outcomes, and for which patients and indications.

Towards a culture of value-based research

The problem, says Grau, is not limited to proton therapy. "Unlike drugs, where the vast majority of trials are undertaken by pharma, in radiation oncology it is largely left to the professional community of independent investigators to assemble the evidence," he says. A key reason is that manufacturers only have to demonstrate their devices are safe to use, but not the impact on outcomes. Research in radiation oncology is therefore heavily dependent on public funding, which is becoming harder to come by as the technologies become more sophisticated and costly.

"We've experienced something of a catch 22 situation in radiation oncology, where many countries want evidence that therapies work in different cancer locations before investing money in infrastructure. But the reality is that you can't undertake research until you have invested in equipment."

Aggarwal agrees that much more needs to be invested in generating evidence in radiation oncology. Given that this type of treatment contributes to 40% of all cancer cures (*Nat Rev Cancer* 2009, 9:134-42), yet accounts for just 5% of the overall cancer treatment budget (*Acta Oncol* 2003; 42: 357–65), it makes sense to invest more in maximising the value for patients.

Aggarwal, Grau and Lievens all hope that developing a single, evidence-based and consistent approach to measuring that value will help win the argument with funders about the value of investing in that research. The prize will be moving towards health systems that promote innovation, avoiding delays in clinical adoption of

The impact of ESMO's Magnitude of Clinical Benefit Scale

Since 2015 The European Society for Medical Oncology has applied its Magnitude of Cinical Benefit Scale (ESMO-MCBS) prospectively to new anti-cancer interventions approved by the European Medicines Agency (EMA), with ESMO guidelines incorporating scale results. It is also used by the World Health Organization to support selection of cancer drugs for their essential medicines list and by patient advocates to lobby for access to drugs that make a real difference. The scale is now starting to be incorporated into health technology assessment processes. Notably, one middle-income country experiencing huge problems with drug prices used the ESMO scale to define their essential medicines list, with the result that they were able to maintain universal health coverage. "Ultimately, the scale helps doctors and patients to sit together to discuss whether they want to use a drug or not," explains Elisabeth de Vries, who chairs the ESMO-MCBS working group.

Richard Sullivan, a member of the initial ESMO-MCBS task force, believes the scale provides a vehicle to slice through the hype of clinical trials, distinguishing cancer therapies with trivial clinical benefits delivering progression free survival advantages of a few weeks from drugs that can substantially improve long term survival. "Just because a drug has received marketing authorisation, the trial has been published in a reputable journal, and the press release proclaims a statistically significant result doesn't mean that the drug is of real value," says Sullivan, from Kings College, London. "The scale provides a mirror allowing you to take a hard-nosed look about whether reported outcomes are clinically meaningful."

Proton beam research: catching up with clinical practice

Europe has generally been slow to invest in proton therapy facilities. However, the number of academic centres actively delivering proton therapy in the EU is progressively expanding, with established centres in Germany, Belgium, Switzerland, Sweden, France, Italy and the Netherlands. The launch of The Christie NHS Foundation Trust Proton Beam Centre in Manchester, UK, in autumn 2018, and the Danish Centre for Particle Therapy in January 2019, together with the anticipated launch of the University College London Hospitals Proton Therapy Centre in the summer of 2020, will further boost Europe's capacity to carry out collaborative research on this unique form of radiotherapy.

Research activities will be in addition to providing a routine proton service for established clinical proton indications. These are currently limited largely to highly complex brain cancers, head and neck cancers and sarcomas, particularly in children, where reducing radiation doses to normal tissue avoids adverse effects on growth, intellectual development, endocrine function, and secondary cancer development. The evidence-based guidelines originated from the American Society for Radiation Oncology (ASTRO) after observational studies at Loma Linda University and the Massachusetts General Hospital.

This new investment comes almost a decade after proton therapy took off in the US market with aggressive marketing campaigns around many indications for which the theoretical advantages of protons have not been confirmed in randomised trials, including prostate, liver, pancreas and lung cancers. The failure to generate strong evidence on the value of proton therapy in these cancers is because proton beam therapy has been mainly performed in privately funded centres that do not undertake research, but seek to maximise their market to make a profit on the huge upfront investment required for proton therapy facilities.

In Europe, the establishment of government-funded proton treatment centres in recent years has resulted from strategic national health business plans estimating that it is more cost effective for health services to set up their own proton centres.

One of the important spin-offs from increasing the number of government funded proton centres across Europe is that 'protected beam time' will enable both basic science and clinical research, says Neil Burnet, from the University of Manchester.

"Together with established centres in Holland, Switzerland, Germany and Austria, we're reaching a critical mass of proton facilities where we are starting to have enough centres to undertake international collaborative research efforts," he says.

One of the first trials planned for patient populations that do not meet the current ASTRO proton therapy guidelines is the phase III TORPEdO trial at The Christie, where intensity-modulated proton therapy is being compared with intensity-modulated radiotherapy in oropharyngeal cancer. "The key thing will be to explore whether protons reduce treatment side-effects, such as difficulty swallowing and dry mouth, in a way that's useful to patients," says Burnet.

Other trials in similar populations of patients are planned in the Netherlands and Denmark in the hope of eventually performing a meta-analysis. No less important, says Burnet, will be the opportunities the new facilities offer to undertake physics-related research exploring where proton beams stop, and cell culture work exploring synergies between protons and systemic treatment.

valuable new treatments and preventing widespread adoption of interventions that offer no benefit or can result in harm.

The *Lancet Oncology* paper is just the beginning of the beginning. It makes a strong case for both the urgent need and the feasibility of developing such a value scale for locoregional treatments. The authors are under no illusions, however, about the length of the journey they plan to embark on. "We're well aware that it will be a really labour-intensive effort that will need additional funding and support," says Lievens.

The group are also mindful that cancer is treated by multidisciplinary teams, and of the need to undertake a whole-system approach to innovation across systemic and locoregional interventions. "Ultimately, we'll need to find a way of aligning value scales for systemic, surgical and radiation oncology so that we can capture in a reliable way what's best for the individual patient," she says.

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Shortages of generic cancer medicines are harming patients. So why can't we fix it?

Despite more than a decade of efforts to address the problem, cancer patients across Europe and the US still cannot rely on essential drugs being available when they need them. **Rachel Brazil** looks at the size of the problem, its impact on patients and professionals, and the efforts to put in place policies and alternative business models that could offer a solution.

For the last decade, headline stories about problems accessing cancer drugs have focused almost exclusively on novel 'targeted' treatments. Less publicised is the story of growing problems accessing traditional cytotoxics and other oncology medicines that are no longer on patent, but remain the real workhorses of oncology care across most cancer types.

Health services have traditionally relied on the generics market to provide affordable copies of brand-name drugs once the patent that gives market exclusivity has expired. But a persistent problem of re-occurring shortages across a wide range of generics is damaging patient outcomes, adding to the workloads of hospital pharmacists and others in

the care team, and raising questions about how to balance the need for competition against the requirement of a guaranteed supply line.

Whilst the problem is not unique to oncology, shortages of generic drugs have hit cancer treatment hard. This is because generics form such an important part of treatment protocols, and because if a particular drug is unavailable, it is often not possible to substitute something similar.

Adrian van den Hoven is Director General of Medicines for Europe, the representative body of the European generics industry. "If you look at the number and the volume of drugs provided to patients for cancer they would mostly be generic medicines," he points out.

A worldwide problem

That countries in central and eastern Europe face the greatest problems may come as no surprise. Less expected, however, are the growing reports of shortages across the whole of Europe as well as the US. After a decade of failure to fix this, it is clear the problem is complex and multi-faceted and will need some radical solutions.

In 2014 the European Association of Hospital Pharmacists (EAHP) published the first pan-European survey on drug shortages in the hospital sector. A second survey published in 2018 indicated that, despite efforts to counter shortages, the problems may be getting worse (bit.ly/EAHP_shortages). Of 1,666 respondents across 38 countries, almost 92% reported experiencing shortages compared with just over 86% in 2014. Almost two in five respondents said the problem occurred on a weekly basis and typically lasted a few months.

The past five years have seen global shortages of at least ten essential oncology drugs: bleomycin, carboplatin, carmustine, cisplatin, fluorouracil, gemcitabine, irinotecan, methotrexate, mitomycin and etoposide. Part of the problem is that it's a "moving target", argues Alexandru Eniu, a medical oncologist at the Ion Chiricuta Cancer Institute in Cluj, Romania. Eniu contributed to a 2017 report on Cancer Medicines Shortages in Europe published by the Economist Intelligence Unit together with the European Society for Medical Oncology. "Shortages occur and then they get solved and then they re-occur," he says.

In Romania, says Eniu, shortages occur almost daily for certain medicines, "and this is affecting the activity of a large number of oncologists and the prognosis of many many patients" – patients like those Eniu was treating two years ago: "I had to treat breast cancer without tamoxifen for six months… There is no replacement for certain breast cancer patients." Medicines predominantly used in childhood cancers are also in chronically short supply, he adds.

In neighbouring Hungary, shortages of generic drugs for cancer started to be reported in 2012. "Previously there were just shortages of vaccines or orphan drugs, but oncology was new," says Róbert Vida, a pharmacy researcher from the University of Pécs. Whilst many shortages are global, says Vida "not all of the drugs are used by all countries, so there is a different pattern of drug shortages from country to country."

The United States also experiences shortages. The FDA (US drug regulator) recorded a total of 306 shortages in 2018. As of December 2018, 16 active chemotherapy drugs were in short supply. "Shortages in general were getting better," says Erin Fox, director of Drug Information at the University of Utah Health Care, "but in the middle of 2017 they started to get much worse, with lots of shortages of very basic products." The biggest impact on oncology patients currently is in supportive care, says Fox, including the saline bags needed to make up antiemetic infusions and pain relief drugs such as morphine and hydromorphone. The problem was caused by manufacturing shutdowns at several large Pfizer facilities.

The past five years have seen global shortages of at least ten essential oncology drugs

One ongoing shortage in both Europe and the US is of the BCG (Bacillus Calmette-Guerin) vaccine, an intravesical immunotherapy used to treat early-stage bladder cancer. "It is very troublesome right now, here in the US, with supplies not being as readily available as we would like," says Fox. This particular shortage started in 2012, when its supply was disrupted in Europe due to a temporary suspension of production in Sanofi Pasteur's Toronto manufacturing facility. In 2016 the company announced production would stop completely by 2018, leaving only an alternative inferior strain.

Shortages can be local, such as the 2012 shortage in Germany of

5-fluorouracil, a cytotoxic used to treat colorectal and a variety of other cancers. This happened as a consequence of Teva Pharmaceuticals pulling out, leaving a sole remaining German manufacturer.

The knock-on effect, however, was felt across eastern and central Europe, says Eniu. "In these countries prices are somewhat lower than in other countries, such as Germany or the Netherlands. So obviously if they have only 100 vials of the drug or tablets, the producers will sell them to the country that pays more."

Vida sees similar 'parallel exporting' in Hungary, "The economic power of a country has an effect on what is available, so countries with more patients and more money get what is left, and countries like Hungary won't get the drugs."

Poland, Romania, Bulgaria, and Greece also suffer in this way, according to Aida Batista, Vice-President of the European Association of Hospital Pharmacists and director of the pharmacy at Centro Hospitalar in Vila Nova de Gaia, in Portugal. She adds that, although against EU law, "In Poland and also in Portugal the governments have taken measures to avoid parallel exports of products that are experiencing shortages in other countries."

Impact on patients

When cancer drug shortages occur they have real impacts on patients.

In Hungary, Vida says he has experienced shortages of the drugs carmustine and melphalan used as part of a multidrug combination for treating lymphoma. "Usually [shortages] can be solved with a generic substitution or individual importation from other European countries," but he says on occasion they have had to settle for a second-line treatment: "it was more expensive and had more side effects."

Similarly, oncologist Umberto Tirelli of the National Cancer Institute in Aviano, Italy, reported carmustine shortages in May 2011, with stocks running out during autologous bone marrow transplantation of nine lymphoma patients. They were forced to modify treatment plans, leading to longer waiting periods for some patients (those already achieving good results) and the use of an experimental alternative drug.

The rate of bladder cancer recurrence increased from 16% before the shortage to 43% in those treated during the shortage

A US study published in 2013 looked at two periods of treatment in 2010 and 2011 at a New York cancer centre, where approximately one in ten patients had their treatments changed due to shortages of paclitaxel (Taxol), which was substituted with docetaxel (Taxotere) – a more expensive alternative. The physicians involved considered the alternatives less effective in almost one in three patients.

The global shortages of the BCG vaccine have meant rationing in many regions. From 2012 to 2016 the French National Agency for Health Products Safety (ANSM) restricted its use to the highest-risk groups and stopped maintenance treatments. Marc Colombel, a French oncologist at Edouard Herriot Hospital, in Lyon, reported on the impact at a recent oncological urology meeting. He looked at outcomes in a patient group that had been 'sub-treated' during this period, and found a significant clinical and economic impact.

The rate of bladder cancer recurrence increased from 16% in those treated prior to the shortage to 43% in those treated during the shortage. The risk of surgical removal of the entire bladder increased. And the overall economic impact was a doubling of subsequent treatment costs.

Given such adverse impacts on outcomes, there is also a worry that, when official supply lines run dry, patients and hospitals may try to source unavailable drugs from black market internet vendors.

Vida and colleagues conducted a study of the vast number of online pharmacies which, while not legal, seem to operate with relative impunity. "We saw that even when they are not available in the legal supply chain, these drugs are available [online]," he says. He identified online sources for all cancer drugs that were in short supply in Hungary in 2016, including cisplatin, oxaliplatin, doxorubicin, fluorouracil, and methotrexate. From previous studies he suspects these drugs were authentic generics, but may have been beyond their expiry date and incorrectly stored. Vida is not yet aware of any patients having purchased cancer drugs online, but says in Hungary there are concerns that private clinics may look to these kinds of sources.

Impact on healthcare professionals

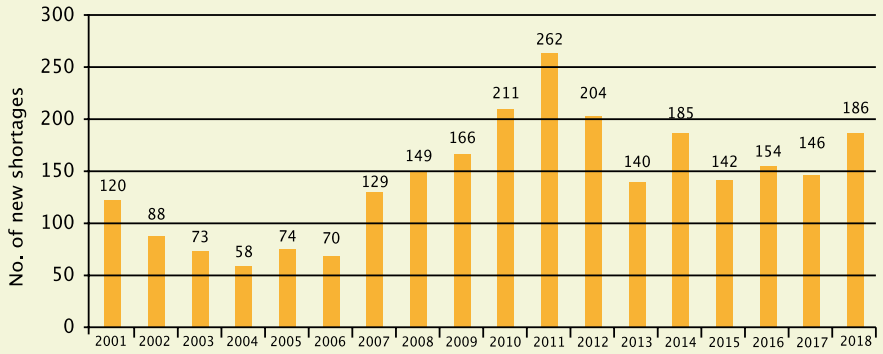
Shortages of cancer drugs also impact heavily on workloads. The 2018 EAHP survey found that almost two in five respondent pharmacists spent at least five hours a week dealing with shortages. "It's always a burden on doctors, pharmacists and nurses,' says Batista. "Suddenly we receive a phone call saying 'We don't have this,' and you have to make lots of calls to another hospital and vendors. We have an informal network between hospitals to ask: 'Please lend me this, and I'll lend you this.'

"We spend a lot of time reaching agreements with the doctor and deciding 'for this patient I want this and for that patient I want that', and we have to get it fast if we don't have it in the hospital."

The lack of information can make the situation worse, and shortages often create wider ripples, she adds. "When there is a shortage of one medicine and we have to change to another, everybody changes together, so the demand increases on that medicine and it provokes a shortage of the other one. It's like a snowball round and round, and sometimes it's quite difficult to find a solution."

Cancer services in the US face similar pressures, according to Fox. "We have to do a lot of work trying to figure out how much we have on hand and then figure out strategies so that we can stretch that supply. We're triaging and rationing." During the recent shortages of saline bags she says many hospitals would administer antiemetics via syringe: "The patients got the same dose at the end of the day, so that was fine, but the computer work that we had to do… we had to update 700 different order sets [which created] over 100 hours of work."

An enduring problem



Statistics from the US reporting the number of new drug shortages in the years 2001 to 2018 show the problem is not getting better. Sixteen of the shortages reported in 2018 related to chemotherapy drugs, of which 15 were injectables

Source: Erin Fox, University of Utah Drug Information Service

The root of the problem

Speaking from the perspective of the European generics industry, van den Hoven argues that the root of the problem lies in policies adopted by "hospitals together with health ministries" in the wake of the 2009 financial crisis. "Over the last few years, for a lot of cancer drugs especially injectable chemotherapy drugs, the policies of most payers has been to try and get the lowest price possible. The end result has been an extreme consolidation of manufacturing. The number of suppliers has really declined dramatically," he says. He cites the example of Portugal, where he says suppliers of oncology injectables have fallen from eight to two over the past five years, and Italy, where he says 15–20% of hospital tenders attract no bids at all.

One consequence, he argues, is that when problems arise with manufacturing quality or supply chains, these can quickly lead to shortages. "These are unfortunately regular occurrences now because the number of manufacturers is so limited… It's very difficult for the industry to invest because the prices are so low. There's no business case." An example of this situation occurred in 2013 when German pharmaceutical giant Boehringer Ingelheim decided to shut down its Ohio-based contract manufacturing unit Ben Venue Laboratories, which produced the Johnson & Johnson cancer drug Doxil – a pegylated liposome-encapsulated form of doxorubicin that had recently gone off patent. After several years of regulatory and quality control issues and periods of suspended production, the company eventually decided the additional investments needed could not be justified.

Policies and forward planning

As far back as 2001, the European Union passed a directive (2001/83/EC EU Directive) that aimed to minimise the risk of drug shortages. It mandates pharmaceutical companies to provide advance notification of production stoppages, whether

permanent or temporary, although they are not obliged to share information on the causes. How this has been implemented varies within EU countries, but only 56% of respondents to the EAHP survey judged their countries' reporting process to be effective. "What is happening in many countries is that you find out today from the pharmacy that they don't have any cisplatin," says Eniu. For patients who are undergoing cycles of chemotherapy this can have a big impact: "Knowing in advance and planning for that is very important and this should be feasible," he says.

"I think one of the difficulties is there's no sharing of information across countries," says Medicine for Europe's van den Hoven, "and as a result, if you have a genuine manufacturing shortage with an impact across several countries, there isn't really good coordination."

One of the most proactive agencies is the French ANSM. "When there is a shortage they establish a process of discussion with all the manufacturers of that product to try to manage the source and increase the supply to prevent a disruption," says van den Hoven. In 2016 France introduced a new regulatory tool that set out sanctions for industry breaches, but Francois Bocquet, a pharmacist specialising in law and health economics at Paris Descartes University, says the regulation has not really fixed the problem, "as the number of drug shortages has never been so significant. The problem remains major and no therapeutic class is spared."

The US seems to have had more success in its regulatory response. In 2012 it passed a law that requires manufacturers to report shortages to the FDA, including the reasons and expected duration. This provides the basis of a searchable public database on the FDA website. The FDA is also able to take measures to avoid shortages, although it cannot require a company to increase production of a specific drug.

"This actually made a tremendous difference," Fox believes, not least because, in dealing with manufacturing and quality issues, the FDA can use regulatory discretion to prevent shortages posing a risk to patients. "For example, if they know there is a batch of vials that have some particles in them, but everything else about the medicine is safe, they can allow the company to sell that product, but with a filter."

They will also work with alternative companies to help them ramp up production, speedily approving new production lines or raw material sources to help increase supplies, adds Fox. "Back in 2012 there was a significant shortage of methotrexate injections, and the FDA was able to approve another supplier to alleviate the shortage very quickly."

The FDA can use regulatory discretion to prevent shortages posing a risk to patients

Eniu would like to see more proactive measures in Europe to predict the likelihood of shortages. In Romania the government does step in and make use of special authorisations to get drugs into the country, "but this is always after the fire has started," he says. "The ideal situation would be a system to prevent it from happening, by taking measures before the shortages actually occur." The 2017 report on cancer medicines shortages in Europe that he contributed to outlined six policy recommendations to prevent and manage shortages (bit.ly/EIU-ESMO_Shortages). In April 2019, in advance of elections to the European Parliament, ESMO worked with MEPs to launch a cross-party call for 'tangible political commitments' to act on these recommendations as a matter of urgency during the 2019–2024 legislative cycle (see box opposite).

A market failure?

The report also focused on creating the right financial incentives for industry to improve production infrastructure. Some see this as a key problem, particularly for medicines with relatively small markets. "There are no financial incentives, they are losing money, so I guess the market laws are not functioning very well in this area, especially in the generic low-profit medicines," says Eniu.

van den Hoven argues that current cost cutting and uncertainty in the generic drugs market makes investment very difficult. "We need to figure out a more long-term predictable scenario so that companies will reinvest again on the manufacturing supply side." He argues that those in charge of buying medicines need to be part of the dialogue. "They should enable tenders to allow for price competition, but there should be a component of security of supply in there."

