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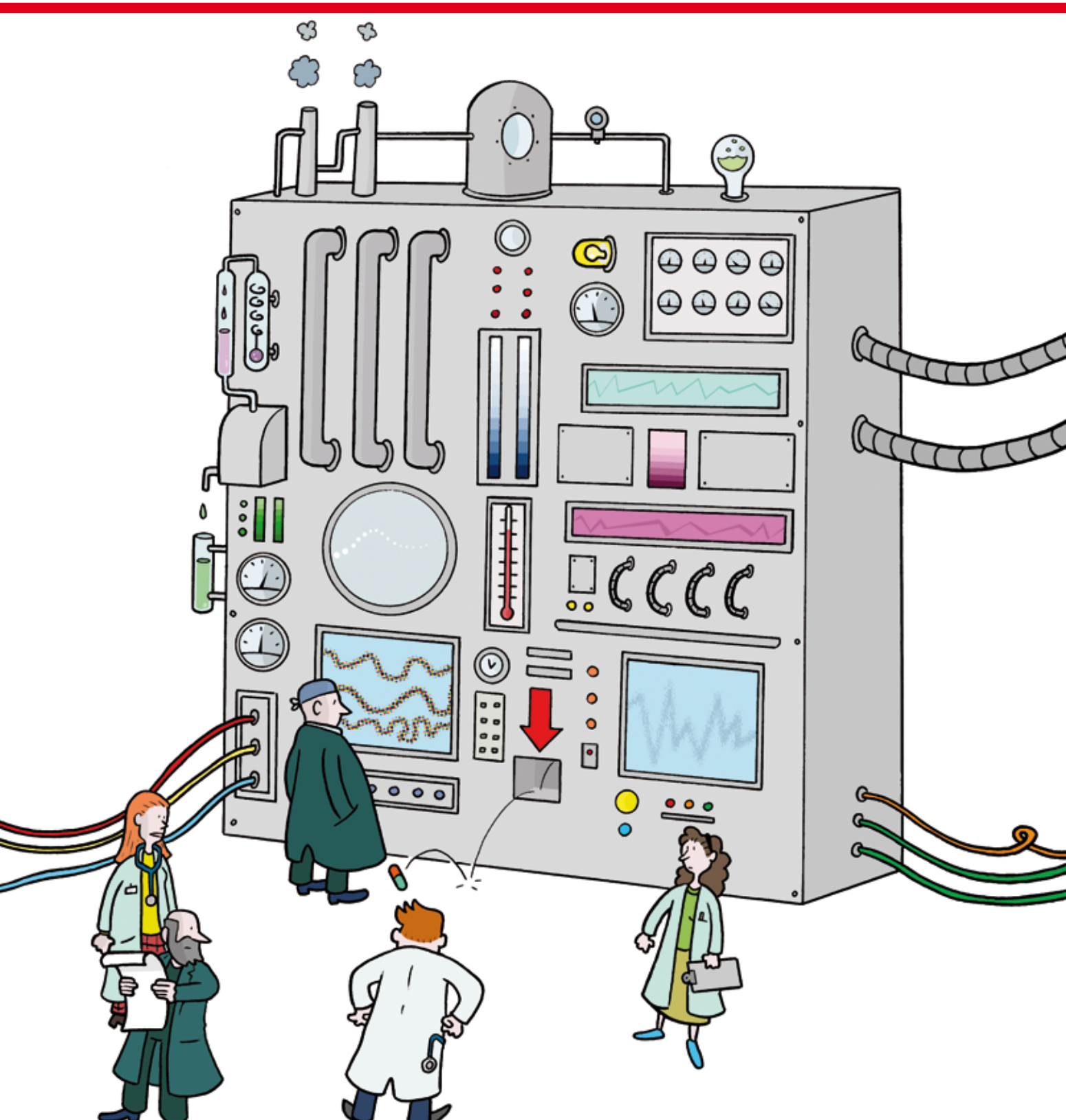

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Alberto Costa

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All enquiries to: ESO Editorial Office,
Via Turati 29, 20121 Milan, Italy
magazine@eso.net +39 02 8546 4522