Medicines for Europe has held internal discussions around procurement models that would offer very-long-term contracts, including a requirement to invest in manufacturing capacity. "This is a very radical

idea, and it's not fully accepted by anybody yet," says van den Hoven, "[but] if we don't come to this, it's just going to be uneconomic to manufacture these super-essential drugs, which are the backbone of cancer treatment."

In the US, one group of healthcare providers is looking at an alternative solution. Intermountain Healthcare, a Utah-based system of 23 hospitals, is leading a collaboration of more than 450 hospitals to form a new not-for-profit generics drug company. This will be the first non-profit generics manufacturer in the US. Civica Rx CEO Martin Van Trieste, an accomplished biopharmaceutical entrepreneur, agrees that the current economic model is broken. "The part that we are doing that really fixes that model is we do not recover a margin, a profit, by selling the drugs."

Civica Rx plans a three-pronged strategy: work with existing manufacturers to make products under Civica's oversight; develop their own generic drugs under their own FDA licence using contract manufacturing capacity; and set up their own manufacturing facilities. "We are working on all three of those simultaneously," says Van Trieste, because "we want to be pro-competitive and have redundant manufacturing [capacity]."

To create a more stable market, but retain a competitive environment, Civica will ask current members to sign long-term supply contracts of five, seven or ten years, at a guaranteed price, for half of their annual volume. And, says Van Trieste, "everybody gets the exact same price, so the smallest hospital in the US, which has 10 beds, will pay the same price as the largest health system that runs 500 hospitals." Fox says she is hopeful that this approach could help tackle shortages in the US.

A call for tangible political commitments

In an effort to push the issue of shortages of generic medicines higher up the European political agenda, the European Society for Medical Oncology launched a cross-party call for action in April 2019, advocating the following six recommendations:

1. Introduce legislation for early notification requirements for medicines shortages.
2. Establish European strategic plans for medicines shortages.
3. Introduce incentives for production infrastructure improvements including financial incentives to address the economic causes of manufacturing issues. Incentives for suppliers to remain in these markets should also be considered.
4. Develop catalogues of shortages based on a common minimum set of data requirements, including a common EU definition of medicines shortages.
5. Develop national essential medicines lists based on the World Health Organization's Model List of Essential Medicines.
6. Establish procurement models designed to prevent medicines shortages, including tender-cycle harmonisation.

van den Hoven says Civica's idea of long-term contracts mirrors his own ideas on stimulating investment. But he is sceptical about whether the 450 collaborating hospitals will be prepared to commit to those long-term contracts. Van Trieste acknowledges their aspirations are ambitious, but adds, "We always say at Civica this is a really hard thing to do, but the reason we are doing it is so important to society that we have to do it."

A European solution

So could a not-for-profit company work elsewhere? "I'm not sure this whole model works in Europe, mostly because of the intervention of the government and multiple governments," says Van Trieste.

What is clear is there needs to be pan-European solutions. "In the EAHP opinion, the EU has not yet done enough to solve the medicines shortage problem," says Batista.

The generics industry is now engaged in discussions at the European level. "We are having a much better dialogue with regulatory agencies and the European Medicines Agency on this issue than we were, say, a year ago," says van den Hoven. The EU has also funded a research network (CA15105 - European Medicines Shortages Research Network) to address medicines shortages and to reflect on the best coping practices and stimulate new solutions. But it's likely that shortages will keep occurring until some of the fundamental problems are addressed.

"This is an issue that shouldn't exist," says Eniu. "The WHO is promoting a list of essential medicines that should be available in Africa, in South East Asia and everywhere, and it's a big surprise to many to hear that in Europe we don't have access to some medicines."

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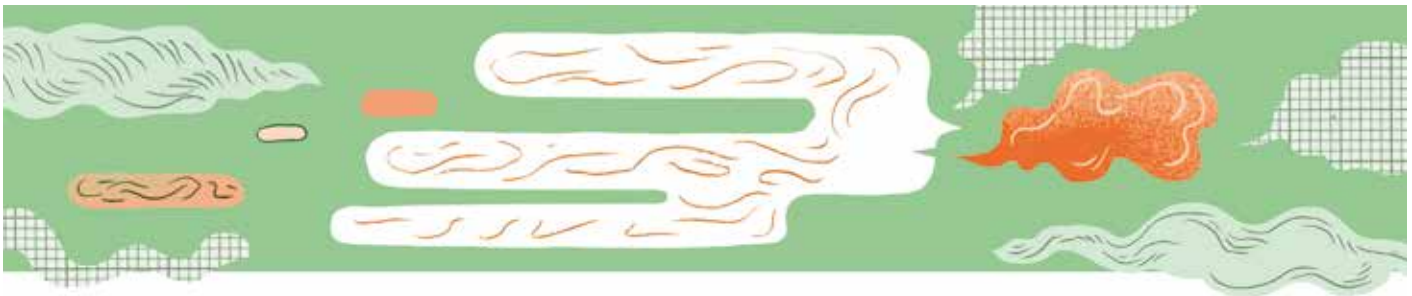

Stavroula Theophanous-Kitiri: a clinical pharmacy service that delivers for patients

It's about getting the right drug, to the right patient, at the right time, in the right amount, with the right patient information on how, when and why to use it. **Peter McIntyre** talks to the woman who built up the clinical pharmacy service at Cyprus's first dedicated cancer centre.

When the Bank of Cyprus Oncology Centre first opened its doors to patients in 1998, Stavroula Theophanous-Kitiri was the sole pharmacist. Under her guidance, the pharmacy service has grown to a department of nine, comprising six pharmacists, one pharmacy technician and two pharmacy assistants.

This remarkable expansion reflects in part the rapid growth in the variety of drugs used to treat cancer over the past twenty years. But it also speaks to her success in demonstrating the value patients derive from well-organised pharmacy services that play a strong role within multidisciplinary teams.

At a day-to-day level, this means working with physicians, other health professionals and patients to enhance the overall quality of care by improving patients' medication adherence, medication management, medication safety and drug interaction issues. This applies not just to anti-cancer agents, but also to medications taken to treat side effects and relieve pain and support patients' mental health and wellbeing.

At a strategic level, it means collaborating with other team members to devise the policies and systems to ensure this work runs smoothly, and guard against mistakes and oversights. A good clinical pharmacy service also delivers an economic benefit for its hospital.

A top quality cancer pharmacy service

The Bank of Cyprus Oncology Centre in Nicosia is run on a not-for-profit basis by a Board of Trustees that includes Government and Bank of Cyprus representatives. The Bank paid for the building and funds capital expenditure; the Government funds operational expenses. It has 34 in-patient beds and dispenses 250 prescriptions a day for in- and outpatients.

For patients, the opening of the new hospital offered the first opportunity to be treated, for free, at a dedicated cancer centre. For Theophanous-Kitiri, it offered the rare opportunity to organise an oncology pharmacy service from scratch, and she was determined to do it to the highest standards.

In collaboration with oncologists, she developed chemotherapy protocols for each type of cancer, including information about doses, pre-medication, appropriate diluents, stability and drugs (such as antiemetics) for the patient to take at home. She introduced a procedure to prevent wastage by fine-tuning prescriptions to fit better with the vial sizes in which drugs are supplied – saving her hospital more than €700,000 in 2018 alone.

In a busy oncology centre, great care has to be taken to avoid double dispensing or other errors. Theophanous-Kitiri was involved in the development of the pharmacy software, Powerpro, allowing dispensing pharmacists to check a patient's drug history and to double-check prescriptions.

"Every time a patient attends our pharmacy we check their medication history, and in this way we find near misses that could lead to medication errors." Pharmacists also correct errors relating to sound-alike look-alike drugs (SALAD) , such as prescriptions made out to anastrozole instead of letrozole, or vemurafenib instead of dabrafenib.

Theophanous-Kitiri joined ward rounds, talking to medical staff and to patients, recommending modified doses where there was impaired renal or hepatic function, adverse effects of drugs, or incompatibilities and drug interactions.

"Clinical pharmacists should be placed on wards, and all hospitals should have at least one in order to influence prescribing, as they have the appropriate knowledge about therapeutics and are in regular contact with prescribers," she says. As she points out, this specialist knowledge is increasingly important as new chemotherapy, targeted therapy and immunotherapy come into daily use.

Clinical pharmacists check patients' charts, collaborate with other staff, and propose changes in treatments based on pharmacokinetics. "In this way, medication errors are minimised and patient safety is increased."

Theophanous-Kitiri encourages her students to spend time on the ward. She teaches medical students of the University of Cyprus and St George's Medical school and serves as a trainer and clinical mentor for pharmacists of Frederick University School of Pharmacy and pharmacy technician students of KES College. Clinical pharmacy students spend a week on ward rounds with her and present patient case studies.

Her own time within the hospital is increasingly taken up working at a governance level. She is part of the decision-making process on a number of significant committees, including those covering chemotherapy, health and safety, pharmacy and therapeutics, clinical governance, infection control and palliative care. She is a strong believer in accreditation as the "key to focusing on quality and improvement". The Bank of Cyprus Oncology Centre was the first medical centre in Greece or Cyprus to be accredited by CHKS-health and care standards for the quality of its service, and has kept this accreditation since 2007.

She also devotes a lot of time to pursuing her special interests in safe handling of cytotoxic drugs, patient safety, medication errors, pain management and end-of-life care, working at a national and international level, passing on her expertise through lectures and training.

Safety first

Theophanous-Kitiri teaches in Cyprus and abroad about patient and staff safety, and trains staff in the use of protective procedures and equipment when working with CMR (cytotoxic, mutagenic and reproductive) drugs. "All these chemotherapy drugs that we use in oncology may have an adverse effect on staff if they are not handled with care."

Working with the European Society of Oncology Pharmacy (ESOP), she helped develop a 'spill kit' to be kept wherever cytotoxic drugs are handled, and she provides information in Greek for the ESOP homepage.

Patient safety is a particular concern, particularly now that an increasing number of drugs are dispensed for outpatients to take orally at home. The hospital sends patients home with clear printed instructions about how and when to take their medication. This includes warnings about possible drug–drug and drug–food interactions (such as drugs that should not be taken with grapefruit juice or milk).

Oral chemotherapy needs to be carefully handled, especially as it remains in body fluids for approximately 48 hours. Patients are advised to wash their clothes separately from those of the family, to flush the toilet twice and to follow instructions for handling any contamination.

They are also warned not to crush or dissolve chemotherapy tablets, but to swallow them whole, to ensure compliance and avoid cross-contamination. She recalls one patient who dissolved her capecitabine tablet in water and put the cup in the dishwasher, without realising that this could cross-contaminate other crockery.

Pain management

Theophanous-Kitiri is passionate about improving pain control for patients with cancer. "A lot of doctors avoid prescribing morphine because of fear of patients becoming addicted. This is called opiophobia, and it contributes to the under-treatment of pain," she says. "Many patients die with moderate or severe pain, and a major part of the population never gets the pain relief that is needed. We know that morphine is the cornerstone for relief of moderate to severe cancer pain, and all patients should have access if they need it."

She conducted a survey on the consumption of opioid drugs at the Bank of Cyprus Oncology Centre and in 31 hospitals in eight countries. The findings, which she presented in Cyprus and internationally, showed that opiate consumption (total morphine-equivalence per person) is low in many countries, and identified the barriers to the effective management of cancer pain.

Theophanous-Kitiri underlines the difference between addiction, tolerance and being physically dependent on opioids. She teaches the catch-up technique, where patients start on a low dose of morphine that is gradually increased and the dosage is carefully monitored.

"We monitor our patients closely. We give them pain diaries where they record their pain scale and the dose they take each time. We check, evaluate, and modify their doses regularly. This is very important because nobody should die or suffer with severe pain. Pain relief is a human right and we have to respect it."

There is also 'invisible pain'. "If you go below the tip of the iceberg you see that the patient may suffer social concerns, psychological and spiritual issues, and end-of-life patients may have depression, anxiety or fear. This kind of suffering is often not talked about."

The Bank of Cyprus Oncology Centre has created a multiprofessional support team that includes clinical pharmacists, doctors, nurses, home care nurses, physiotherapists, social workers, psychologists and a spiritual counsellor. Father Marios from the nearby Greek Orthodox Church comes to the hospital weekly to offer spiritual counselling.

Europe-wide networking

Theophanous-Kitiri found strong European support in her drive for quality. She met Klaus Meier, President and founder of the European Society for Oncology Pharmacy in 2000, and became a delegate member of ESOP from 2000 to 2010, before serving as Vice-President from 2010 to 2016. Since 2016 she has been the ESOP Board member with a special brief for pain management and palliative care.

Klaus Meier was the inspiration behind the development of ESOP Quality Standards for the Oncology Pharmacy Service (QuapoS), now in its sixth edition. Theophanous-Kitiri was involved from the beginning and, in 2018, coordinated the chapter on pharmaceutical care, which she presented at the QuapoS conference in Brussels. She personally translated QuapoS into Greek so it could be posted on www.esop.eu, and presented the QuapoS standards at conferences in Cyprus and Greece.

Theophanous-Kitiri has published several articles in the *European Journal of Oncology Pharmacy* on clinical pharmacy interventions in oncology, spillages, and occupational exposure to cytotoxic drugs. In 2007 she co-authored a paper on the risks from contaminated packaging when cytotoxic drugs

are sent to hospitals. In 2017, ESOP gained recognition from the European Commission to promote the 'Yellow Hand' warning symbol, where cytotoxic drugs are stored or handled.

In 2004, Theophanous-Kitiri spent a month at the Beatson Oncology Centre in Glasgow and since then has visited hospitals in Luxembourg, Hamburg and Prague. She conducted a survey of 27 hospitals from 21 European countries about the activities and structures of Pharmacy and Therapeutics Committees. "I feel I have greatly benefited from all this networking", she says. "All the different systems I have seen, I try to implement in my hospital."

A habit of hard work

Hard work and efficiency have been hallmarks of Theophanous-Kitiri's character from an early age. Born in Athens, where her parents were studying – her father to become a surgeon and her mother an English teacher – the family returned home to Cyprus when Stavroula was five years old. While at school, she often accompanied her father Michalis Theophanous to hospital and watched operations. She wanted to follow in his footsteps.

Her parents were concerned that a spinal operation she underwent at the age of 11 might prevent her spending hours in an operating theatre, and encouraged her to try something else. The young Stavroula decided to study pharmacy, as she loved chemistry and biology. She excelled in her final school exams and in the highly competitive exams to study pharmacy at the University of Athens. "I used to study a lot. When you are organised and under pressure, you force yourself to be more efficient," she says. Her dream was always to work in a hospital and help people. She followed her Bachelor degree in Pharmacy Science, with a Master's Degree in Clinical Pharmacy, opening the path to the hospital job she cherished. "I love working with patients and dealing with their medications to ensure that the right drug is prescribed for the right patient at the right time in the right amounts, and that the patient knows how, when and why to use it."

Her Master's research focused on the use of amiodarone for patients with abnormal heart rhythms, but after exposure to various specialities in many of the Greek capital's most prestigious hospitals, she found her vocation. "I liked oncology. I found it very interesting and pharmacists can play a significant role," she says. "Oncology Pharmacy is an amazing job and a great profession."

"I used to study a lot. When you are organised and under pressure, you force yourself to be more efficient"

A colleague demonstrates safe handling of cytotoxic drugs, at one of the training courses led by Stavroula Theophanous-Kitiri

Athens was an exciting city in which to be a student, and here at the age of 18 she met her husband to be, Evros Kitiris, then a medical student also from Cyprus. He is now a surgeon with special interest in breast and thyroid surgery, and one of the cofounders of the Breast Centre of Cyprus. "I feel blessed for my husband, as he has always been a great support for me," she says.

The couple have three daughters, aged 18, 13 and 11. The oldest Mikaella is in her final school year and planning to study medicine. Efficiency is now essential to balancing health, family and work.

"I want to give my kids the same energy that I'm giving to my work. When I am with my kids, I put everything away and I am fully with them as they deserve my time. I have a strong relationship with my daughters and I feel blessed for my family that is the most important thing in my life."

But, as she points out, keeping up to speed with a fast changing therapeutic area demands life-long learning, which means using free time to study, so that she can implement best practice. "I give myself deadlines, which motivate me to finish faster," she says. "I like being organised as I think this is the key for achieving [my] goal."

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Access to quality cancer care

Is the cross border healthcare directive helping or hindering?

The EU cross border healthcare directive – officially the 'Directive on the application of patients' rights in cross border healthcare' – has been in force across member states for more than five years now. It enshrines the right of EU citizens to access healthcare in any EU country, to be reimbursed by their home country, allowing patients to travel abroad specifically for treatment.

The right applies to treatments they would normally be entitled to according to the standard of care in their own health system. Patients pay up front and apply for reimbursement.

But how much are cancer patients actually benefiting? Tit Albreht, Senior Health Services and Health Systems Researcher at the National Institute of Public Health of Slovenia, argues that the directive is not fit for purpose. It does nothing to build the capacity and expertise of health systems, and it may be exacerbating inequalities in access to high-quality cancer care, he says. Antonella Cardone, director of the European Cancer Patient Coalition, disagrees: patients need access now, she says, and with all its flaws the directive helps them get it.

Simon Crompton asked them both to put forward their arguments to clarify where they fundamentally disagree and look for points of agreement.

Tit Albreht

The motivation behind the directive was to equalise social services markets in Europe. But its promoters never wanted to focus on how it would work with complex conditions such as cancer. What emerged was based on some specific cases that had been dealt with at the European Court of Justice, such as spectacles prescription, outpatient and diagnostic visits, and single-treatment episodes such as for hip replacement. It is much better suited to simple one-off procedures.

The directive asks patients to pay for their treatment, and then get reimbursed. If you're just getting some lab tests or a simple diagnostic procedure, this may not be a challenge. But in cancer, that diagnosis is the first step in what is often a complex process.

Even once a multidisciplinary team has decided on the extent of disease and the need for treatment, it may be impossible to predict the final cost of treatment over, say, six months. Treatments might cost in total, say, €100,000 – which could be catastrophic for many people, even if they get reimbursed at a future date.

Subsistence costs and travel costs are not covered by the directive. So if I decided to be treated for cancer in Paris on an outpatient basis, I would need to stay somewhere – possibly for weeks or months – and I'd need someone to come along to support me. The travel and accommodation costs for two people would put such a venture out of most people's reach.

Language is also a big challenge. We may all think we can get by in a different language, but talking about physical problems, emotions, health issues, is not simple. Being understood by the person advising you, and understanding their advice, might both be difficult. There's only so much advance planning you can do.

So, as far as cancer is concerned, the end effect of this directive might be greater health inequality in Europe. Mobility is only available to those with higher socio-economic status and health literacy – people with the time and resources to sort out everything beforehand, draw in interpreters, pay for accommodation, get information.

At the same time, the directive does nothing to address current inequalities in cancer care provision and facilities in Europe. People are often simply temporarily moved from countries with poorer cancer care to countries with better cancer care, leaving issues around equalising standards of care unaddressed.

Antonella Cardone

Tit makes some good, provocative points. I agree with much of what he says. But I don't see the failings of the directive as a reason to say it is not necessary. On the contrary, they are reasons for us to strive to make it better. The directive is potentially extremely valuable to cancer patients throughout Europe, but it needs to be implemented properly. This is what we are fighting for at the European Cancer Patient Coalition.

Tit says that the end effect of this directive could be greater health inequality in Europe, because only the well-off are able to afford the travel and accommodation costs that come with going abroad for long periods to receive cancer treatment.

I agree there is a problem here. There are social disparities between richer and less well-off people within individual countries that need to be addressed.

The way to do this is for each country of origin to allocate a budget to support or reimburse the travel and accommodation costs of its own citizens.

There are other issues that need to be resolved surrounding treatment and reimbursement for cancer patients. For example, if I travel from Romania to France to get treatment, I may be prescribed drugs that are available in France but not in Romania. So what happens when I return home? I still need the drugs, but how am I to get them?

Equally, there may be problems with reimbursement. Say, again, I travel from Romania to France for treatment, and I'm prescribed drugs that are reimbursed in France. When I get home to Romania, the

drugs are available – but they are not reimbursed. So who is going to pay?

Both these issues need to be fixed at European level. There must be some sort of harmonisation. But these are not reasons for the cross border agreement not to exist. It needs to be more functional.

I believe the European Reference Networks offer far more hope for cancer patients. They were set up to facilitate discussion on complex or rare conditions that require highly specialised knowledge and treatment. They work on the broad principle of helping countries build their capacity in cancer care – not simply asking other countries to take charge of patients you are uncertain about how to proceed with.

For many countries in Europe, particularly smaller countries like my own, this sort of international collaboration works very well, helping us draw on expertise so that we can better address rarer cancers and difficult cases, training and educating our professionals and carers to work better in the future.