Correspondence should be sent to The Editor at editor@eso.net

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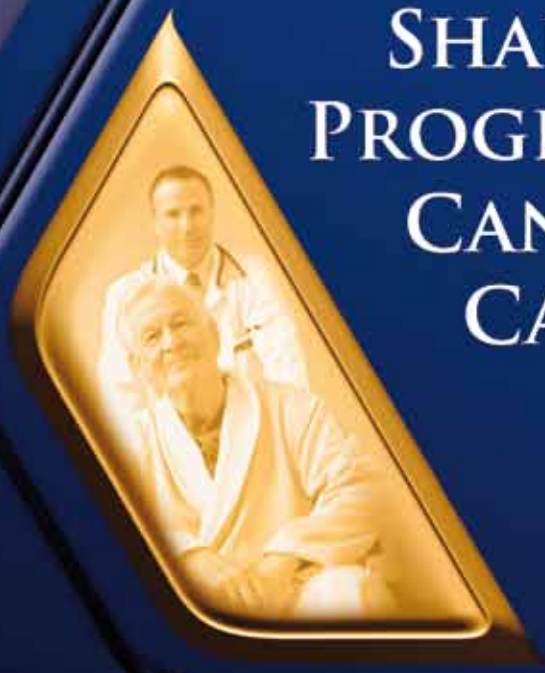
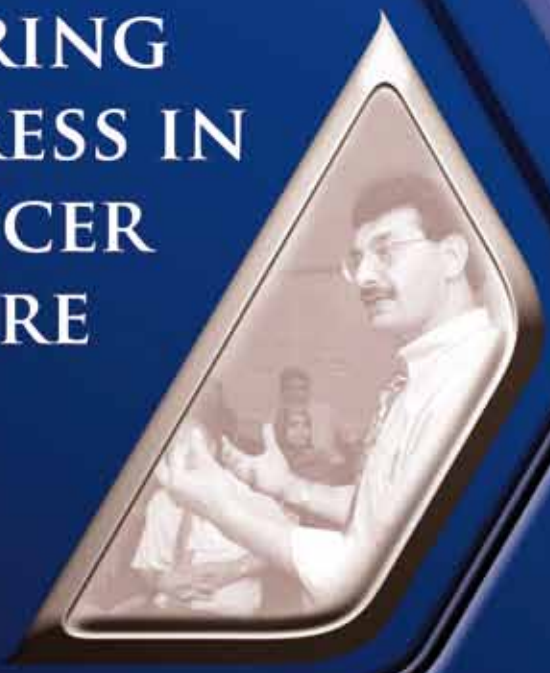
European School of Oncology

Learning to care

Sharing Progress in Cancer Care





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Hats off to the patient advocates

Alberto Costa, Editor

"A room full of healers." This is how Larry Norton, Medical Director of the Evelyn H. Lauder Breast Center at Memorial Sloan Kettering, described the feel of the auditorium during the 4th Advanced Breast Cancer conference, which took place in Lisbon last November.

The ABC conference is about healing, in that it addresses the full spectrum of challenges that people with advanced breast cancer face in sustaining their overall health and wellbeing and their capacity to live active and fulfilling lives.

But Norton was referring not to the agenda so much as the healing qualities of the words and sentiments being articulated. This was more than a forum on how to 'manage' the disease and the patients. Thanks to the integration of patient advocates into all aspects of the programme, the conference was also about medicine as an act of listening to patients and taking their side.

Medicine is not medicine without passion and empathy, without the time to listen and support. We know, from a large number of carefully conducted studies, that even the most patient-centred of doctors routinely underestimates the severity of the burdens patients feel.

Belgian urologist Louis Denis, for instance, spent much of his career arguing – including in the pages of *Cancer World* – for his specialism to be more honest with patients about the impact long-term side effects could have on their lives, when discussing the risks and benefits of radical treatment for low-risk prostate cancer. Yet, after he himself developed prostate cancer, he admitted he had been astonished when he found out the true depth of exhaustion brought on by his radiotherapy treatment – and frustrated at ending up with impaired bladder control because he was persuaded, against his better judgement, to accept that extra boost to the dose.

None of us knows what it is to suffer cancer, and the short- and long-term impact of cancer treatments, unless we've been through it. The new YOU protocol that EORTC, the leading European cancer trials organisation, hope to introduce by the end of 2018 (see 'Gathering long-term data on what happens next', p62), should offer a welcome source of data on long-term impacts including on functional and societal aspects of patients' lives.

But to play the healing role we aspire to, we need to understand what those impacts mean to people who live with them, and that means learning to listen, really listen, to the patient advocates who know what it is like to live life as an oestrogen-deprived woman, or a testosterone deprived man, or with damaged salivary glands, long-term neuropathy, relentless fatigue, fear of recurrence, chemobrain and all the many different impacts that go with being a cancer survivor.

So we say "hats off!" to cancer patient advocates, who not only manage to cope with the disease and tough treatments, but also find the strength and motivation to engage with the clinical science, educate cancer professionals about the reality of the lived experience, and fight for their rights and those of their fellow patients, to make medicine more effective and also more human.

To comment on or share this Editorial, go to bit.ly/CW81_patient_advocates

Too high or too low?

ESMO's clinical benefit scale fuels debate over approval thresholds

Should regulators insist on robust evidence that a new drug shows clear benefit to patients as a condition of approval, or are demands for such levels of certainty unrealistic, or even unethical? **Marc Beishon** reports on how ESMO's new scale for scoring clinical benefit has added a new dimension to this long-running debate.

About 10 years ago, oncologists were confidently predicting that, by now, we would have a large portfolio of highly effective targeted drugs against cancer that would be the equal of the ones that kicked off the excitement – namely trastuzumab (Herceptin) and imatinib (Glivec). But that mostly hasn't happened – although the latest immunotherapy checkpoint inhibitors are now being seen in this class.

There are just not many new cancer drugs that qualify as real game changers, particularly for solid tumours, although some are certainly huge money spinners for the pharmaceutical companies, owing to eye-watering price-tags.

There are though many recently approved cancer drugs, with more in the pipeline, and, while much has been said over the past few years about lack of effectiveness of many of the agents, we seem now to be reaching a tipping point. Certain oncologists are calling for at least a searching appraisal of the current regulatory model, which they say is sending too many agents of questionable value onto the markets of countries with hard-pressed health systems – and that now includes nearly all countries.

Meanwhile two of the world's major cancer societies – ESMO in Europe and ASCO in the US – have launched tools to help oncologists to determine the 'real world' clinical value of cancer drugs. By providing scores for agents based in particular on overall survival (OS) and quality of life (QoL), it is hoped that health technology assessment (HTA) authorities, and also oncologists and patients, will be able to make better decisions about value and prescribing options – although offering value for money does not in itself mean that a drug is affordable.

ASCO has also launched CancerLinQ, a 'big data' initiative that is gathering information from oncology centres about the treatments they are providing, to feed into the picture of clinical value in patients seen in everyday practice – as opposed to those selected for clinical trials. There has also been a pipeline of papers and commentary about the shortcomings of the drug development process and the clinical trial system, with emphasis on highly costly phase III randomised controlled trials (RCTs) – often applied to a large population with little discrimination – and attendant issues such as regulatory burden, the declining proportion of research driven by academia versus pharma, and more generally the changing nature of cancer research, as drugs are targeted towards smaller 'personalised' groups.

In the middle of this highly complex debate is the regulator, principally the EMA in Europe and the FDA in the US. The regulatory system has been singled out as 'broken' by one high-profile commentator, Vinay Prasad, assistant professor of medicine at Oregon Health and Science University, who among his writing argued in the *British Medical Journal* last October that, at some point in the lifecycle of a cancer drug there needs to be demonstration of improved OS or QoL, if these were not demonstrated in the principal trials (*BMJ* 2017, 359:j4528).

Some say this should be before marketing authorisation by the regulator, others when surrogate measures turn out later to show benefit. But as Prasad says, the answer should not be 'never' – a point he makes by citing two studies from the US and Europe that show that a majority of drugs enter the market without showing OS or QoL, and only about 15% of these have since done so. It's evidence, he says, of the breakdown in the regulatory system.

The study from Europe, published in the *BMJ* (2017, 359:j4530), was picked up by the mainstream media, fuelling the debate about the cost and value of new cancer drugs. It used ESMO's Magnitude of Clinical Benefit Scale (MCBS) to highlight that a majority of recently introduced agents fall well short of the highest levels of benefit. Other studies have shown no relationship between price and clinical benefit of FDA-approved drugs, and only 9 of 47 indications provided by the England's Cancer Drugs Fund scored highly using MCBS.

"A majority of drugs enter the market without showing OS or QoL, and only about 15% of these have since done so"

For Ian Tannock, another medical oncologist known for commentary on the cancer drug lifecycle, MCBS is a good example of a tool that could be used to improve the regulatory process – and in so doing could lead to drugs not being approved that otherwise would be. "Indeed, I am saying that certain drugs should not have been given marketing authorisation. I have no problem about approving a drug with a surrogate endpoint, provided there is follow up to show it helps

patients live longer or better. But that isn't happening with enough drugs. Even one that was withdrawn by the FDA, bevacizumab [Avastin] for breast cancer, is still in the NCCN [National Comprehensive Cancer Network] guidelines in the US. Approving drugs that do virtually nothing is very bad for patients and health systems. There must be connections with value and cost at the regulatory stage."