The problem with that approach is that a patient with cancer today needs to solve their problem today. If I'm in a country where there's no appropriate treatment, should I have to wait 10, 20 years for things to improve, for law and policy to change, for health professionals to be trained, for professional culture to evolve?

Thanks to the cross border healthcare directive, I don't have to wait that long, and can go and get treated in another country if what I need isn't available in my own country. I have a chance. It may not be the best chance, it may not be perfect, but at least my situation can be improved. And it can happen now, because the directive gives me that right.

I'm not saying we should stop improving capacity at a country level – we must go on doing this. In cancer, improving national capacity is essential, but also hugely expensive, time-consuming and complicated – partly because there are so many rare cancers, each requiring its own expertise. So at the same time as looking at capacity we must improve the directive, because it is an immediate answer available now.

My argument is not that the directive should not exist, but that it has some serious flaws in its current form. The point of the directive is to make complex treatments accessible abroad if they are difficult or impossible to access at home. But its faults mean that this is not happening. For most people, treatment is also difficult to access abroad.

Antonella suggests that the way to address the problem of people being unable to afford travel and accommodation is for each country of origin to allocate a budget to reimburse travel and accommodation costs. I have two objections to this.

First, wouldn't that money be better used to develop capacity at home? Second, such funds are likely to be used up for high-demand procedures such as hip replacements, simple outpatient visits, and diagnostic tests, which are already dominating

European travel for health. These procedures are much more accessible than cancer care, and one cannot realistically see funds being earmarked for cancer treatment abroad. Such a specific allocation would not be permitted under any constitutional court because you cannot favour one condition over others.

Antonella defends the directive on the grounds that it provides the prospect of immediate action to help patients get cancer treatment. However, the significant flaws she identifies will take a long time to overcome. For example, she says that issues about variations in drug reimbursement from country to country need to be resolved through harmonisation. But how realistic is it to harmonise such a wide variety of economies? The ratio of GDP between Denmark and Bulgaria is currently eight to one. Such disparities cannot be overcome in the short term.

I also disagree that people will have to wait to see the benefits of European Reference Networks. We do not need to wait 10 or 20 years for improvements that can be achieved today through successfully transferring knowledge via European Reference Networks. It is about updating and upgrading the practical knowledge of medical oncologists, surgical oncologists and radiotherapists. Malta managed to overcome long stays of Maltese patients in London by training local medical oncologists at the Royal Marsden in a matter of three years!

I think in many ways we agree. We both think the directive should exist, but has flaws. We are just seeing things from different perspectives. Tit says we should focus on developing capacity and knowledge at country level rather than cross-border European level. I say we need to focus on both levels. There's no doubt that the cross border directive should be improved, but it's a good starting point.

Yes, we need to be pushing more towards European Reference Networks, but we also have to say that these too have their problems. They still lack an IT platform to make them fully operational across all European countries. They have problems with funding, and the European Commission is concerned about their sustainability to the point that they are looking into financial alternatives to public funds. The commission has put in place a working group, including patient representatives and industry, to look at how the financial sustainability of European Reference Networks can be guaranteed in the future.

And then there's the issue of where these centres of excellence can spread their knowledge. They are not perfect. They are already overloaded. They need a supply of specialised experts and this requires investment in training.

Tit provides the example of improvements in Maltese cancer services after a training collaboration with the Royal Marsden. But training does not always bring benefits so quickly. It takes two to three years to set up a training project and make it happen.

You have to allocate funds and bring in specialists, and to make use of the actual training outcomes at local level, it takes much longer.

So we have a lot of work to do on European Reference Networks to make them effective in cancer, just as we have work to do on the cross border directive. We should, as Tit says, be pushing for harmonisation of health technology assessment across countries so that treatments are consistently available. It's a huge issue in some countries, and harmonisation would help reduce barriers to introducing innovative treatments and reduce disparities between countries.

Work on all the areas may be slow, but it's the only way we're going to help patients properly. All the changes we've talked about are complementary. One does not preclude the other. We have to do our best to accelerate the process, which is why, at the European Cancer Patient Coalition, we are putting pressure on MEPs and the European Commission.

The directive created new options for patients to be treated across the European Union, but its faults have become increasingly clear. It works very well for patients who need a single simple procedure which does not require a long hospital stay. But in cancer it brings only very limited advantages. For it to bring real benefits, the directive would have to be re-worked or completely rewritten. I believe a much better option would be to strengthen cross-border mechanisms through the use of European Reference Networks, Comprehensive Cancer Centres, or Comprehensive Cancer Control Networks. All of these represent alternatives to single patients seeking care, and at the same time provide both quality assurance and training of professionals at a predefined high level. Obviously, these should be enhanced through national and EU funding. Final benefits would easily overweigh the initial investments.

The directive establishes that all patients have the right to access the best treatment available in Europe regardless of the limitations of their own health system. This could be a powerful lever to drive up quality of care for everyone everywhere in Europe.

At the same time we have to recognise that the directive is far from exhaustive or perfect. For example, health technology assessment should be harmonised across Europe to avoid duplication and unnecessary delays in treatment accessibility in some countries. This will allow cancer patients to move from one country to the other within Europe and at least be reimbursed for the cost of treatment at the same level everywhere. This will help promote equality of access.

Regarding European Reference Networks, they are already a positive consequence of the directive, as with them it is the knowledge that travels rather than the patient. Both the directive and the ERNs are elements towards the vision that we both share of better treatment for all.

As a patient organisation we want all patients across Europe to receive the best quality of care available. There is still a lot of work to be done.

To comment on or share this article go to bit.ly/CW86-Help_or_Hindrance

Does your metastatic breast cancer (MBC) patient have a germline *BRCA* (g*BRCA*) mutation?

THERE'S

POWER

IN

KNOWING

THERE'S POWER IN TESTING FOR g*BRCA*

4th ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer

In the ABC setting, results from genetic testing may have therapeutic implications and should therefore be considered as early as possible.

Genes to be tested depend on personal and family history; however, at present, only germline mutations in *BRCA*1/2 have proven clinical utility and therapeutic impact.[1]

What g*BRCA* mutations account for

~5-10%
of female breast cancers[2-5]

~4-16%
of male breast cancers[6]

~25%
of hereditary breast cancers[2,3]

Testing at MBC diagnosis

Testing for a g*BRCA* mutation at MBC diagnosis may help inform treatment planning.[7*]

*Relevant for patients who did not receive previous g*BRCA* testing and/or for patients who received only somatic *BRCA* testing.

ABC=advanced breast cancer; *BRCA*=breast cancer susceptibility gene; HER2=human epidermal growth factor receptor 2; HR=hormone receptor; TNBC=triple-negative breast cancer.

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Pfizer Oncology

Why join the OECI?

OECI
Organisation of European Cancer Institutes
European Economic Interest Grouping

The OECI is a non-governmental, non-profit Organisation founded in Vienna in 1979 and remodeled in 2005 into OECI-EEIG, a European Economic Interest Grouping.
OECI regroups about 100 Members, including some of the most prominent European Cancer Centres and Institutes.

The activity of the OECI is based on a structure where the Accreditation & Designation Programme and the Working Groups cooperate to improve quality in Cancer Education, Research, Care and Rehabilitation, whilst fostering exchange amongst its Members and promoting partnership between Cancer Institutes and Patient Associations.

A&D Programme

In 2002 the OECI launched a quality control system for cancer care, which formally became the Accreditation and Designation Programme in 2008. ***https://oeci.eu/Accreditation/***

Working Groups

The OECI Working Groups are tasked to develop the OECI Multiannual Programme.

BIOBANKS AND MOLECULAR PATHOLOGY	COLLABORATION FOR GOOD PRACTICES WITH PATIENTS	SUPPORTIVE AND PALLIATIVE CARE	CANCER OUTCOMES RESEARCH	CANCER ECONOMICS AND BENCHMARKING

Each Working Group has a Chairperson who is charged to interact with the Delegates of the Members that demonstrated interest to be involved in the specific programmes of activities.
https://www.oeci.eu/WorkingGroupsMW.aspx

Communication and Dissemination

OECI is a Publisher registered at the Royal Library of Belgium. The main editorial activities are related to the publication of the OECI Yearbook, the Magazine, the Accreditation and Designation Manual.
The Communication and Dissemination is coordinated by the Liaison Office which collaborates with ecancermedicalscience, the official OECI Journal, Tumori Journal and Cancerworld.
The communication aims to promote the OECI Programmes and Events and to inform the Members so as to encourage their participation to the running activities.

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ECCO
EUROPEAN CANCER ORGANISATION
corner

Philip Poortmans - ECCO President (2018/2019) and Head of the Department of Oncological Radiotherapy at Institut Curie, Paris

Unleash the full force of the EU against cancer!

Our call to the new European Commission President

Elections, within any organisation, provide an opportunity for renewal. Fresh ideas can be articulated and new faces can come forward for leadership. This was much on my mind in the run up to the recent EU-wide elections to the European Parliament.

I was pleased to note that, taking a cue almost directly from my predecessor's June 2017 editorial in *Cancer World* – 'The EU and Cancer: It's time for a bold vision Mr Juncker' – cancer made its way on to the election agenda. Not only is the content of a future EU Mission on cancer a matter of hot discussion, but a potential 'European Masterplan' to fight cancer is also being proposed. It is heartening to see candidates to become the next European Commission President competing to offer suggestions to the public as to what the EU can do more of to elevate all countries' efforts against cancer.

The 'why' of an EU Cancer Mission and Masterplan against cancer appears clear. Two in five of us will face cancer in our lives, and all of us can be assumed to be touched by the issue, as friends and family go through diagnosis and treatment. There is more to be done to improve the quality and outcomes of treatment, and the EU can unblock many of the obstacles by improving opportunities for collaboration in all areas, including by astute legislative initiatives if required.

With that element settled, I want to focus briefly on the 'who' and the 'how' of such activity.

Concerning the 'who', my appeal to those elaborating the detail of the EU Cancer Mission and potential Masterplan is to never forget that the combat against cancer is conducted across many fronts. It therefore involves a very wide range of stakeholders, including the panoply of healthcare professions represented within ECCO, too numerous to list in this short article. The contribution of every oncology-related healthcare profession in achieving missions and goals in cancer must be fully considered.

Then in respect to the 'how', an EU Cancer Mission and potential Masterplan is a chance for meaningful EU engagement with the public that must not be missed. Any review of charity donations testifies to the wide desire by citizens for more to be done against cancer sooner. An ambitious EU initiative on cancer will be energised by summoning that public will:

- to ensure the public resources required for research breakthroughs can safely be put in place,
- to improve the environment for achieving legislative actions around matters such as data sharing and protecting cancer survivors from financial discrimination,
- to bring about the fullest participation of all EU countries within European-wide cancer collaborations.

In summary, the exciting scientific times we live in, with respect to cancer treatment, are getting more exciting politically too. Whoever is the next EU Commission President has the potential to achieve a wonderful legacy – to finally unleash the full force of EU cooperation towards improving cancer care and treatment.

That would be a record for any politician to be proud of.

'Putting a person on the moon: how to deliver mission-orientated cancer activity', will be an opening session of this year's ECCO 2019 European Cancer Summit, Brussels, 12–14 September 2019. More information can be found at www.eccosummit.eu

‘Relentless and debilitating’

Why is nausea still a problem, and how can we do better?

A whole armamentarium of antiemetic drugs have dramatically reduced the level of vomiting related to cancer treatment. But nausea, in particular, is still troubling patients. **Sophie Fessl** explores the causes, and asks: why is this still such a problem for patients, and how can it be sorted?

There was a time when uncontrolled vomiting and being treated for cancer were inextricably linked in the public mind. The dread of having to go through the treatment added significantly to the fear of being diagnosed with disease. So much so that, when the American Society of Clinical Oncology celebrated their 50 year anniversary in 2014, they listed progress in controlling chemotherapy-induced nausea and vomiting (CINV) among their “Five top advances in modern oncology”.

In a supporting statement ASCO argued that, “approval of the antinausea drug, ondansetron (Zofran) – in 1991, as well as other supportive care drugs in the following years – dramatically changed the experience of cancer treatment, bringing unprecedented improvements to patients’ quality of life.”

The data certainly support this assertion. A randomised trial in 1979 showed that, in cancer patients treated with placebo, 83% suffered nausea and 78% vomiting, and that treatment with the antiemetics available at the time “failed to alter significantly the incidence, severity or duration of nausea and vomiting,” (*BMJ* 1979, 1:1323–4).

By 2004, the incidence of acute nausea and vomiting in the first 24 hours had fallen to 35% and 13%, respectively (*Cancer* 2004, 100:2261–8). This remarkable advance is attributed mainly to new antiemetic therapies that directly target the pathways that contribute to CINV, including ondansetron and newer generations of serotonin receptor antagonists, as well as neurokinin-1 receptor antagonists and the atypical antipsychotic olanzapine.

All is not well

However, the picture is not quite as rosy as it may seem. While great progress has been made in particular in controlling vomiting, for many patients the problem of nausea remains an invisible but chronic problem – an issue that was flagged up in the 2004 study.

Alex Molassiotis, Head of the School of Nursing at the Hong Kong Polytechnic University, who helped develop consensus recommendations for treating CINV (*Ann Oncol* 2016, 27 suppl 5:119–133), has studied the impact on patients' quality of life. He believes controlling nausea must be the next important step in tackling the problem.

"We have managed to control vomiting quite well, but nausea not so much. Nausea is still an unmet need for patients. We know from patient data and information that feeling nauseated is worse than actually vomiting, and it bothers patients a lot."

Kes Grant, who underwent stem cell transplantation to treat myelodysplastic syndrome, agrees. "The feeling of nausea is much worse. After you are sick, at least you feel a little better for a while. But nausea is relentless, it just goes on and on. Nausea is debilitating."

What causes nausea?

Nausea and vomiting are often considered and treated together. But the mechanisms behind the two side effects may differ, which may have implications for treatment, says Molassiotis: "Currently, antiemetics work on receptors that control both the vomiting centre and the nausea. But with the new generation of antiemetics, vomiting seems to be helped more than the nausea. There could be a different biological pathway behind nausea, but we don't know that yet." A lack of understanding of the pathophysiology of nausea also precludes the development of drugs specifically for nausea, he argues.

To find out more, Molassiotis asked whether nausea groups with other symptoms into a 'symptom cluster'. Surprisingly, among the co-existing and interrelated symptoms, vomiting was not the most consistent one. "Other symptoms, including taste changes and lack of appetite, were

"After you are sick, at least you feel a little better for a while. But nausea just goes on and on"

Kes Grant, UK, who is on treatment following stem cell transplant for myelodysplastic syndrome

"I've suffered from myelodysplastic syndrome since 2000 and received a stem cell transplant. I still take two types of anti-nausea medications so that I can just try to eat something. Last summer, the nausea was so bad that I lost 22 kilos. I couldn't eat and I couldn't drink. If I could choose between a cure for my illness and a cure for nausea, and had to keep the other one forever, I would choose a cure for nausea.

"Nausea is poorly understood and poorly communicated. Doctors and nurses are not very good at talking about nausea. And no one mentioned to me that the antiemetics can also have side effects, like the one which affected me so much that I thought I had depression.

"By now, I have learned what works for me in terms of anti-nausea medication, and can up the dose or reduce it, depending on whether I'm having a bad day or a good day. Clinicians know the theory, but we patients know the reality.

"I wish that nausea and vomiting were seen as the quality of life issue that they are, and given the resources needed to make a difference to the patients who are affected. I feel that doctors don't see it as much of a medical problem – until it tips into one. Nausea isn't life threatening, but it stops you enjoying life."

more strongly related with nausea than even vomiting. We're seeing that nausea perhaps is a much bigger symptom." Viewing nausea as a symptom cluster may be a way forward in breaking the impasse in finding an effective anti-nausea treatment, says Molassiotis. "This is perhaps the way of the future of how to manage symptoms. If you manage interrelated things together, the whole result is better."

Underreported and misunderstood

One reason why nausea continues to be a problem, more so than vomiting, may be that nausea cannot be assessed objectively. While 'use of rescue medication', for instance, is objectively measurable, it has been shown to significantly underestimate the extent of the problem. A survey conducted in 2015 by Terry Ng and colleagues at the Ottawa Hospital Cancer Center showed that, among participating patients, 71% experienced nausea (and 26% vomiting), but only 57% of these patients took any rescue medication (*Oncologist* 2015, 20:576–83). The authors concluded that 'use of rescue medication' is an inappropriate surrogate for nausea control, because it significantly underestimates nausea. "Not surprisingly," they add, "patients strongly favoured a CINV end point that included the absence of both nausea and vomiting."

"Nausea is a completely misunderstood problem," says Matti Aapro, who chairs the Antiemetics Study Group of the Multinational Association of Supportive Care in Cancer (MASCC). "For us clinicians, nausea is defined as the feeling that you have to throw up, but you don't throw up. We have developed several ways of assessing CINV, which ask patients whether they have been nauseated. But nausea is a subjective feeling, and patients may mix several things under the concept of nausea: that they don't feel well, that they lose their appetite, that their sense of taste has changed."

In a 2015 survey, patients ranked nausea over vomiting as the 'most feared side effect of chemotherapy'

Who should ask?

In the survey by Terry Ng and colleagues, patients ranked nausea over vomiting as the "most feared side effect of chemotherapy". And it might be this expectation and fear of nausea and vomiting that contributes to difficulties in treatment. "Patients often don't tell us the full picture of the

symptoms, particularly for nausea and vomiting, where they think it's part of the deal. They've seen it on TV and in movies, where it is always happening, and then they don't mention it," says Molassiotis.

But should the burden of reporting symptoms always lie on the shoulders of the patients? Katie Golden, who has been living with neuroendocrine tumours for eight years, thinks that patients sometimes hesitate to ask for more, or different medication. "Sometimes, patients just don't have the confidence to ask for different drugs or for more drugs. During treatment, I was feeling so dreadful that I probably didn't seek extra medication. I didn't ring up to tell nurses that I felt really dreadful, because they see so many patients. You think this is just how it's meant to be, and don't want to be a bother."

Golden feels that having someone else initiate the conversation about side effects could help patients overcome this fear. "I think that for cancer patients, it's just having someone actually ask the question, are you okay? Coming from the nurses would be better than a patient always feeling like they need to ask for more help. Because we all try to be tough and get through it, but sometimes we are not okay."

This mirrors Molassiotis' experience. "If we give patients the okay to report things, they will tell us. As clinicians, we need to ask patients directly about symptoms, including nausea and vomiting. And patients should also be more aware that they should be talking about it."

Guidelines help but aren't followed

Even when patients can communicate the impact of nausea, doctors frequently do not follow existing guidelines on antiemetic treatments. In one article, Aapro suggests that the poor adherence to existing guidelines is "perhaps the biggest barrier to the effective control of CINV," (*Support Care Cancer* 2018, 26:S5-S9).

Guidelines for treating CINV have been developed by a number of groups, including MASCC jointly with the European Society for Medical Oncology, ASCO and the US National Comprehensive Cancer Network. Yet the evidence shows that patients do not receive antiemetic therapy in line with the guideline recommendations.

The Pan European Emesis Registry (PEER) prospective observational study found that, over a five-day period, CINV is better controlled when patients receive guideline-consistent treatment (*Ann Oncol* 2012, 23:1986–92). Yet, according to the same study, only just over half of all patients (55%) receive guideline-consistent therapy during the acute phase of CINV, and less than half (46%) receive such therapy during the delayed phase.

Aapro, one of the investigators of the PEER study, acknowledges that one barrier may be that NK-1 receptor antagonists, recommended in the guidelines, are still not available in some countries for the control for CINV. But he says clinicians are also letting their patients down. "Clinicians have a lot of fantasy. They think that they can do better than the guideline, that they know the patient better than the guideline, or that the patient is not at such a big risk for CINV. They feel that the guidelines are exaggerating, but they don't realise that there are situations in which they could have prevented nausea and vomiting."

"Clinicians think that they can do better than the guideline... They feel that the guidelines are exaggerating"

As Aapro points out, following guidelines is also cheaper. "In many countries, the fact that someone with poorly controlled CINV has to be seen on an emergency basis costs much more than what you would have to invest to improve control and decrease the percentage of patients seen between routine appointments or treatment cycles."

Aapro would like to see better education about the existence of the guidelines and the importance of using them, not least among nurses and patients. "I strongly believe that if nurses and patients know that there are guidelines and ask the doctor, 'Why don't you give what is in the guideline?', that would help." Pharmacists could also flag this up to the prescribing physician, he adds.

Unmet needs and the way forward

Not all aspects of CINV are yet covered by guidelines, however. These include treatment of delayed nausea, which occurs only 24 hours after chemotherapy is given, and multi-day chemotherapy. "Because we have no adequate studies, we have no strong guidance on what to do when chemo is not given on one day, but instead spread out over three, four, or even five days," says Aapro. Studies on treating CINV caused by oral chemotherapy are also still lacking.

So what's the way forward? For Molassiotis, it is

Katie Golden, Australia, who is on treatment for neuroendocrine tumours

"Nausea is just not one of those things that you can just toughen up and go through it. Pain I can deal with, you can kind of push on. But nausea is so debilitating, it is like a complete body shut-down. In discussions in our patient groups, nausea seems to be one of the big issues that people have.

"I feel patients often don't have the confidence to ask for more drugs or other drugs. I was feeling so dreadful, I didn't seek extra medication. Often you deal with it at the time because everyone expects that there is nausea, pain and vomiting with chemo. But it would have been good to have more information on whether I could take an extra dose of a drug, or take it at a shorter interval, when I was feeling very bad.

"In an ideal world, it would be good if there was more conversation between the patient and the nurses who administer the chemo. And if there was a follow-up, maybe 24 hours after you leave hospital, a call to check how you are doing."

optimising how existing drugs are used. "Different antiemetics work in different pathways and different receptors. Some drugs are better at improving vomiting, some are better at improving nausea, so the combination might be the best option." Such combinations also have the advantage of simplifying treatment by administering different agents together, or allowing a multi-day use, argues Aapro.

Molassiotis would like to see a more risk-stratified approach. "It's time to start looking at patients who are at higher risk for treatment-related nausea and vomiting and manage them on a more personalised basis," he says. Factors known to put cancer patients at a higher risk of CINV include: expectations, anxiety, history of nausea/vomiting, younger age and female gender among others.

Together with Aapro and colleagues, he has developed an online risk prediction tool (*Ann Oncol* 2017, 28:1260–7). "If colleagues are uneasy about using a double or triple combination of drugs, for example because it is approved but not reimbursed," Aapro explains, "they can use these risk factors to argue that the patient clearly needs more antiemetic therapy."

"It's time to start looking at patients who are at higher risk for CINV, and manage them on a more personalised basis"

Such tools might also help raise awareness about risk factors amongst both health professionals and patients. Kes Grant, who finds the nausea induced by her myelosdysplastic syndrome treatment so debilitating, says she has always suffered from motion sickness, but was never forewarned that this might increase her risk for developing CINV.

Complementary approaches

In their efforts to find solutions, cancer patients have long been exploring complementary therapies, and evidence is building to show the effectiveness of some of them. Like drugs, says Molassiotis, "complementary approaches… are not a panacea. Sometimes they work, sometimes they don't. But if we look carefully in good-quality literature, we see that things like acupuncture have quite a few trials that show positive effects."

Lorenzo Cohen, director of the Integrative Medicine Program at MD Anderson Cancer Center, has carried out several studies on the use of acupuncture. Some caution should be exercised with patients receiving high-intensity chemotherapy, he says. "For acupuncture to be delivered safely to cancer patients, it is ideal if acupuncturists have experience working with cancer patients and communication exists between the acupuncturist and the treating physician. But if patients are cleared for chemotherapy, they are typically cleared for acupuncture."

Cohen also recommends hypnosis, and says there is also positive evidence for the use of ginger. "There are many

Belinda Cuffaro, UK, who is on treatment for a brain tumour

"When I started chemo, I just assumed everyone has nausea and vomiting. At the beginning of therapy, my doctors went through all the side effects and prepared me for everything. I felt very well informed, also about the side effects, and felt that I could ask questions if needed.

"I received oral chemotherapy, and the doctors and nurses gave me anti-sickness tablets to deal with any nausea or vomiting. I actually didn't need them at all, the most I felt was a bit of queasiness, but it was good to know that the tablets were there in any case.

"My doctors took side effects very seriously. At all the check-ups and scans and appointments, they asked me about side effects and always made sure that I felt well.

"It was a really positive experience, as everyone at the hospital was very reassuring and I felt very at ease there."

things that patients can do to help control the negative side effects of chemotherapy. Integrative medicine is something to consider in addition, not necessarily in place of pharmacological approaches. And the good thing is that it is not an 'either/or' situation. There is no contraindication for doing some guided self-hypnosis, having ginger tea multiple times a day, and receiving acupuncture."

Other than ginger, one 'ingestible' that is often discussed in relation to managing CINV is cannabis. For Donald Abrams, past chief of Hematology-Oncology at Zuckerberg San Francisco General, the answer is clear. "I've been an oncologist in San Francisco for 36 years and I've clearly seen the benefits of inhaled cannabis in patients receiving chemotherapy. Many of my patients choose to forego the currently available antiemetics, which can frequently cause severe constipation, in favour of using cannabis to treat their symptom."

However, as cannabis is a 'Schedule 1' drug in the US, and banned in many countries, not many trials have been carried out on its effectiveness for treating CINV. For Molassiotis, there is reason to be cautious. "We do not have the evidence that this can be an additional way of managing patients. The studies that have been published so far don't show an effect."

His point cuts to the heart of what it means to practice evidence-based medicine. "We always have patients that come to tell me cannabis works for them – and that's absolutely fine. But when we make clinical recommendations, we need to base them on evidence," argues Molassiotis.

"I don't really need randomised placebo-controlled clinical trials to tell me that cannabis is an effective antiemetic drug," counters Abrams, "I see it with my eyes all the time. I think the weight of the evidence should be directly proportional to the potential for the intervention to do harm. The risk here is so low, I don't think that the strength of the evidence needs to be as strong as oncologists in general demand with potent therapies. How much evidence do we really need when there is so much anecdotal evidence? And here, the absence of evidence does not indicate evidence of absence of an effect. It is just evidence of a lack of placebo-controlled trials, which I don't think we're ever going to have."

"There is no contraindication for doing some guided self-hypnosis, having ginger tea, and receiving acupuncture"

Even with the evidence-based treatments available today, challenges still have to be overcome until cancer therapy no longer causes nausea and vomiting – and the communication between patients and healthcare professionals, in both directions, clearly will play a role. Or, as Matti Aapro has put it: "By working together, patients and clinicians can continue to strive for perfection and make nausea and vomiting associated with chemotherapy a thing of the past."

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Management of toxicities related to immunotherapies

Immunotherapy agents are being used to treat a growing range of cancers, but emerging evidence from randomised trials and clinical practice shows very different patterns of toxicity compared to chemotherapy. **Jean-Marie Michot** reviews what doctors should look out for when treating patients with immunotherapy, and the action to take.

This grandround was first presented by Jean-Marie Michot, from Gustave Roussy Cancer Campus Grand Paris, Villejuif, France, as a live webcast for the European School of Oncology. Marco Siano, from Cantonal Hospital, St Gallen, Switzerland, posed questions raised during the presentation. It was edited by Susan Mayor. The webcast of this and other e-sessions can be accessed at e-eso.net.

The management of toxicities with immunotherapies used to treat cancer is relatively new, as these therapies have been used in clinical practice for only the last four years. The main classes of immunotherapy are monoclonal antibodies, immuno-conjugated agents, bispecific monoclonal antibody CAR-T cells, and immune checkpoint inhibitors (see table p 42). Each of these classes is associated with different types of toxicity. This article will focus on managing toxicities with immune checkpoint inhibitors, which are mainly auto-immune-like adverse reactions.

How checkpoint inhibitors cause immune-related adverse events

Checkpoint inhibitors enable activation of T cells so they can attack tumours cells, resulting in tumour death. There are essentially two ways to reduce the anti-tumour tolerance of T cells and enhance their capacity to attack tumour cells: first, using agonists to activate T-cell receptors such as CD28 or OX40; and second, using antagonists for inhibitory receptors including CTLA-4 and PD-1. Agents currently available include the anti-PD1 drugs nivolumab and pembrolizumab and the anti-PD-L1 drugs atezolizumab and durvalumab.

Following treatment with checkpoint inhibitors, tumour specific T cells (CD8 cells) increase in number. The numbers of effector T cells increase rapidly after treatment, followed by

Immunotoxicities with different types of immunotherapy

Class of agent	Examples of drugs in this class	Type of toxicity	Mechanism of toxicity
Monocolonal antibody	Obinutuzumab	Infusion-related reaction	Immuno-allergic
Immuno-conjugated	Brentux-imab vedotin, inotuzumab ozogamicin, ibritumomab tiuxetan	Cytotoxicity, direct	Chemotherapy-like
Bispecific monoclonal antibodies CAR-T cells	Blinatumumab	Cytokine release syn-dromes (CRS), neurologic	Cytokines (IL-6 and interferon-gamma), T cell migration to the CNS
Immune check-point blockade	Anti-CTLA4, anti-PD1, anti-PD-L1	Immune-related adverse events	Auto-immune like

Source: J M Michot et al (2016) *Eur J Cancer* 54:139-48; DW Lee et al (2014) *Blood* 124:188-95

an increase in memory T cells after several months (see figure opposite). The effector T cell response can result in very effective tumour control, with responses lasting for many months or even years in some patients treated for metastatic melanoma, although the tumour response depends on the quality of the immune response evoked by checkpoint inhibition.

In addition to an anti-tumour effect, checkpoint inhibitors can cause an auto-immune response by expanding an autoreactive clone of CD8 cells. This can result in a wide spectrum of toxicities that have not been seen with previous types of cancer therapies. These toxicities include skin reactions, such as maculopapular rash and psoriasis, inflammatory colitis, uveitis and pneumonitis, although the pattern of toxicity is quite different with PD-1 inhibitors and with PD-L1 inhibitors.

Toxicity of immunotherapy vs chemotherapy

Overall, immunotherapy is better tolerated than chemotherapy. For example, a study comparing the PD-1 inhibitor nivolumab with docetaxel showed a lower rate of treatment-related adverse events with nivolumab (69%) than with docetaxel (88%) (see table opposite) (*NEJM* 2015, 373:1627–39). The rate of severe adverse events (grade 3–4) was also lower with immunotherapy (10% vs 54%) and, importantly, fewer patients stopped treatment due to adverse events (5% vs 15%). In practice, I explain to patients that immunotherapy is better tolerated than chemotherapy, but it is important to inform them that they may experience adverse events that they have not had with chemotherapy. It is also important to explain that adverse events with immunotherapy are unpredictable and can happen at any time during treatment, and sometimes even afterwards, and that they are reversible by steroids. Adequate patient information about adverse events is one of the crucial points in their management.

Frequency of immune-related events with immunotherapy

Immunotoxicity differs according to the class of immune checkpoint inhibitor. Immune-related events are much more frequent with CTLA-4 inhibitors than with PD-1 and PD-L1 inhibitors (see figure p 44). Skin reactions can occur with CTLA-4 inhibitors, but grade 3–5 gastrointestinal adverse events, including colitis, are a particular concern with this type of immunotherapy. It is essential to have a gastroenterologist in the cancer network to manage this problem.

The pattern of immunotoxicity is quite different with anti-PD1 agents, with pneumonitis, thyroiditis and arthralgias being the most frequent adverse events, while immune-related adverse events are less frequent with anti-PD-L1 agents (*NEJM* 2018, 378:158–68).

The immunotoxicity occurring with immunotherapy also varies according to the type of tumour being treated. Patients treated for melanoma have higher rates of vitiligo (around 10%), while patients with non-small-cell lung cancer (NSCLC), and those with renal carcinomas, are more likely to experience pneumonitis, and those treated for thymic carcinoma may have myocarditis, which affects less than 0.5% of patients (*NEJM* 2018, 378:158–68).

Combination immunotherapy

Immune-related adverse events are more common when patients are treated with a combination of immunotherapy agents, with a study showing that grade 3–4 immune-related adverse events were additive in patients treated with a combination of nivolumab plus ipilimumab (*NEJM* 2015, 373:23–34). Adverse events with combination immunotherapy can be quite difficult to manage, and combined immunotherapies should be used with caution.

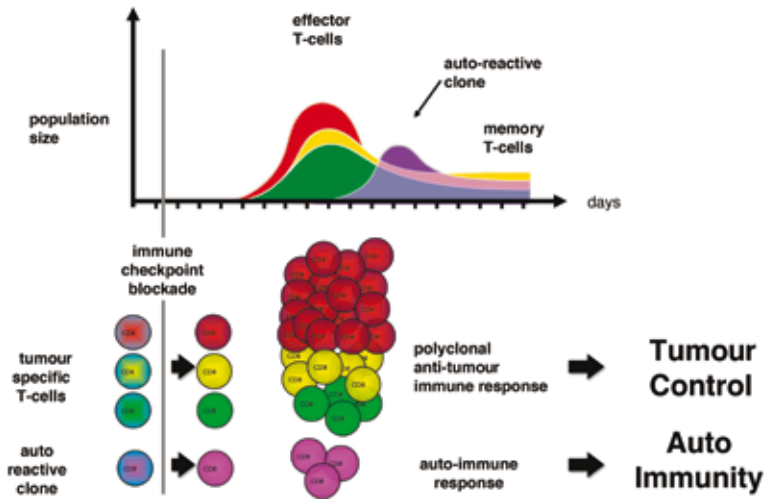
Diversity of adverse events

The diversity of adverse events with immunotherapy is perhaps more important than the frequency when managing toxicity (see figure p 45). Patients treated with immunotherapy agents experience a wide range of adverse events not previously seen with other types of cancer treatments. These include Guillain–Barré syndrome, myasthaenia, gastritis, pancreatitis, adrenal insufficiency, and retinitis, and theoretically any organ could be affected by an immune-related adverse event.

There are three 'red alert' categories of toxicity with immunotherapy: cardiovascular, including myocarditis, pericarditis and vasculitis; neurological, including neuropathy and encephalopathy; and haematological, including haemolytic anaemia, thrombocytopenia and aplastic anaemia. Patients suffering even grade 1 cardiovascular, neurological or haematological adverse events should promptly put treatment on hold and be rapidly and comprehensively investigated for these three organs: heart, brain and nervous system, and the haematopoietic system. Those suffering grade 1 adverse events affecting other organ categories can generally continue immunotherapy while further investigations are carried out.

Given the potential risk of encephalitis with immunotherapy, patients experiencing neurological symptoms should stop immunotherapy immediately and be further investigated by brain MRI, and be tested for specific antibodies against central nervous system compounds in the context of cancer, i.e paraneoplastic antibodies. Patients with any respiratory symptoms, including shortness of breath, should be discussed with a specialist, recognising the risk of pneumonitis and myocarditis. The risk of these serious adverse events underline why it is

Kinetics of T cell response: tumour control and auto-immunity



Different types of T cell responses kick in at different time points

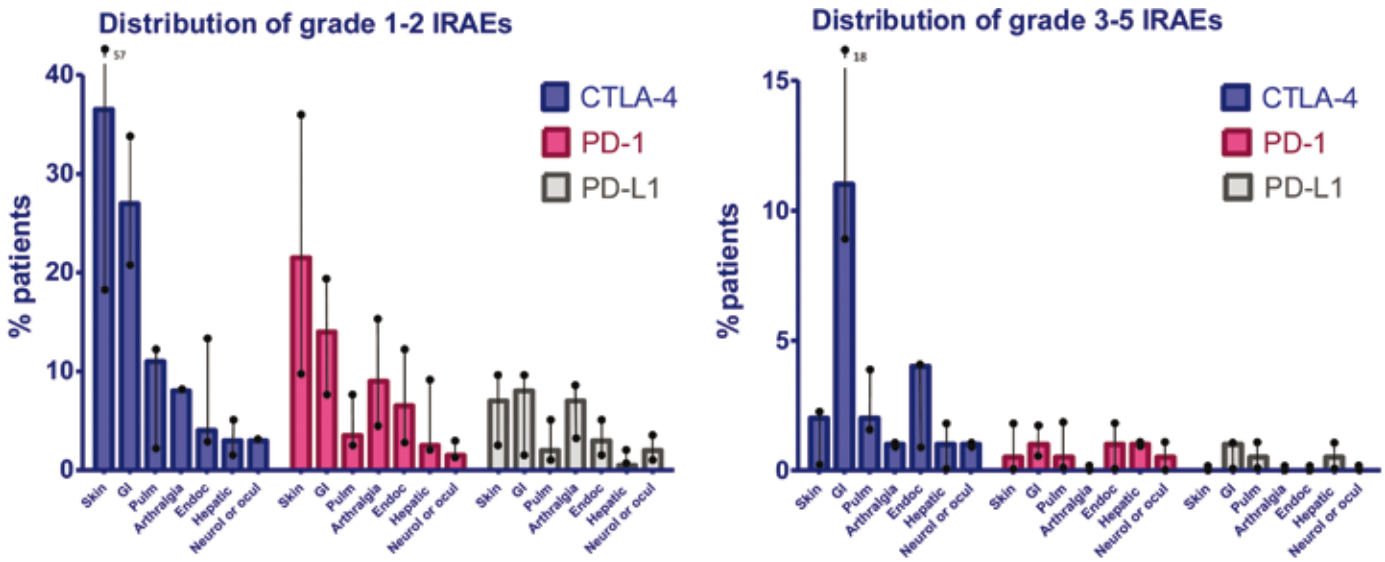
Nivolumab vs docetaxel toxicity in NSCLC

	Nivolumab n = 287	Docetaxel n = 268
All Grade AEs, any cause	98%	99%
Treatment-related AEs	69%	88%
Grade 3-4 AEs, any cause	46%	67%
Treatment-related Grade 3-4 AEs	10%	54%
Grade 5 AEs, any cause	8%	5%
Patients withdrawing from treatment due to AEs	5%	15%

Overall, immunotherapy is better tolerated than chemotherapy, as shown here with the adverse event (AE) rates for nivolumab versus docetaxel in patients with non-small-cell lung cancer (NSCLC)

Source: H Borghaei et al. (2015) *NEJM* 373:1627–39

Frequency of immune-related adverse events with immunotherapy



Immunotoxicity differs according to the class of immune checkpoint inhibitor

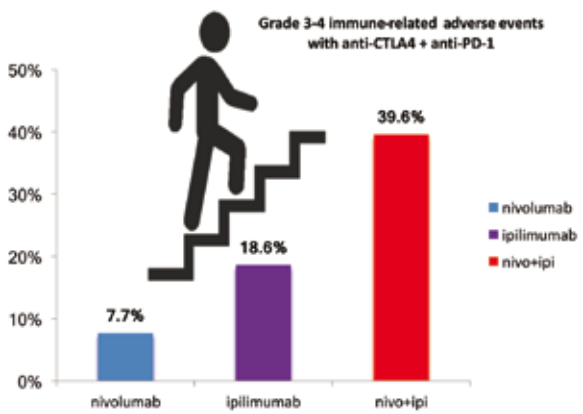
IRAEs – immune-related adverse events, GI – gastrointestinal, Pulm – pulmonary, Endoc – endocrine, Neurol – neurologic, Ocul – ocular

Source: J M Michot et al (2016) *Eur J Cancer* 54:139–48, reproduced with permission from Elsevier

essential to work closely with specialists in internal medicine to investigate and manage the range of toxicities that can occur in cancer patients treated with immunotherapy.

Our understanding of the immunotoxicity that can occur with immunotherapy is growing over time. For example, fulminant myocarditis was reported with combination immune checkpoint blockade in a report in 2016 (*NEJM* vol 375, pp 1749–55) and a case of paraneoplastic acral vascular syndrome has been documented in a patient with metastatic melanoma treated with immune checkpoint blockade (*BMC Cancer* 2017, 17:327). In some hard-to-manage cases, advice from a specialist in general internal medicine could be useful and add value.

Toxicity increases with combination immunotherapy



Immune-related adverse events are not so rare when used in combination, as shown by these data for patients treated with a combination of the CTLA4 blocker ipilimumab and the PD-1 blocker nivolumab

Source: Courtesy of S Champiat and J-M Michot, Gustave Roussy Institute, Paris

Kinetics of onset and resolution of adverse events

It is important to be aware of the likely timing of the onset and potential resolution of immune-related adverse events with immunotherapy agents. A pooled analysis of patients with advanced melanoma treated with nivolumab showed that most adverse events occurred at around 10 weeks (*JCO* 2017, 35:785–92). However,

adverse events can occur at any time during treatment with immunotherapy (*Lancet Haematol* 2019, 6:e48–e57). There are two key messages: 10 weeks is the 'warning zone' when it is essential to check patients for possible immune-related adverse events, but clinicians should monitor patients for adverse events very regularly during their therapy.