"I have no problem approving a drug with a surrogate endpoint, if there is follow up to show it helps patients live longer or better"

A recent and "ridiculous" example, he says, is FDA approval for using adjuvant sunitinib for renal cancer. "Of the two trials, a larger one of 2,000 or so patients was totally negative, and a smaller one of 600 was only positive for progression-free survival but not for overall survival, and it has substantial toxicity." There is a big difference between results such as this and those for clearly efficacious drugs, he notes, mentioning abiraterone for prostate cancer and the immunotherapy drugs for melanoma. Plots of the survival curves tell the story – those with little value show no significant overall survival benefit over time compared with the control, while effective drugs tend to show either a significant separation or no initial survival differences, but then a 'tail' for a small number of patients showing large effect.

"We do have some great new drugs," says Tannock. "But I am concerned for patients who have little idea how to judge which ones are effective and end up selling everything to get them."

He argues that the progression-free survival (PFS) findings from trials may be biased, citing the BOLERO-2 trial, which showed that adding everolimus – an mTOR inhibitor – to exemestane, doubled PFS in patients with advanced HER2+ breast cancer. "But toxicity was such that 25% of patients left the trial – and while the PFS was impressive, longer-term survival was negative. If you have an agent that improves PFS with minimal toxicity, such as aromatase inhibitors, that's fine, but for those with high toxicity such as everolimus or sunitinib it is misguided to approve them."

Tannock also notes that studies show a clinic that has run a trial and seen modest PFS can then see overall harm using the same drug in clinical practice on a mixed patient group that includes patients with comorbidities.

In a commentary entitled 'Relevance of randomised controlled trials in oncology', Tannock and colleagues say the design and reporting of many RCTs can render their results of little relevance to clinical practice, and they argue that the bar for demonstrating clinical benefit should be raised for drug registration (*Lancet Oncol* 2016, 17(12):e560-e567). He feels that it should not be necessary to enrol thousands of patients to detect statistical significance if the drug is really of benefit compared with risk – and that using a certain '*P*-value' to prove a hypothesis is a misreading of the statistical process – as the American Statistical Society has itself been at pains to point out.

Tannock is not going as far as to call the regulatory system broken, but says it needs to be revised. He argues that the EMA and FDA are too constrained by their current remit.

We're doing our job, say regulators

Francesco Pignatti, head of oncology at the EMA, rejects the idea that the methodology they use for risk–benefit assessment is flawed or has too low a threshold for approval. "I do not think regulators need to change their regulatory value judgements about benefits and risks. But when we are recommending a conditional approval to bring early access to a drug for patients, there are uncertainties. We can sometimes assume that what looks like a remarkably high response rate will translate into a significant effect on OS, but this is still an assumption. We have the legal tools to take these uncertainties into account, but it needs to be understood that the expected benefits may not materialise. It does not mean the net risk–benefit is negative and that we should not have approved the drug, as there may be good reasons why such benefits are difficult to observe, or because there are other types of benefits, such as controlling the disease and associated symptoms for longer.

"That we are over-reliant on statistical significance is a myth. In our reports we go far beyond a tick box approach to approvals, carefully weighing all sources of evidence. But I believe that in specific situations there is room for patients' choices and preferences about drugs, even if

they may have a relatively low probability of success, and that our approvals should not be influenced by cost. We are constantly criticised for approving too many or too few drugs, but healthcare systems are stretched by cost – that should be the focus, not the regulatory threshold. If drugs were cheaper we wouldn't be talking so much about it."

Pignatti took the unusual step of responding to the *BMJ* paper – among his points are that OS can be hard to detect when patients switch to the test drug in an RCT, or when subsequent lines of drugs are used; and that, in specific situations, PFS is a valid efficacy endpoint.

He also defended single-arm trials, saying that in some cases they are justified as evidence instead of RCTs, and argued that QoL is often hard to measure. "It just is not the case that the only way to show that a drug has benefits is to show a significant improvement in OS – in certain cases doctors have for years been convinced by other types of evidence such as high response rates and response duration, or long time to progression of the disease," he says.