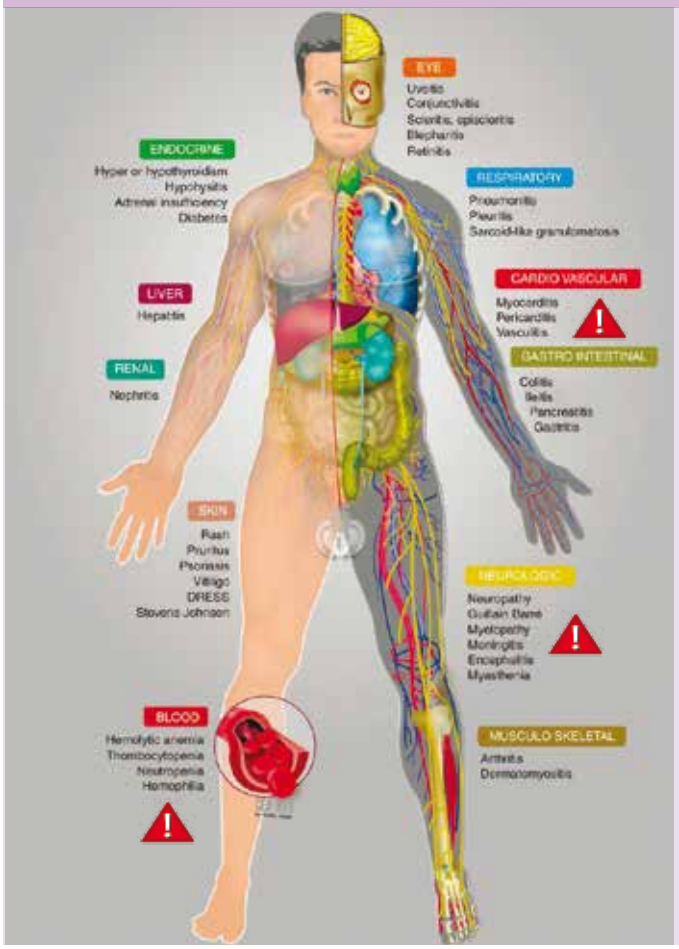
Relationship between immunotoxicity and dose

Immunotoxicity is related to dose for anti-CTLA4 agents. However, there is no dose relationship for anti-PD1 and anti-PD-L1 agents, although it may be helpful to reduce the frequency of dosing in patients experiencing immune-related adverse events (*NEJM* 2018, 378:158–68). Nevertheless this correlation is tricky, as the general outcome of patients by progression free survival and overall survival is not modified in prospective studies.

What is the significance of immunotoxicity for tumour control?

There have been suggestions that immunotoxicity may be associated with improved tumour control. A pooled analysis of studies in patients with advanced melanoma treated with nivolumab showed that the occurrence of immune-related adverse events was associated with a higher overall response rate (48.6% in patients experiencing any immune-related adverse events vs 17.8% in those experiencing none, $P<0.001$) (*JCO* 2016, 35:785–92). This suggests that patients showing immunotoxicity will also show response to immunotherapy.

Three red alerts among a wide range of toxicities



A wide range of toxicities are associated with immunotherapy. Those in the cardiovascular, neurological and haematological categories should trigger a red alert even when the severity of the adverse event is assessed as grade 1

Source: S Champiat et al (2016) *Ann Oncol* 27: 559–74, republished by permission of Oxford University Press

What is the mechanism for immunotoxicity?

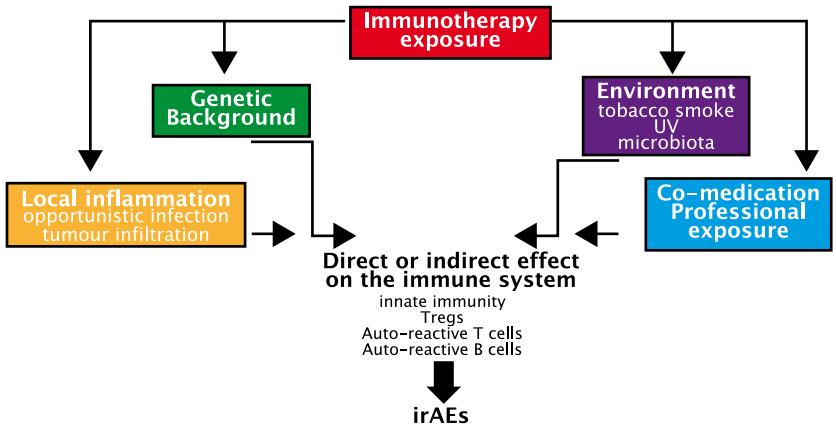
The immunopathogenesis hypothetical model for immunotherapy immune-related adverse events implicates several factors, including local inflammation, genetic background, immunotherapy exposure, environment and co-medication, which have direct or indirect effects on the immune system (see figure p 46). It is important to check a patient's medical history for these factors. Patients at particular risk for immunotoxicity include those with:

- Underlying autoimmune disease
- Chronic organ dysfunction: renal failure/dialysis, respiratory failure, COPD, heart failure
- Chronic viral infection: HIV, viral hepatitis
- Organ transplant.

These are not contraindications for immunotherapy, but it is important to check with the specialist managing these pre-existing conditions that they are well controlled.

Patients with pre-existing autoimmune diseases raise a particular challenge when treating cancer with immunotherapy. The problem is quite common, with a study in patients with lung cancer showing that 13.5% had autoimmune disease of any kind, including rheumatoid arthritis and

Immunopathogenesis hypothetical model for immunotherapy immune-related adverse events



Several factors are implicated in the pathogenesis of immune-related adverse events in patients treated with immunotherapy

IrAEs – immune-related adverse events

Source: Courtesy of S Champiat, Gustave Roussy Institute, Paris

ulcerative colitis (*JAMA Oncol* 2016, 2:1507–8). These patients are at risk of a flare-up of their autoimmune disease if treated with immunotherapy. Studies show a risk of 30–40% (*JAMA* 2016, 2:234–40; *Ann Oncol* 2017, 28:368–76; *EJC* 2017, 75:24–32). It is essential to check that their autoimmune disease is well controlled before starting immunotherapy and to inform and discuss with their specialist.

A study in patients with pre-existing autoimmune or inflammatory disease whose cancers were treated with anti-PD1 antibodies showed significantly increased risk of immune-related adverse events but similar overall survival to patients without autoimmune disease (*EJC* 2018, 91:21–9). This underlines that autoimmune disease is not a contraindication to immunotherapy for cancer treatment.

Considering patients with underlying infections, there have been a few cases of tuberculosis related to immune checkpoint inhibitors, and the reported cases have been close to immune reconstitution syndrome.

Another issue to be aware of with immunotherapy is hyperprogressive disease. It is defined as a more than two-fold increase in tumour growth rate while on treatment compared to a reference period, and represents a new pattern of progression seen in patients treated by anti-PD1 or anti-PD-L1 agents.

A study indicated that 9% of patients treated with these immunotherapy agents had hyperprogressive disease in the first few weeks of treatment (*Clin Cancer Res* 2017, 23:1920–8).

This phenomenon was seen across all tumour types; it was more common with older age and was associated with worse overall survival. It is important to detect hyperprogressive disease and treat promptly with chemotherapy.

Summing up

A recent position paper on managing toxicities associated with immunotherapy for cancer recommends that the first step is prevention, informed by awareness of the spectrum of toxicities that can occur, and education of the patient and their carers (*Ann Oncol* 2016, 27:559–74).

Potential immune-related adverse events should be anticipated, and patients monitored with a baseline examination and regular follow-up during and after stopping treatment.

Laboratory tests should include: complete blood count, serum electrolytes and liver enzyme tests, endocrine tests for thyroid stimulating hormone (TSH), thyroxine (T4) and triiodothyronine (T3), urine dipstick test and virology tests for HIV, hepatitis B and C, plus tuberculosis or tuberculin skin test when clinically indicated. Patients should also have a CT scan of the lung and an electrocardiogram.

Any immune-related adverse event should be detected early, and progression of toxicity prevented. Patients should be examined and asked about symptoms that may be associated with immunotoxicity at the same time as evaluating possible association with tumour progression or concurrent events such as infection.

Adverse events should be treated symptomatically, and patients provided with information on what has happened.

Treating clinicians should consider suspending immunotherapy, referring to a specialist in the organ affected by the adverse event, and treating with corticosteroids or other immunosuppressants.

Before starting corticosteroids it is essential to check that patients do not have an infection. Also, a patient starting steroids will switch to an immunocompromised status, and should be given antibiotic and antiviral prophylaxis (usually trimethoprim sulfametoxazole and aciclovir). Steroids should be tapered progressively over a

period of at least one month. Patients should then continue to be monitored with resolution of the adverse event and for any recurrence or complications of immunosuppression.

Given the diversity and complexity of immune-related adverse events, multidisciplinary networks are essential for effective management of immunotoxicity.

Guidelines from the European Society for Medical Oncology (*Ann Oncol* 2017, 28:iv119–iv142), the American Society of Clinical Oncology (*JCO* 2018, 36:1714–68) and the Society for Immunotherapy of Cancer (*J Immunother Cancer* 2017, 5:95) set out recommendations on general management of immune-related toxicity.

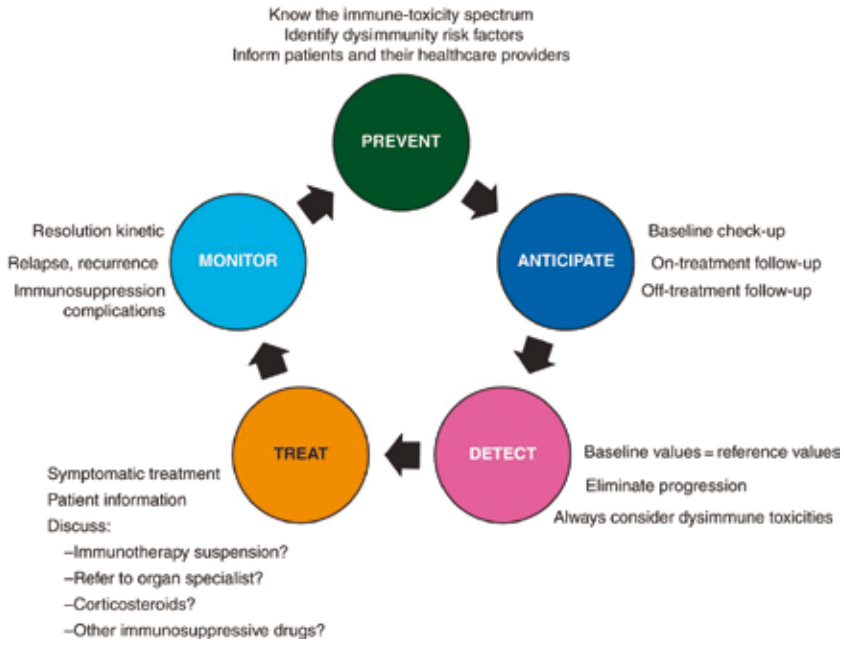
These include symptomatic treatment for grade 1 adverse events, suspending immunotherapy and oral corticosteroids for grade 2 adverse events, and intravenous corticosteroids for grade 3 or more severe adverse events, in addition to consulting a specialist in the organ affected, and considering an alternative immunosupressive therapy if clinically indicated, generally when steroids are not sufficient to control some severe and persistent immune-related adverse events.

However, there are exceptions to these recommendations, such as endocrine toxicities, where steroids are not generally required, and management is based on adequate hormonal replacement, and where treatment can be continued even at grade 2.

In contrast, cardiac, neurological and haematological toxicities indicate that immunotherapy should be stopped immediately and specialist advice requested urgently.

To comment on or share this article, go to bit.ly/CW86-Immunotherapies_toxicities

Managing toxicity associated with anti-PD1 therapy



The five pillars of immunotherapy toxicity management

Source: S Champiat et al (2016) *Ann Oncol* 27:559–74, republished by permission of Oxford University Press

Question & Answer session with Jean-Marie Michot

Marco Siano, Cantonal Hospital, St Gallen, Switzerland, posed questions.

Q: Centres in Switzerland just give TNF-alpha immediately when a patient is hospitalised with colitis associated with immunotherapy. Do you agree with this approach or do you consider diagnostics including colonoscopy before deciding on treatment? Steroids are often not sufficient for patients who are hospitalised with colitis, and concern about the risk of perforation makes clinicians afraid to lose time before treating.

A: If a patient needs to be hospitalised with colitis, the severity will be at least grade 3. I carry out clinical examination and investigations including colonoscopy, in close collaboration with a gastroenterologist. I treat with intravenous steroids (2 mg/kg,) and if a patient does not respond satisfactorily after five days then I start anti-TNF-alpha. My experience is that 80% of patients respond well to adequately given steroids, so the anti-TNF alfa may be reserved for patients with severe, resistant, or reccurrent colitis.

Q: How do you taper steroids in a patient with colitis treated with mycophenolate mofetil or other agents, who remains on steroids?

A: Generally at our hospital we treat with three weeks of steroids full dose, and then reduce the dose by 10 mg each week until stopping. Be also aware that some immunosupressive therapies such as mycophenolate mofetil begin to be clinically active only after three weeks of continuous use.

Better outcomes, better experiences

Why cancer nursing is a job for specialists

The European Oncology Nursing Society has compiled the evidence to show the value of the work cancer nurses do, and the specialist training and education they need to do it. Now they're calling on policy makers to recognise cancer nursing skills, as outlined in the EONS Education Framework, as a speciality across Europe. **Kate Griffin** reports.

"When we first started, people asked: 'What do we need clinical nurse specialists for?'" Janet Hayden, clinical nurse specialist at King's College Hospital in London, has seen big changes over her 14 years in the role. "What's happened is this huge shift. Now we're so embedded within the service it can't run without us."

Her team isn't an exception. Specialist cancer nurses all over Europe are seeing their roles expand, sometimes to cover areas that were formerly the responsibility of doctors. A position paper from ECCO, the European Cancer Organisation, suggests that this trend should go further, as a way of addressing the shortage of doctors in the context of increasing demand for cancer services. "Optimising the contribution of each profession… [would] ensure the best possible patient outcomes." ECCO suggests that more nurses should, for example, prescribe medicines and undertake clinical investigations.

Janet Hayden explains what this shift means for her team at King's.

"The clinical nurse specialist role has evolved for multiple reasons – not just to meet patient needs and expectations but also to meet service needs and fill the junior doctor deficit. When I think about what the junior doctors used to do years ago, we do most of it now. Patient follow-up, discharge planning, all of those sorts of things. The doctors used to arrange the patient's admission, but now we do all of it. Arranging for lines to be put in, organising the tests before they come, organising their beds and acting as a central point of communication with the whole team – as well as the patient."

For most cancer patients, nurses are their first or main point of contact. Nurses are there when you're having a routine screening, they support you when you're diagnosed, they're the first person you see when you come round from surgery, they help you manage the side effects of chemotherapy. Having the same nurse as your designated key worker throughout your cancer journey helps patients navigate the complexities of the system at a bewildering, frightening time.

It's the multi-faceted nature of the nursing role, combined with the fact that nurses are the largest group of cancer professionals, which gives nursing such great potential for optimising its contribution.

Realising the full potential of nurses to do what they do best needs to start with describing the wide range of contributions to care they are already making. Achieving such a description is the goal of an ambitious research project currently in progress. RECaN (Recognising European Cancer Nursing) has been gathering evidence on what cancer nurses are contributing to patient outcomes.

It is led by the European Oncology Nursing Society (EONS) and supported by ECCO.

Evidence of benefit

Phase 1 of the RECaN project involved combing through the existing literature on trials of interventions delivered by cancer nurses. The study, published in 2018, is the first systematic review to focus on defining the impact of cancer nursing on patients' experiences and outcomes across the spectrum of cancer (*Int J Nurs Studies* 2018, 86:36–43).

"When I think about what the junior doctors used to do years ago, we do most of it now"

More than two hundred studies (with almost 250,000 participants) were included in the evidence synthesis. They covered interventions delivered across the cancer continuum, from prevention and risk reduction to survivorship, but the majority related to the treatment phase, with most having a teaching, guidance or counselling component (see p 50). Almost three quarters of the interventions were nurse-led and a majority were delivered by specialist cancer nurses or advanced cancer nurses.

The findings, say the review authors, show that, "Cancer nurses are performing multiple and increasingly complex roles in a variety of settings across the care continuum. The roles are diverse, requiring considerable expertise in many specialist areas of clinical cancer care, in addition to research skills."

Yet, as they point out, the intervention studies in the literature search represent "only a fraction of those actually delivered by cancer nurses internationally," because nurse-led interventions are historically underexamined and also researchers often don't make it clear in their papers who is leading the intervention they are trialling.

Sulosaari Virpi, a Finnish clinical cancer nurse now working in education, agrees that successful nurse-led interventions don't always get recorded as such: "We have many examples of nurse-led interventions, such as the education intervention when the patient is starting chemotherapy, or a follow-up for breast cancer patients. Our weakness is that we rarely publish the results." One reason may be time constraints: unlike physicians, it is very rare for nurses to have contracts that allow them to ringfence a proportion of their time for research.

Impact on patient safety

Phase 2 of the RECaN project compared aspects of cancer nursing across four European countries, with a particular focus on safety, working conditions, recognition and management. The countries were Estonia and Germany, where the nursing role is less developed, and the Netherlands and the UK, where it is more advanced.

One way they did this was by asking cancer nurses from the four countries to fill out the Hospital Survey on Patient Safety Culture (bit.ly/AHRQ-PatientSafetyCulture). Developed by the US Agency for Healthcare Research and Quality, the survey measures a hospital's safety culture

The literature review

A systematic review of the impact of nursing on patient outcomes and experiences, drawing on international evidence, covered hundreds of successful nurse-led cancer care interventions.

While the majority related to the treatment phase, they revealed the important role nursing plays at every stage of the cancer journey. Examples include:

- **Public Health:** a report by the World Health Organization presents two decades of evidence that nurses have a key role in reducing tobacco use, and growing evidence that nurses help to reduce harmful use of alcohol (WHO 2013, *Human Resources for Health Observer* – No. 12).
- **Screening:** the same WHO report describes nurses' work in cervical cancer screening as one of the "best buys" to tackle the global burden of cancer.
- **The Cancer Journey:** Canadian research finds that cancer nurses are uniquely positioned to 'translate' clinical information for patients and navigate them through their cancer journey. The report found that nurses "provide the highest level of service and support for patients" (*Eur J Cancer Care (Engl)* 2011, 20:228–36).
- **Palliative Care:** a study published in *Seminars in Oncology Nursing* acknowledges the contribution of nurses to the evolving field of palliative care (*Semin Oncol Nurs* 2010, 26:259–65)

The RECaN review covered 214 studies involving almost 250,000 participants. The authors commented, "This review provides novel insights to enhance our current understanding of cancer nurses' evolving roles as trialists, and identifies the focus, to date, for the delivery of complex interventions by cancer nurses. As such, it forms the basis of an ongoing dialogue that we hope will transform awareness of the extent and level of contribution that cancer nurses are making to improve cancer care. In an era of distributed knowledge and search for cost-effective innovation to meet demand we suggest that the contribution of cancer nursing should be better recognized."

Source: A Charalambous et al. (2018) A scoping review of trials of interventions led or delivered by cancer nurses. *Int J Nurs Studies* 86:36–43

across 12 dimensions, focusing on how managers and staff understand their organisational values, beliefs, and norms about what is important and what attitudes and behaviours are expected and appropriate.

Many of the dimensions relate to interpersonal relationships between medical staff. 'Communication openness', 'teamwork within unit' and 'teamwork across hospital units' are all seen by HSPSC as predictors of safety outcomes. So too is 'non-punitive response to error'.

The purpose was to investigate how different aspects of a patient safety culture vary across countries with differences in the status and roles of cancer nurses. The survey attracted almost 400 responses.

Preliminary results show that, overall, cancer nurses in the UK and Netherlands rated the patient safety culture significantly higher compared with the other two countries. Cancer nurses in the Netherlands gave the highest ratings for 'number of events reported', 'communication openness' and 'non-punitive response to errors'. Cancer nurses in the Netherlands and the UK gave the highest rating for 'frequency of event reported'.

EONS President Lena Sharp says the statistical findings of poorer patient safety culture being associated with a less developed role and status for nurses was supported by anecdotal evidence, which included reports of nurses being explicitly told not to question what a medical colleague says, regardless of whether they are right or wrong. Failing to recognise the central role nurses play in patient care can put patient safety at risk, she says.

"Cancer nurses' role in patient safety is important and requires better recognition, in all countries."

Quality of care

Martina Spalt, an advanced practice nurse at Vienna University Hospital, is clear that care is better when nurses are respected and their contribution is recognised. "Knowledge from nurses is underestimated, and could inspire and enrich other health professionals in the team. It is well known that nurse professionals are closest to patients and build up a therapeutic relationship with them. If nurses are recognised for providing trustworthy and reliable information and help, treatment can be improved towards a higher level of quality.

"From my own experience, when the appreciation of nurses was low, the quality of care provided was low. Communication only works out if everybody is respected and valued. Then a productive discourse can take place between equal partners and the best solution can be found."

Anu Viitala, President of the Finnish Oncology Nursing Society, has specialist skills in pain management and palliative nursing, and currently works as Clinical Research Manager at Tampere University Hospital. She argues that respect for the contribution made by specialist nurses, and their expertise, is one of the reasons Finland enjoys one of the world's highest cancer survival rates. "The oncology outpatient clinic and palliative care unit in Tampere has teams of doctors and nurses, and many times there are situations where a nurse's efforts in patient care are needed a lot, even more than a physician's. A care-pathways working group might be as many as 15 people – doctors, nurses, social workers – and still have a nurse as the lead of that group, and it is fine by all group members."

These observations are echoed by responses to the annual NHS England National Cancer Patient Experience survey, as noted in the executive summary of the 2014 survey: "a Clinical Nurse Specialist working with the patient to support them is the factor most likely to be associated with high scores in every one of the 13 tumour groups that we use to analyse the data."

Investing in specialist education

Some countries are now doing more to recognise the role of specialist nurse – and reaping the benefits for patients. The Netherlands seems to be leading the way, as the only country with a one-year cancer nursing programme, based on a national curriculum. There is also a MSc degree in Advanced Nursing Practice, different from the one-year cancer nursing programme, which qualifies you as a nurse specialist.

The role of nurse practitioner has only been officially recognised by Dutch law since September 2018, but it isn't a new concept for oncology professionals, says Suzan Ras, an oncology nurse practitioner at Franciscus Gasthuis & Vlietland general hospital in Rotterdam. "It's only the government recognition that is new. The nurse practitioner role was trialled for five years. Then the government realised it's very good for patients, it's very good for care, so they made it official in special law."

In many countries, however, while postgraduate qualifications in cancer nursing exist, they are not officially recognised and confer no change in status, role or pay. Austria is a case in point, says Spalt. "A cancer nurse in Austria may have advanced training in oncology, but currently there is no official differentiation between a registered nurse and a cancer nurse."

In Portugal, the Ordem dos Enfermeiros (National Nursing Board) gives specialist certification in six healthcare areas, but cancer is not one of them. Joana Silva works at an outpatient unit at the Vila Nova de Gaia central hospital, where she administers chemotherapy and immunotherapy and helps patients manage the side effects.

Silva always intended to work with cancer patients, but as cancer is not a recognised nursing specialty, after her basic nursing qualification she opted for specialist training in mental health/psychiatric nursing, focusing her studies and coursework on the mental health aspect of cancer nursing wherever possible.

She studied in her own time and at her own expense, and says she was motivated by the need to evolve as a healthcare professional and improve patient care, "mainly because the cancer area is constantly updating knowledge, and nurses must provide evidence-based care." The thing that frustrates her most is the lack of career opportunities to use the additional knowledge and skills she has.

"Getting a qualification in a recognised specialism means that the OE [National Nursing Board] gives you a certificate and you get to call yourself a specialist nurse, but it doesn't automatically translate into a pay rise or new responsibilities."

What frustrates her most is the lack of career opportunities to use the additional knowledge and skills she has

Not so long ago, she says, getting a specialist nursing qualification would almost automatically fast-track you into a management position, which gave added responsibilities and higher pay, but no opportunity to actually use your specialist skills to benefit patient care.

Nowadays, nurses get more of a chance to use their specialist skills, but often without formal recognition of the higher value of their contribution within the care team. "Your employers might recognise your new skills, especially if you're actually applying them in the job, and give you new

responsibilities or a pay rise on the strength of them, but they might not."

What this means for her own career options, says Silva, is she can either apply for a job in her specialty area, at a psychiatric day care unit or a psychiatry ward, which would mean no longer focusing her work with cancer patients. Or she can stay where she is, not use her additional skills and not get a pay rise. Or she can stay where she is, try to apply her additional mental health and psychiatry nursing skills, and hope she will get rewarded with higher pay.

Heleri-Mall Roosmäe, President of the Estonian Oncology Nursing Society, who was involved with the RECaN project research in her country, tells a similar story. "Cancer nurses in Estonia have been trained by themselves independently while working in the department of oncology (or haematology, or onco-surgery). But official recognition [of cancer nursing as a specialism] would mean that specialist nurses received professional training and became more aware of the disease, its treatment, the side effects of that treatment and also safety measures. It would be enormously better for the health of the patients."

In some countries, in the absence of any leadership from governments, specialist oncology training schemes are being implemented independently by educational bodies and cancer nursing societies. This is what happened in Austria, where universities and colleges took the initiative to organise a nationwide cancer nursing education programme, without any input from the government.

Passing the programme entitles a nurse to be called a certified cancer nurse, says Christine Schneider-Worliczek, a registered nurse working in the oncology department of the University Hospital of Salzburg. There is no official title, however, and nurses with this qualification don't automatically get paid more – although some hospitals voluntarily choose to give qualified cancer nurses a pay rise.

AHOP, Austria's national cancer nursing society, also delivers training programmes for cancer nurses that were developed by EONS. These include 'TITAN' (to improve skills and knowledge when working with patients with cancer-related thrombocytopenia, anaemia and neutropenia) and 'target' (to give nurses a greater scientific understanding of targeted therapies including immunotherapy). Training on specific topics such as nausea or mucositis is also carried out, free to members, at AHOP's annual spring convention.

When the role of cancer nurses is respected within multidisciplinary teams, it's hard for policy makers to withhold recognition

"The better the nurses are qualified, the better they can accompany a patient along the journey through cancer. Side-effect management, psychosocial guidance can be delivered on a much higher level," says Schneider-Worliczek. "Getting a diagnosis of cancer means standing at the edge of life," she adds. "This is a situation where it is essential to have a well-trained nurse at your side."

The groundwork for establishing national cancer nurse courses and qualifications has already been done by EONS. Its Cancer Nursing Education Framework identifies the fundamental knowledge and skills required for a nurse working in cancer care, and can be used as guidance for developing a national training programme. Since the Framework was launched in 1991 as the Post-basic Curriculum in Cancer Nursing, it has been extensively revised multiple times to reflect the expanding roles of nurses, along with other developments within cancer care (see p 54).

But we have a catch-22 situation: if, despite demonstrably improving patient care, specialist knowledge and skills are not recognised with formal qualifications and status, that lack of respect for the value of the specialist nursing contribution makes it hard to convince the authorities to introduce such qualifications.

Germany is an example of a country with strong political opposition to higher education for nurses. The Care Professions Reform Act (Pflegeberufereformgesetz), which passed in 2018, originally represented a move *away* from specialism, with plans to merge the three previously separate care qualifications (in nursing, paediatric care and geriatric care). It caused controversy because of concerns that, if all nurses had the same generalist training, they could move between roles more easily and that nurses in the badly-paid field of geriatric care would switch to a different occupation. (The idea of reducing this risk by paying geriatric nurses more does not seem to have featured in the debate.)

In the end, legislators compromised by creating a two-year generalist qualification, to be followed by a third year, where nurses can choose whether to specialise or continue with general training. The idea of encouraging nurses to specialise in cancer care through the creation of a clear career path and appropriate remuneration,

Cancer nursing varies widely across Europe

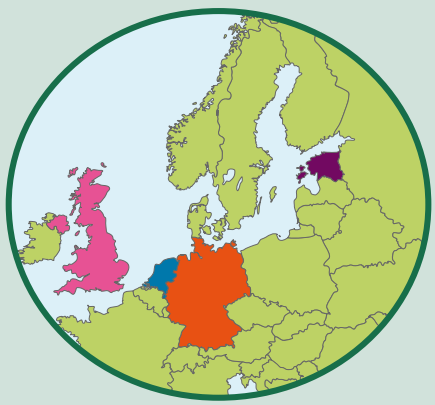
The second phase of the RECaN (Recognising Cancer Nursing in Europe) research project compared the roles, education and status of cancer nurses in the Netherlands, the UK, Germany and Estonia. The four countries had in common that cancer nurses are devoted to their jobs, they have important relationships with patients and their families, and they are overloaded with work. Important differences were found in: tasks and responsibilities, levels of education, recognition, professional status and autonomy, career possibilities, safety issues, teamwork and support.
The full findings of the RECaN case studies have been submitted for publication in the *Journal of Advanced Nursing*.

Germany

- Variation in training, most nurses have no academic degree
- Nurses report less autonomy = hard to develop practice
- Nurse shortages
- Nurse competences are not used effectively
- Two-year education programme in cancer care (not academic)
- Lobby groups have opposed higher education for nurses
- Advanced nursing roles are being developed but in very few institutions. Pay increments that apply for other health care professionals with Master's degrees do not apply
- Little response when nursing organisations try to impact political leaders
- Nurses report there is no/little recognition for nursing care

The Netherlands

- Two-year cancer nursing programme based on national curriculum
- National standards require that 50% of nurses in cancer care should be qualified (by 2022)
- All cancer drugs should be delivered by qualified oncology nurses
- Good clinical career possibilities
- Advanced nursing roles well established and regulated
- Initial resistance overcome by successful lobby work
- Autonomy and recognition
- Strong support by patient organisations
- Fewer nursing shortages compared with the other countries



United Kingdom

- Specialist training in cancer care
- Good clinical career possibilities
- Autonomy and high professional status
- Advanced cancer nursing roles well established
- Initial resistance
- Teamwork
- Severe nursing shortage, migration
- Importance of leadership
- Systematic work on safety

Estonia

- No specialist training in cancer care*
- Few career possibilities in clinical cancer nursing
- Little autonomy and recognition
- Many nurses need more than one job
- Long shifts
- Nursing shortages
- Importance of leadership
- Support from some leading physicians

**As of September 2018 a nursing Master's degree is up and running*

Source: Lena Sharp, presentation at ESMO Congress 2018, Munich

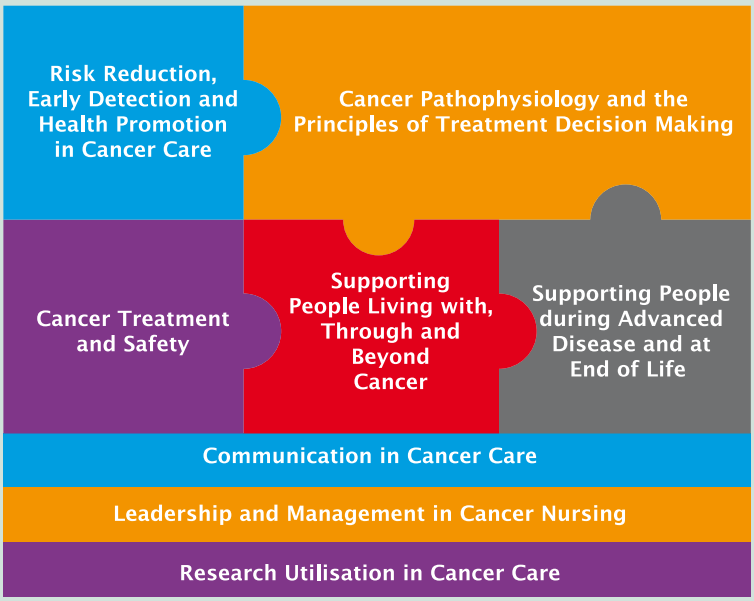
however, seems very far away.

Contrast that with the neighbouring Netherlands and its official cancer nursing programme. There was political opposition there too, says Suzan Ras, but doctors played an important role in supporting the professional recognition of cancer nurses.

"It's always difficult to introduce a change," she comments, "so you have to show them you're worth it. If you have an oncologist who is very fond of your role as a nurse practitioner, I think that's half the battle, but if you have to convince your oncologist, I think then you have a big struggle."

When it's normal for cancer nurses to have their specialism respected

EONS Cancer Nursing Education Framework



The European Oncology Nursing Society launched its Cancer Nursing Educational Framework in May 2018. It replaces the Post-Basic Cancer Nursing Curriculum, which had been created in 1991 and revised many times over the following years.

It identifies the knowledge, skills and competencies required by nurses who care for people affected by cancer, and can be used as the basis for developing national curricula.

It uses the European Credit Transfer and Accumulation System (ECTS) – the international standard for identifying how much studying is involved in a course. The Framework is equivalent to about 60 ECTS credits, which means roughly one full year of academic study.

http://www.cancernurse.eu/education cancernursingeducationframework.html

within multidisciplinary teams, it's hard for policy-makers to withhold that recognition, especially when doctors speak up as part of the wider national conversation.

Recruitment and retention

Gordana Lokajner, former medical director for nursing and care at the Ljubljana Institute of Oncology, in Slovenia, argues that the lack of a career path and a failure to recognise and reward specialist nurses appropriately is a major driver behind a shortage of nurses in her country. "Unfortunately, we do not yet have access to oncology nursing specialisation, which naturally represents one of the biggest obstacles to attracting and retaining young people in oncology nursing."

Standards of cancer nursing are still high, she insists, but only thanks to the enormous effort put in by staff, which is simply not sustainable. "But decision-makers only react when the situation presents a risk to patients, which is of course too late. In the long run, this could bring our healthcare system to the verge of collapse," she says.

She is arguing for urgent changes on a number of fronts: "Correct and fair payment for excellent nursing care, a safe work environment, sufficient staffing and a good skill mix in nursing, the possibility for professional growth, and listening to nurses when forming healthcare policy."

Lokajner's comments have implications for the strategy backed by ECCO, as well as the EU, to expand the size and competencies of the specialist nursing workforce as a key response to the increasing demand on health services as people are living longer with chronic conditions. The strategy requires investing in nursing services, including rewarding advanced knowledge and skills and greater responsibilities with higher pay.

Germany is an interesting case; nursing is the only healthcare profession where gaining a Master's degree does not result in a salary increase.

Even in the comparatively well-paid Netherlands, says Suzan Ras, pay has not increased to reflect the added value nurses contribute as a result of their specialist training and expanded roles. "These days the care is more complex than 10 years ago. Wages have kept up with inflation, but the job is more difficult. You can't do anything on automatic pilot… you have to educate yourself about all these different treatments with different side effects, now including immunotherapy, and you have to make the right decision. Patients have other diseases, intersecting problems, and you have to treat everything. Nurses should be paid more because it is hard work, physically and mentally."

At the other end of the scale, many countries simply don't pay nurses enough to live on. RECaN found that

11% of nurses in Estonia have more than one job. Many arrange their working week to fit in their other jobs, which means 24-hour shifts are common. "Many nurses [in Estonia] have two jobs, and often both are full-time," says Roosmäe. This all reduces the time spent on self-development, resting and positive attitudes. Irritated and tired nurses do not do their best work or communicate properly with patients or colleagues. They are burning out."

Spalt believes that this comes back to false assumptions about nursing. "Often nurses are ranked on the emotional level and doctors on the knowledge level. Of course building up a therapeutic relationship with patients is an important part of nursing, but this doesn't happen without extensive underlying knowledge. At the moment, the expert knowledge of nurses in oncology is not adequately recognised, either by doctors or by patients."

The problem is not just the failure to value nurses for their knowledge, she adds, but a tendency also to undervalue the 'soft skills' of caring and communication, even though these skills are highly valued by patients and linked to better patient outcomes.

Next steps

Challenging these assumptions is the focus of phase 3 of the RECaN project, which is looking at how to better promote cancer nursing as a recognised speciality across different political or health contexts within Europe. Key to this advocacy will be the evidence generated by the RECaN literature review and the case studies comparing cancer nursing in the UK, Netherlands, Germany and Estonia.

As EONS President Lena Sharp points out, that evidence may not be "revolutionary" but it is important, as it spells out the value that cancer nurses contribute when they get the chance, and by implication, the opportunities being lost in health systems that unnecessarily restrict the nursing role.

Sharp is optimistic that the project will help change attitudes and policies. She cites the example of Estonia, which started its first Master's programme in nursing in September 2018, with 120 nurses now enrolled. This initiative followed meetings that EONS held with hospital leaders and other stakeholders in 2017, in the context of RECaN. "The leading people, including Kristi Rannus, the Nurse Director in Tallinn, say the RECaN project was an imporant factor behind this achievement," she says.

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For a laugh

"Open wide."

If it's approved but not reimbursed, what do you say?

> *"There are doctors who do not inform the patients about [non-reimbursed options] because it is less stressful."*

> *"I explain to them that if they were treated in more developed countries, the treatment strategy would be different, and show them where they can find information about it."*

> *"When you have learned from a clinical trial or a congress that there is a new indication for treatment, there may be a lapse of time from the moment the treatment is approved at the European level until the treatment is reimbursed by the government. In that period of time we do not discuss those treatments with our patients because we, as a public hospital, cannot offer them. We do not speak about them because the great majority of the patients cannot afford that treatment."*

Clinicians have a duty to discuss all the options with their patients, to help them decide what's best for them. But are 'options' that are unaffordable and not reimbursed truly options?

Does telling patients about treatments that could benefit them, but they cannot access, help efforts to reach the right decision or just confuse the issue and add to the patient's distress?

Should doctors wait for patients to ask about therapies that are only available to those who can pay?

Should you selectively mention non-reimbursed options, depending on your judgement of the value to the patient and whether they might have the resources to consider paying out-of-pocket?

Is it never right, under any circumstances, not to tell a patient about a therapy that might benefit them?

And how do you conduct the conversation with a cancer patient, when you know that choosing a particular option may have severe financial consequences for them and their family?

Cancer World asked alumni of the European School of Oncology to tell us about how they handle these conversations, about the principles that guide their approach, and about any guidelines or laws that may affect what options they discuss.

We contacted medical/clinical oncologists, radiotherapists and surgeons – these conversations are not only about unaffordable medical options, but also diagnos-

tic tests and imaging, specialist surgery, better targeted radiotherapy techniques… and even timely access to standard radiotherapy.

And we contacted readers from across Europe. The number of therapeutic options not reimbursed, and their potential value to patients, is certainly higher in the less wealthy parts of Europe. But it is a challenge for doctors and their patients in high-income countries as well, due to delays between regulatory approval and a decision on reimbursement, as well as the cost and marginal benefit of some new treatments or indications. More than seven in ten respondents from the low-income countries said the issue arose 'very often' or 'quite often', compared with three in ten from the most wealthy countries.

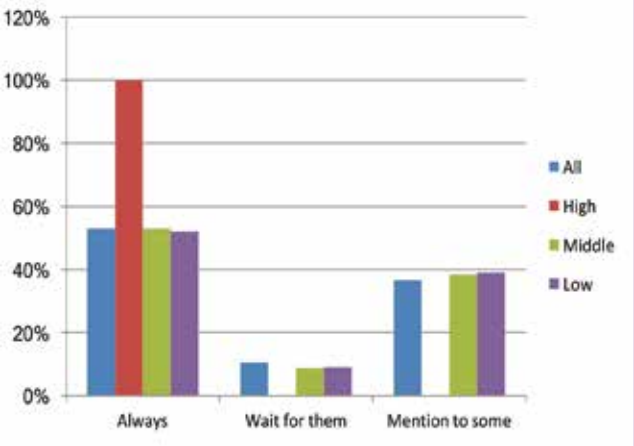
More than 100 cancer professionals (78 medical/clinical oncologists, 17 radiotherapists and 26 cancer surgeons and two dermato-oncologists) responded to the survey. Details of which countries are represented are given in the box on p 60, along with details of how we categorised them into high-, middle- and low-income groups. (The categories high, middle and low are relative to the European, not global, context.)

Do you mention it?

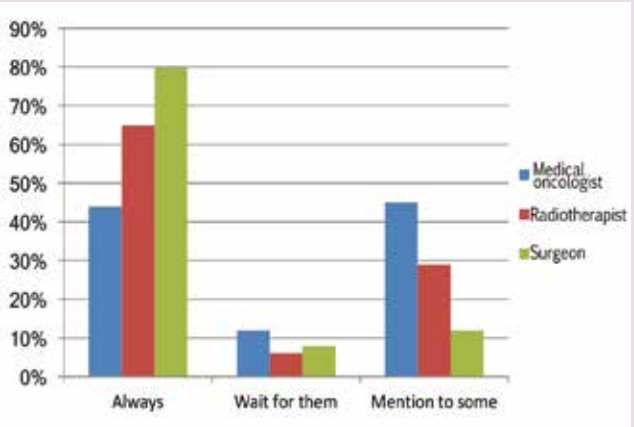
Just over half of all respondents said that, if there is an approved therapy that they know might benefit their patient, but they think the patient cannot access, they will always mention it. Almost four in ten said they mention it to some

Do you mention it?

Responses by country per capita GDP level



Responses by discipline



and not others. Only one in ten said they never talk about it unless the patient takes the initiative to ask about it.

There is a notable difference between the richest countries and the rest. Every respondent from the countries with highest income level said they would 'always' mention it. This may, in part, reflect that it is easier to talk to patients about non-reimbursed options in settings where the great majority of therapies that can really make a difference are in fact reimbursed.

"The positive effect of most [of these] therapies is mostly minimal, so the loss of not having a certain treatment is limited," was one comment.

A slim majority of the respondents from low- and middle-income countries in Europe also said they mention all therapeutic options to all their patients, while a substantial minority mention it only to some.

Some respondents, mainly in middle-income countries, said they try to help patients get funding, for instance, from charities and 'medical need' programmes, or find somewhere where a drug that has been approved but not yet authorised for reimbursement may be accessible via a clinical trial.

They are also aware of the added responsibility of not overstating the potential benefits when considering treatments that could have such a lasting impact on the finances of the patient and their family. "I approach it with caution, not to give false hope to patients." "In any case I submit the proposal to more experienced colleagues or to my multidisciplinary group."

Some respondents in low-income countries stressed the need to be transparent about the standard of care in international guidelines. "I explain to them that if they were treated in more developed countries, the treatment strategy would be different, and show them where they can find information about it," said one.

"I think that I have to inform them fully of the options and prices. The most difficult part is to explain why the price of medicine is so high – this is completely incomprehensible for the patients," said another.

Other comments indicate a tendency to stick to what seem realistic options for the patients in front of them, such as: "Most of my patients in a public hospital can't afford to pay for expensive treatments," or "We live in low-income country."

There is also a notable difference between disciplines, with medical oncologists being the least likely to always mention it, and four times more likely than surgeons to be selective about to which patients they mention approved options that are unaffordable and not reimbursed.

This may reflect the fact that they see many more patients with incurable cancers. As one respondent noted, a toxic drug that could increase the chances of a cure given as an adjuvant or neoadjuvant in a medium- or high-risk curative setting could offer only marginal advantage to a patient with incurable disease. Medical oncologists may feel it therefore makes sense to be selective about who they mention the option to, particularly given the high cost of these therapies, which makes private payment out of the question for most people.

Rules and Guidelines

In many cases the choice of what to tell patients is influenced by laws and guidelines operating at a national or local level. These may be designed to promote 'individual patient choice', or to standardise treatment offered within a public healthcare system.

Responses to the survey question: "Are there rules governing what therapeutic options doctors are obliged to mention?" may not be very reliable, as respondents from the same country did not always agree. However, taken as a whole, there does seem to be a signal that the wealthier countries and the poorest have more regulations and guidance regarding which options should be discussed than middle-income countries. "In France we cannot ask patients to pay for their treatment," said one respondent. Another, from Spain, commented, "In our system, any mention of an expensive therapy not covered by the system is out of the question. Depending on the potential benefits for the patients, there may be a frustrating situation for me."

Respondents also see an upside to having such guidelines, however. A clear majority feel that on balance the rules and guidelines are workable for oncologists, and a slim majority feel that on balance they also work in the best interests of patients. Comments referred to the possibility of bias in the way oncologists present information about potential risks and benefits, either due to their own prejudices or financial vested interests. One respondent pointed out that having guidelines on what to mention, "makes our job easier," and another noted it could be "especially useful for less experienced oncologists. They make it possible to give information in the same way. Less confusing for the patient."

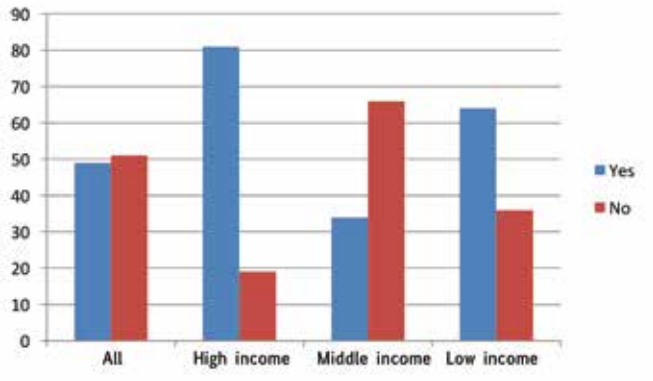
A stressful conversation

Whatever the guidelines for discussing options may say, there is a widespread feeling that, too often, oncologists are being left to take the strain of the gap between what is approved and what patients can access.

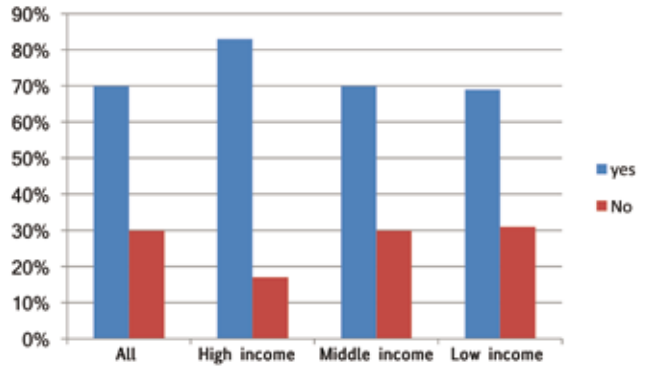
This problem is most starkly illustrated, perhaps, in one Balkan country, where according to one survey respondent, oncologists are sometimes obliged to take personal financial responsibility for costs incurred from prescribing certain anti-cancer drugs.

"In some oncological institutions, physicians are obliged to sign a paper in which they state that they will prescribe only medicines that are reimbursed, or they will pay out of pocket the treatment which is not reimbursed, since the health insurance fund will charge the hospital for this treatment," he says. "So, most physicians don't mention the standard of care treatment based on

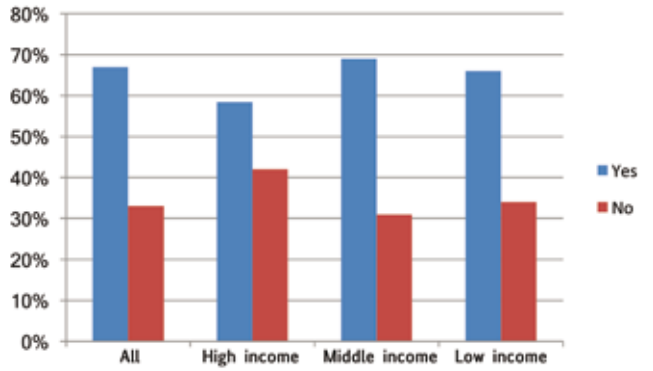
Rules and guidelines?



Workable for oncologists?



Best interests of patients?



Survey respondents: where they practice

The survey was sent to more than 3000 alumni of the European School of Oncology who define their discipline as Medical Oncology, Clinical Oncology, Radiation Oncology or Surgery and who practice in a European country. We received 113 responses (78 medical/clinical oncologists, 17 radiotherapists, 26 cancer surgeons and two dermato-oncologists). Respondents came from the following 32 countries: Albania, Austria, Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, Cyprus, Denmark, France, Georgia, Germany, Greece, Hungary, Italy, Latvia, Lithuania, Montenegro, Netherlands, North Macedonia, Poland, Portugal, Romania, Russian Federation, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey, Ukraine, UK. Countries were grouped into high-, middle- or low-income using the 2018 International Monetary Fund data for GDP per capita at purchasing power parity, using the IMF brackets of >$50,000, $30-50,000 and >$30,000.

European guidelines to their patients if this is not reimbursed, unless this is a patient they personally know and they can trust."

The situation arises he explains because, while in principle healthcare is a universal constitutional right, in practice hospitals cannot afford all the recommended treatments. Oncologists, however, do not want to adapt European guidelines in a way that would exclude treatments that can significantly prolong patients' life, improve their quality of life and even induce long remissions. So the hospitals end up putting pressure on individual oncologists to restrict their prescribing.

Obliging oncologists to take personal legal responsibility like this for the cost of non-reimbursed prescriptions is probably an exception. But responsibility for talking to patients about therapies that could help them but are unaffordable is in any case a difficult conversation to have. This is another reason doctors often choose not to mention it, says another practitioner from the Balkan region, who treats patients with advanced melanoma. "I try to explain to every patient what are the options and that there is no reimbursement," she says, "[but] there are doctors who do not inform the patients about this possibility, because it is less stressful than to explain every day what is the best option for them.

"The problem is this space between new innovations in medicine that are developing very fast, and our system that is not able to adapt to it, to negotiate for example prices with companies. And then the doctors are left to deal with it, to wait for the reimbursement, and patients – they are in the worst situation, of course – and that is really a very large frustration… As a result, many doctors are leaving the country."

Ironically, that frustration may be even higher in many wealthier countries, with stronger public healthcare systems, where people have higher expectations about their right to access therapies approved for their indication – and again it is the oncologists who have to handle those conversations. Sometimes the reason is because the authorities decide that a new therapy or a new indication for its use represents poor value for money. Often, however, the problem is the delay between being approved for market and getting a decision on reimbursement. When the therapy is seen as quite effective, those conversations can be seriously stressful for all parties.

"This happened a lot at the beginning of immunotherapy," said one oncologist from Spain, where 95% of all cancer patients are treated within the public system. He remembers discussing options with a patient who wanted to be treated with immunotherapy before a decision had been taken to reimburse it. He had to explain that, even if the patient were to pay for the therapy, it is not possible to administer it within the public health system.

During the time period between approval and reimbursement, he added, "we do not discuss those treatments with our patients, because we, as a public hospital, cannot offer them. In fact, we do not speak about them because the great majority of the patients cannot afford that treatment."

In Italy a recent change to the law means doctors can now prescribe and administer drugs that are not reimbursed by the public health system. Oncologists are now likely to feel more responsibility to ensure that such an option is discussed with patients, even though in practice, the high cost poses an insuperable barrier for most.

The issue arises at least once a week, according to one genitourinary oncologist, who has seen his own patients with metastatic bladder cancer unable to get the PD-1 inhibitor, pembrolizumab during the gap between approval for that indication and a decision on reimbursement. "I very seldom found patients who were willing to pay for a cancer drug," he says. "The only recent case that

I can recall is a colleague's patient who was diagnosed with ROS-1 rearranged lung adenocarcinoma but could not receive crizotinib through our health system because it was not yet approved by AIFA [the Italian Medicines Agency] for that indication. He paid for five months of therapy, after which crizotinib was eventually approved. He told me that he would have been able to pay for not longer than one year of therapy."

In rare cases, he adds, it may be possible to find somewhere the drug is being trialled, for instance in a combination therapy. But even this solution doesn't work for most patients, he says, because they can't face the travel or simply prefer to be treated in a familiar environment where they know the physician, nurses and other caregivers.

In some eastern European countries, discussing out-of-pocket options is common practice. "Frequently, we have a situation that involves supplementary costs for patients without talking about the treatment," says one Romanian oncologist. "For instance, in the case of an investigation like PET-CT, for covering it by National Health Insurance House, a commission gathers once a month and approves the cases that need the investigation. There are patients who do not want to wait for a month and prefer to pay around €1,000 to obtain this investigation faster."

Doing the right thing

What is the right thing to do? Should doctors always mention every 'option' to every patient, even when they are certain that the information does not add to their options in any meaningful way, yet could add to their stress by focusing on what cannot be achieved. Should doctors ever make assumptions about what is or is not relevant information for their patients?

There are no simple answers, says Giovanni Boniolo, Professor of Philosophy of Science and Medical Humanities at the University of Ferrara, Italy. "In principle, the best strategy should be to tell all the possibilities in a truthful way. Of course, this kind of communication should be made with great care. But there could be instances in which the omission of certain information could be beneficial."

He feels oncologists should get more support and training in how to handle difficult conversations like these in a way that balances principles of truth telling and transparency with a responsibility to avoid adding unnecessarily to the distress of patients.

"Doctors are not trained to face ethical questions," he says, "they rely on 'common sense'." He would like to see ethical issues and ethical reasoning being taught as part of medical training. Ensuring doctors feel better equipped to handle these difficult conversations could not only benefit patients and their families, he adds, but could lessen the stress felt by doctors, which, he says, "is one of the main elements leading to burnout syndrome."

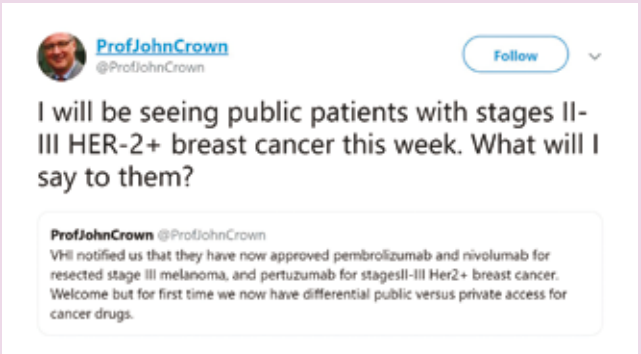
Interviews and reporting by Geta Roman.

To comment on or share this article go to bit.ly/CW86-WhatDoYouSay

Join the conversation

Cancer World's series of 'Getting personal' articles aims to offer a clinicians' perspective on ethical dilemmas that are common on consultations with cancer patients. Thanks to all the respondents who took time to answer our survey questions and do follow-up interviews for this article. If you would like to contribute information about your own experiences handling conversations with patients about options they cannot afford, please go to the online article at bit.ly/CW86-WhatDoYouSay and leave a comment.

What will I say?



John Crown, leading Irish breast oncologist and political cancer activist, responds on Twitter to the news that "For the first time we have differential public versus private access for cancer drugs", following the approval by Ireland's largest health insurer to cover costs of certain immunotherapies for additional indications.

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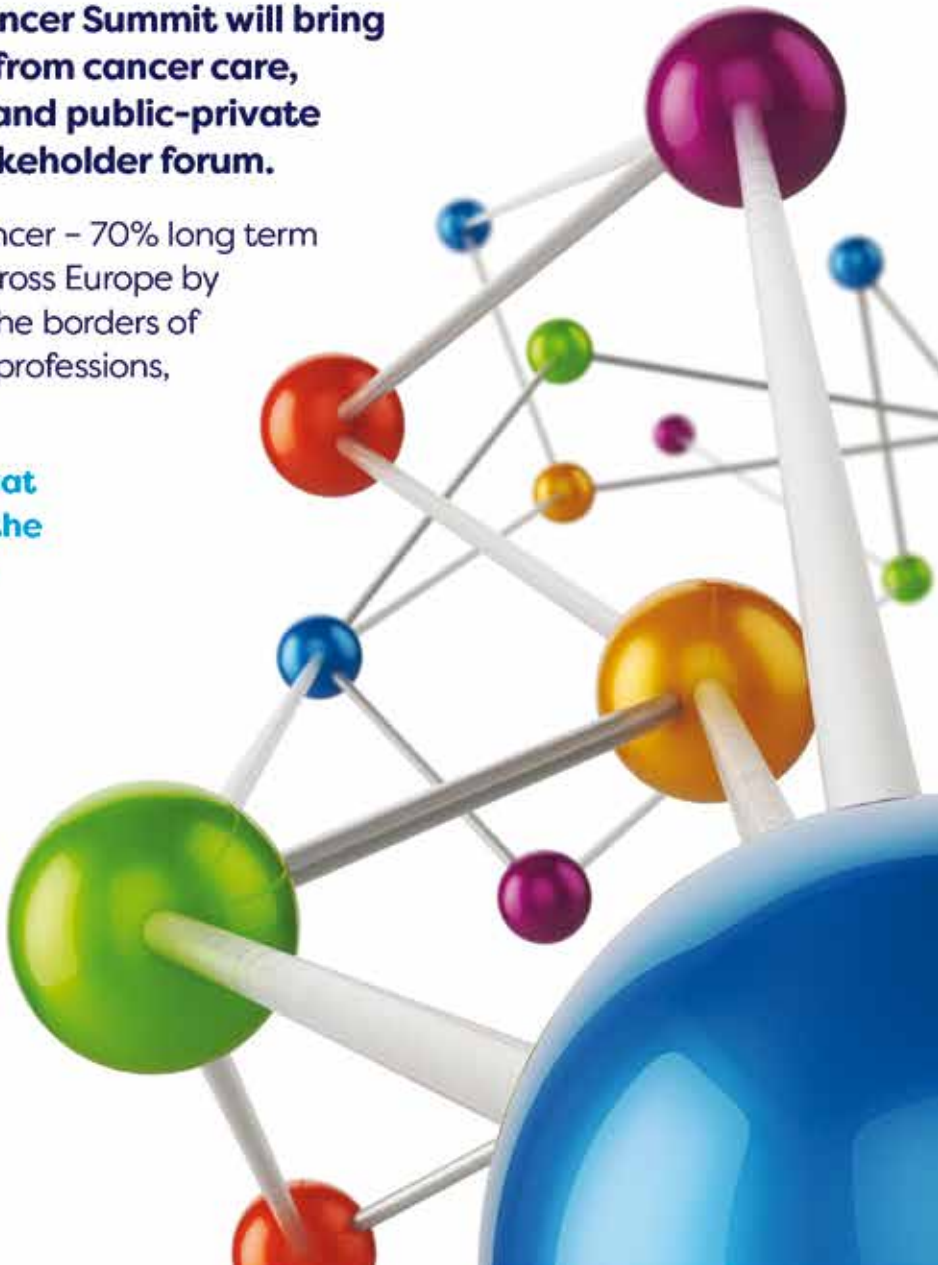

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Tibor Kovacs, President of ESSO, Chair of BRESO,
Consultant oncoplastic breast surgeon, Guy's and
St Thomas' NHS Foundation Trust, London

A European accreditation platform for breast surgery

Women affected by breast cancer should be treated by specialists trained and accredited in breast surgical oncology. This is the vision of BRESO, the Breast Surgical Oncology Platform, which was launched by ESSO in Vienna, last September. BRESO aims to promote accredited specialist breast surgical care for all breast cancer patients and women at high risk of breast cancer.

Other leading bodies in the field have now joined the platform, namely the European School of Oncology, the European Society of Breast Cancer Specialists (EUSOMA), Europa Donna, the Division of Breast Surgery within the UEMS (European Union of Medical Specialists) and the European breast cancer research association of surgical trialists.

BRESO is promoting the highest quality and most innovative, evidence-based breast cancer care. It intends to develop the highest standards of breast surgical oncology in a multidisciplinary setting for the benefit of patients. It is committed to providing a gold standard of available care that should be transcendental in nature and available to all European patients regardless of their geographical location.

BRESO is supporting breast cancer patients to receive their treatment from accredited breast cancer surgeons within a multidisciplinary environment, benefiting from the expertise of highly-skilled surgical oncologists.

BRESO aims to achieve this goal by offering the leading platform for quality education and training in breast surgical oncology, including courses, workshops, masterclasses, and university-linked diplomas, fellowships and observerships. Providing a Europe-wide certification of specialist breast cancer surgeons is another key objective, which will be achieved with an examination delivered jointly by the UEMS in collaboration with ESSO and EUSOMA. In conjunction, training fellowships adhering to the UEMS & ESSO Breast Surgery Curriculum will be recommended.

BRESO further aims to promote and initiate multinational audits of standards in breast cancer surgical care, and prospective data collection in collaboration with EUSOMA. It also wants to facilitate availability and compliance with multidisciplinary guidelines and practice of quality cancer care, including the availability of oncoplastic breast surgery and reconstruction for all cancer patients across Europe. Moreover, BRESO can lead on, and collaborate with, policymakers on the homogenisation of quality breast cancer management within Europe, to achieve the best long-term outcomes and patient satisfaction.

BRESO plans to bring together specialists involved in breast cancer, surgical oncology, and reconstructive surgery within a multidisciplinary environment, and foster collaboration with core members of the multidisciplinary breast cancer care specialties. It will work closely with patient advocacy and support groups, to offer them guidance in achieving the common goal of the highest quality cancer care for all European breast patients. BRESO will also publish position papers, guidelines and reviews.

The BRESO Project Board is keen to collaborate and communicate with patient organisations and policymakers, to establish strategic directions for the group and **lobby for European recognition of breast cancer surgery as a surgical oncology subspecialty**.

BRESO will continue to have a widely inclusive approach in creating a platform for representatives from leading educational, training, research and accreditation organisations, and will strive to achieve its goals in a collaborative manner, keeping in mind the best interests of our patients across Europe.

Four working groups have been created, each focusing on the specific components of the project (theoretical knowledge, practical knowledge, examination and organisational structure. I hope to be able to report back on the work in progress in the next few months in a future 'ESSO Corner'.

The unreported results that are still undermining evidence-based medicine

The scandal of unreported trials has been known about for decades, prompting a variety of initiatives, legislative changes and campaigns. **Sophie Fessl** asks what impact these have had on reporting practices, and how far patients and clinicians can be confident that the evidence they can now access tells the full story.

In 2010, Alessandro Liberati, former director of the Italian Cochrane Center, explained his struggle to decide on his treatment options for multiple myeloma. "When I had to decide [in 2003] whether to have a second bone-marrow transplant, I found there were four trials that might have answered my questions, but I was forced to make my decision without knowing the results because, although the trials had been completed some time before, they had not been properly published… I believe that research results must be seen as a public good that belongs to the community – especially patients."

Sixteen years after Liberati was frustrated by non-published trials, it remains the case that far from all

studies make their results public after completion. Slightly less than half of all clinical trials conducted in Europe posted summary results on the European Clinical Trials Register, according to an analysis published in the *BMJ* in 2018 (*BMJ* 362:k3218). And while commercial trials have a publication rate of 68.1%, with just 11% the rate is much worse for non-commercial trials (*ibid*).

The problem with secrets in medicine

Non-publication affects everyone, says Till Bruckner, founder of UK-based transparency advocacy organisation TranspariMed. "On the one hand it makes it really hard to assess whether treatments are safe and effective. On the other hand, a huge amount of research is going to waste. The same trials might be duplicated several times, with patients volunteering hundreds of hours of their time to participate in clinical trials.

"And patients also do this because they want to help scientists find new treatments. When results are not published, it's just a betrayal of patient rights."

An unpublished trial doesn't just let the invested funds go to waste, but may lead to a duplication of essentially the same trial and the same cost.

How much evidence remains hidden?

This 'filing drawer problem' cuts to the heart of evidence-based medicine. Or, to paraphrase Bruckner's first point, how evidence-based is evidence-based medicine, if we don't have all the evidence? Withholding of results, or a selective publication of positive results, has affected both clinical decision-making and health technology assessment.

"The results of unpublished studies are, tendentially, not as positive as the results of published studies"

IQWiG, the German Institute for Quality and Efficiency in Health Care, wasn't able to draw a conclusion about the harm or benefit of stem cell transplantations for the treatment of multiple myeloma, as 10 years after their completion, the results of three large trials had not been published, says IQWiG's director Jürgen Windeler.

"We get a distorted view of reality. For one trial, which was conducted in Germany with public money and is essentially finished, we cannot get access to the results." But the situation can be handled differently – an Australian research group provided individual patient data to IQWiG, and with additional analyses, IQWiG arrived at a positive conclusion in the assessment of an added benefit.

Jörg Meerpohl, a paediatric oncologist and director of the Institute for Evidence in Medicine, at the University of Freiburg, Germany, points to several known sources of evidence distortions.

"We know that a substantial proportion of trial results is not reported. We also know that the results of unpublished studies are, tendentially, not as positive as the results of published studies. Therefore, there can be situations – and they are known to have occurred in the past years – in which systematic reviews of published studies came to a different result, and therefore indicated a different conclusion, than when, at a later time point, the results of all studies that had actually been carried out were looked at."

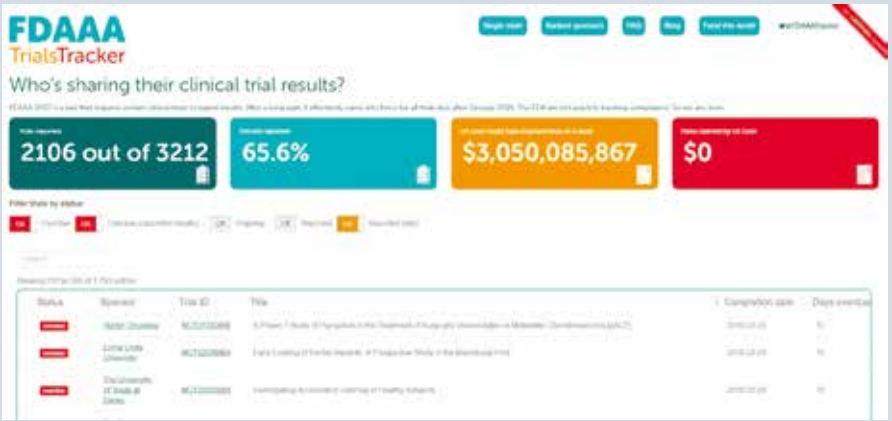
These examples included the positive assessment of oseltamivir, which led to several billion dollars being spent on Tamiflu, with questionable effectiveness.

A question of ethics

Apart from the scientific dimension, the problem of non-publication has an ethical dimension, as Roger Wilson, honorary president of Sarcoma Patients Euronet, points out. "You have to ask, why do patients enter trials? One reason, of course, is because they are looking for a treatment which is better than the standard of care that exists at the moment. And the second reason is altruistic: they want to help other patients, they want to improve the standard of care, for the benefit of everyone."

Wilson argues that a moral contract is established when a patient enters a trial. "When you give a patient the option of entering a trial, you, the clinician making that offer, are taking on the moral responsibility for addressing that altruistic ambition of the patient. And that altruism is only going to be met if the trial is published."

Shining a light on dark data



The FDAAA tracker site publishes details of trials registered on the US ClinicalTrials.gov website that fail to report their results on time. This screenshot, taken on 16 May 2019, shows that on 14 May 2019, the time of the latest update, 65.6% of trials had reported by their due date. It also shows the total amount the US regulators, the FDA, could have fined sponsors who are late in reporting (more than $3 billion dollars) and how much the FDA has actually imposed in fines ($0). The site was built by the Evidence-Based Medicine DataLab at the University of Oxford, and is run as part of the AllTrials campaign.

Source: https://fdaaa.trialstracker.net/

Legislative steps have been taken

The revised Declaration of Helsinki from 2013 notes the ethical obligation to report clinical trial data, whether positive or negative. Legislators have recognised that non-publication of trial results is a problem, and have taken – some – steps to address it. In the US, the FDA Amendments Act 2007 (FDAAA), requires sponsors to post results on the ClinicalTrials.gov database within 12 months of completion. However, this requirement only extends to certain types of trials. The situation in Europe appears even murkier. Several interviewees disagreed over whether there are any legal requirement for trial sponsors to post summary results to the EU Clinical Trials Register (EUCTR), and if so, whether such a requirement would extend to all types of clinical trials.

The analysis published in the *BMJ* in 2018 examined the publication of trial results on the EU Clinical Trials Register on the basis that "following the 2012 EC guideline 2012/c302/03, sponsors must ensure that all trials registered on EUCTR since 2004 disclose their results to the EMA within 12 months of trial completion; phase I trials are exempt unless they are denoted as being part of a paediatric investigation plan."

Academic trials have a much worse track record than industry-led trials

At the time the study was published, only 49.5% of trials where results were due had posted results to the EUCTR (*BMJ* 2018, 362:k3218). The real reporting rate might, however, be even worse: 29.4% of trials listed as completed did not include a completion date, although required, so the authors could not assess whether results were due to be reported. One caveat is that publication in a journal article, conference presentation, or as part of a meta-analysis was not included as, according to the study authors, this does not meet the requirements of the EC guideline.

This study pointed out that academic trials have a much worse track record than industry-led trials: sponsors doing fewer trials and non-commercial sponsors both have low rates of reporting. "Often, people have this impression that evil pharma withholds data," says Windeler, "But in this case, academic groups are no better than industry. It might have been different about ten years ago, but now, industry is clearly under stricter observation and cannot afford to hide things."

Non-reporting is prevalent for oncology trials

How bad is non-reporting in oncology? Jaime Perez-Alija, medical physicist at Hospital de la Santa Creu i Sant Pau in Barcelona, decided to investigate this question for radiation oncology, together with his colleague Pedro Gallego – initially, just for fun, he says. "We were dealing with cancer, so we thought publication of trial results would be more or less okay. We were very surprised to find what would look like a massive failure to

publish results of completed trials."

The observational study, published in 2017 (*BMJ Open* 7:e016040), showed that 84% of trials in radiation oncology registered with the ClinicalTrials.gov database did not post summary results within at least 16 months of trial completion, and only 45% reported results in a peer-reviewed journal. Again, industry-funded trials had higher reporting rates in the registry. A separate analysis found that four to six years after clinical trial abstracts are submitted and reported at ASCO, 39% of oncology trials remain unpublished in a peer-reviewed journal (*The Oncologist* 2016, 21:261–8).

Reasons for non-publication

Why are so many trial results relegated to the filing drawer? The OPEN Consortium (to Overcome failure to Publish nEgative fiNdings) was set up in 2011 to explore possible reasons and develop "evidence-informed recommendations focused on reducing dissemination bias".

Meerpohl, who led the Consortium, sees it as a collective problem. "It is a complex problem with many different players, involving everyone from researchers, journals and funding agencies, to ethics committees. Each of these groups contributes to the problem a little bit."

Ana Marušić, Chair of the Department of Research in Biomedicine and Health at the University of Split School of Medicine, in Croatia, and editor of the *Journal of Global Health*, questioned authors about reasons and solutions for non-publication as part of the OPEN Consortium. "In our focus group, authors said that: yes, they are guilty of not publishing. But they also said that the problem is that the system is not supporting them, that they have to rush from grant to grant without any time or funding to finish everything up."

Journals, on the other hand, are often not interested in publishing negative results, IQWiG's Windeler points out. "Negative results are often seen as boring and not worthy of publication. Journals and journal editors are often not interested in negative results, as positive results are seen as easier to sell and more important for progress, but that is of course nonsense." Marušić, too, sees the pressure to publish as detrimental to full transparency. "Everything in the academic system now is geared towards publication. Maybe there should be incentives for posting results in registries, and journals should take on another role – picking up interesting results, providing a space for post-publication review after summary data or full data is published."

The higher rate of industry reporting may be partly due to better awareness of requirements, says Windeler. "If you ask around in German universities whether researchers are aware that they should register and publish their trials, I think that in many cases you would encounter a lack of understanding and awareness. There is no support in this system for researchers to fulfil European requirements – and the institutions who should support this, including universities, funding agencies and ethics commissions, are not asking researchers to adhere to regulations."

Finding a way forward

UK universities are now questioned about their adherence to European requirements for publishing results. In October 2018, the Science and Technology Committee of the House of Commons released a report, calling for increased transparency in clinical trial reporting. Norman Lamb, the chair of the committee, wrote to more than forty UK universities asking them to verify that the institutions are putting systems in place to comply with all reporting requirements. Universities whose track records are not improving may be questioned about their non-compliance in the autumn of 2019.

"Ethics committees should introduce this idea of 'no further study from you will get through ethics until you have published'"

In his letter, Lamb acknowledges the efforts of the AllTrials campaign, an international initiative co-founded in the UK in 2013 by Ben Goldacre, journalist and researcher at the University of Oxford, with the mission to get "All trials registered, all results reported". Many patient groups support AllTrials. "The whole theme that AllTrials has driven has had a very strong patient input from day one, and I've supported the campaign right from the very start," says Wilson.

While patient pressure appears to have some effect in the UK, Windeler does not see anything similar happening in Germany, which has quite a poor track record on reporting results. "At the moment, I cannot see statements or other forms

of public activities from patient groups in Germany that exert pressure on politics or funding agencies, unfortunately."

Other ideas for solutions are being proposed. "One possibility, and the one that usually comes first to mind, is using money to solve the problem," says Windeler. "Funding agencies could tie part of the funding to the publication of results – so a part of the money is only released once the results are made publicly available. Or funding agencies could ask for proof that results of previous trials have been published before processing an application for new funding."

TranspariMed's Bruckner agrees: "Why should tax money be given to universities and other research institutions that have behaved unethically by not reporting results? That's definitely a question funders should ask."

A stronger involvement of ethics committees in the oversight of trial reporting is also proposed. "Ethics committees should introduce this idea of 'no further study from you will get through ethics until you have published'," Wilson suggests, "and the researcher's employer, e.g. their university, should be advised of this. Ethics committees should take a look at studies that appear to have passed their proper publishing date."

Measures aimed at solving the problem of non-publication will never be effective unless they are actually implemented. In the US, the FDA can levy fines of up to $10,000 for each day that has passed since a trial is due to have published its results. However, as far as is known, this sanction has never yet been applied.

Meerpohl sees both the problem and the solution as collective in nature. "When we investigated the reasons, our impression was that all the players involved blame each other. But we think that the solution has to be a concerted one. Everyone can contribute to solving this problem."

If we replace "researchers" with "research system" the question posed by Alessandro Liberati in 2004 still holds true (*BMJ* 2004, 328:531): "How far can we tolerate the butterfly behaviour of [the research system], moving on to the next flower well before the previous one has been fully exploited?"

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Dina Tiniakos

President of the European Society of Pathology

Precision cancer medicine has put a spotlight on the role of pathologist, whose job it is to provide an accurate diagnosis as well as prognostic and predictive information on which to tailor the treatment plan. *Cancer World* asked Dina Tiniakos, President of the European Society of Pathology, how pathologists are rising to the challenge.

Cancer World: *Cancer pathology was once all about grade, size and spread. Has the era of precision medicine changed that?*

Dina Tiniakos: Histological interpretation is still the main diagnostic tool in surgical pathology. The role of morphology in the molecular era will remain significant, as emerging morpho-molecular correlations enable the prediction of underlying molecular changes based on histological subtyping, at least in some types of cancer. In addition to established prognostic information based on tumour size, histological grade, depth of invasion and lymph node spread, pathologists can now provide additional prognostic and predictive data at the tissue level, such as cell proliferation indices for neuroendocrine neoplasms, hormone and tyrosine kinase receptor expression in breast carcinoma, response to immunotherapy by assessing PD and PD-L1 expression or indirect information on gene mutations, e.g. beta-catenin mutation in hepatocellular adenoma, which is indicative of higher risk for malignant transformation. During the last two decades molecular diagnostic technology has progressively expanded and, with the growing demands for molecular tumour subclassification and information on prognosis, response to treatment and molecular therapeutic targets, this field will expand further.

CW: *How confident can oncologists be that the pathology reports they use to guide treatment decisions are reliable and would be replicated in other labs/centres/countries?*

DT: Internal quality assurance (IQA) systems are in place in most pathology laboratories in Europe. This ensures testing of quality of histological techniques, special histochemical stains, immunohistochemistry, and molecular diagnostic methods. In addition, external quality assurance (EQA) programmes, also known as proficiency testing, are key tools to periodically assess all the above by inter-laboratory comparison. These assist laboratories in monitoring their assays and improving their performance, as well as with evaluation of results whenever needed. The European Society of Pathology (ESP) and other organisations run such EQA programmes continuously to ensure optimal accuracy and proficiency for biomarker testing across all participating countries.

For the accuracy of molecular diagnostic testing, the quality of tissue for analysis is the most important variable, and the pre-analytical phase plays a major role. Simple steps, such as specimen fixation, are critical in ensuring that the tissue available for testing will be of optimal quality. Therefore, 'tissue is the issue' and will continue to be, whatever

new diagnostic technology will be implemented. Accreditation of pathology laboratories according to quality standards is becoming more common in continental Europe after its introduction almost three decades ago in the UK.

Of course, certifying that pathologists are adequately trained, their diagnostic skills are appropriate, and their knowledge is up to date, is critical for the reliability of histopathological diagnosis. For this reason, more countries now follow the UK example, where EQA programmes for different pathology subspecialties testing the competency of pathologists are run once or twice a year.

CW: *What are the biggest barriers to improving pathology practice, and how is the ESP addressing them?*

DT: The ESP promotes high-quality diagnostic practice, applied and translational research, and under- and postgraduate education in the field of human pathology. The biggest barrier to improving pathology practice in Europe is the heterogeneity of pathology services among different countries. Through our educational programmes and by working closely with the national societies of pathology, the ESP strives to diminish inequalities in postgraduate education in pathology, including molecular pathology. The ESP Foundation provides EQA programmes that enable participating laboratories to monitor their performance in specific molecular testing, ensuring high-quality services.

CW: *What challenges do tumour heterogeneity and clonal evolution pose for pathologists?*

DT: Genetic tumour heterogeneity can lead to underestimation of the tumour genomic landscape portrayed from a single diagnostic biopsy or surgical specimen, and may present major challenges to personalised medicine and biomarker development and validation. Genomic diversity within a given tumour, as well as temporal heterogeneity as the tumour evolves, may lead to erroneous results regarding the underlying key genetic changes, and may lead to therapeutic failure, especially when treatment is based on results from a minute tissue sample.

The challenges for molecular diagnostics are basically paralleled across all types of tumours, and resolving these issues will require technology improvements in addition to a greater understanding of tumour biology. Sampling from more than one site within the tumour and re-assessing the tumour following recurrence are ways to overcome this problem. For the latter, circulating biomarkers may prove useful to monitor and/or modify treatment. The logistical challenges of implementing the next generation of molecular diagnostics into clinical practice are equally important, taking into account the need for multiple tumour sampling. More investment is therefore warranted in information technology infrastructure, data storage, pathways in sample processing, and training and professional developments in histopathology.

CW: *Will pathologists need to play more of a role beyond the initial diagnosis, and if so, how will that affect capacity issues?*

DT: One of the current challenges in pathology is that pathologists need to adapt methods and techniques in the laboratory to meet the new therapy options and modalities, with immunotherapy as the best example. The course of neoplastic disease during immunotherapy is still not fully predictable, making prognosis even more difficult. A key recommendation for preventing therapy resistance, owing to tumour heterogeneity and cancer adaptation, is to perform frequent tumour biopsies to monitor emergence of new aberrations and eradicate significant sub-clones as early as possible. It can be anticipated that, in the era of precision medicine, the number of molecular markers that need to be assessed will steadily increase per sample. The challenge for the diagnostic laboratory is to select high-performing technological methodologies that enable reliable detection of all mutations required, at a high sensitivity, with a limited amount of tissue, within short turn-around times and at low cost.

A further challenge is the low rates of recruitment of pathology trainees, which poses additional stresses on the capacity of laboratories to face the increasing numbers of sample testing that will be required in the future. It is envisaged that artificial intelligence systems will aid pathologists in performing simple measurements of cells positive for a given biomarker or counting *in situ* hybridisation signals, allowing them to concentrate on the more complex process of histological interpretation, which is the cornerstone of cancer diagnosis.

To comment on or share this article go to bit.ly/CW86-DinaTiniakos

Dina Tiniakos is President of the European Society of Pathology (2017–2019). She is Professor of Pathology at the National & Kapodistrian University of Athens, Greece, an academic pathologist at the Institute of Cellular Medicine at Newcastle University, UK, and sits on the Board of the International Quality Network for Pathology. She is also Director of the Department of Pathology at Aretaieion University Hospital in Athens, and specialises in hepatobiliary pathology.

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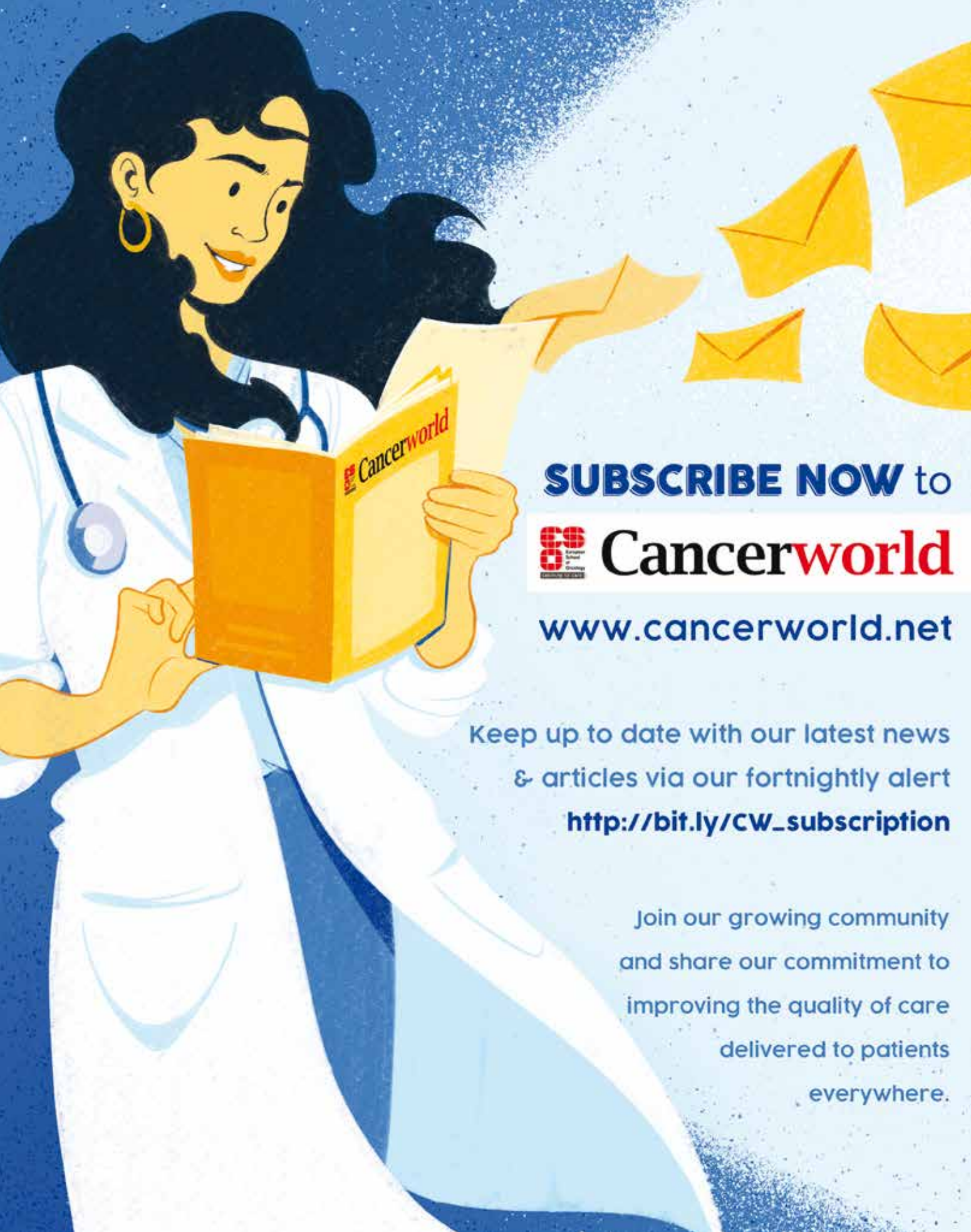

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