"Healthcare systems are stretched by cost. That should be the focus, not the regulatory threshold"

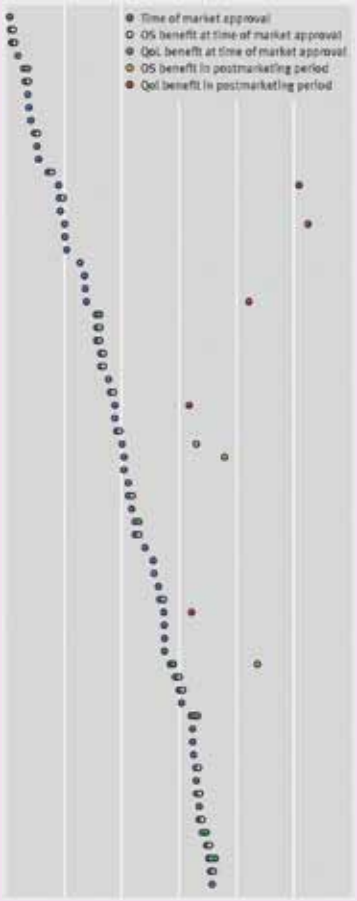
Of course, some cancer drugs are rejected by the EMA owing mostly to lack of efficacy from RCT evidence: "When I last looked it was about one in four," says Pignatti, adding that it is important for the regulator to help improve the drug lifecycle at both ends. He mentions refining tools for studying drugs for rare cancers, where a single-arm study may be the only option, and taking into account other research such as real world observational studies. Closer collaboration with HTA organisations to build an understanding of real world effectiveness is also underway, and national HTA organisations are also advancing in European harmonisation among themselves.

Pignatti points out that the EMA has been transparent in guidelines and reports in discussing the scientific and organisational issues involved in, say, early access to cancer drugs and the challenges of setting thresholds for new agents, and how careful planning of development and study design can help regulatory and post-marketing follow up.

It is critical, he stresses, that all actors in the drug lifecycle have clarity about what the objectives, roles and boundaries are, and that there is transparent debate about these issues, as the picture is getting yet more complex – and costly – with treatments such as CAR-T cell immunotherapy on the horizon. "We make complex decisions and choices in other fields, such as education, all the time with stakeholders that have different objectives that are sometimes conflicting. Healthcare is no different," he says.

Markus Hartmann, a consultant who works with both pharma and academic clinical researchers, argues regulators are right to approve drugs even if the benefit–risk equation is small. He says that oncology is multimodal and proceeding in a multitude of small steps, and it is interdisciplinary action that mostly makes the best steps. "We also have much better understanding of genetic oncology and the subtypes

Overall survival and QoL: what we know



From 2009 to 2013, the European Medicines Agency approved 48 cancer drugs for 68 indications. Of the 44 drug indications that did not show a survival benefit at time of approval, and with a median of 5.4 years' follow up (3.3–8.1 yrs), three (7%) were subsequently shown to extend life after market entry, and five (11%) were associated with some improvements in quality of life.

The figure was adapted (details of agents and indications excluded) from C Davis et al. (2017) *BMJ* 359:bmj.j4530, and reprinted under a Creative Commons licence.
Details of the agents and indications referred to in this figure can be found in the original (open access) article.

in cancers – it may seem we have a lot of drugs approved for some cancers, but do we in fact have enough to get the best response rate across the subtypes?"

He agrees, however, that the current system is not sustainable, "...where we see countries such as some in Eastern Europe that cannot afford to give drugs such as the new immunotherapies, and in the UK up to 40% of approved novel drugs are not making the final step on their way towards clinical routine use."

But he argues that high drug prices are in part the result of the high costs of meeting regulatory demands, which he says used to be far less stringent in the days when most clinical trials were run by cooperative groups rather than commercial enterprises.

He sees regulatory moves towards greater use of conditional and accelerated licensing – and more recently adaptive licensing – which allow phased approval through what the FDA calls "progressive reduction of uncertainty", as signs of a rollback.

Is initial uncertainty really being reduced?

Adaptive licensing has though come under fire, again in the *BMJ*, where authors say that it "seems to be poised to weaken many of the regulatory changes that thalidomide produced", and "phase II studies do not provide enough data to make good decisions about efficacy and safety; post-marketing studies are often delayed for prolonged periods and even when these studies are done regulatory authorities are slow to act on negative evidence; reliance on real world data is not a substitute for well-done RCTs; and once drugs are on the market abandoning them is extremely difficult" (*BMJ* 2016, 354:i4437).

In a short paper in 2017, Pignatti and colleagues recognise the challenges in designing confirmatory studies that follow on from approval and could offer HTA agencies some of the information they need to make decisions (*Clin Pharmacol Ther* 2017, 101:577–9). "We as regulators too rarely meet well-planned, well-powered, and well-executed exploratory studies." By this they mean studies that complement the usual data on exposure/adverse events/tumour response with, for example, "use of functional imaging and tumour and liquid biopsies, with the aim of stratifying drug development, and an early confirmatory approach with respect to predictors of patient benefit."

They also mention defining factors for resistance and tumour heterogeneity after treatment and, on immunotherapy checkpoint inhibitors specifically, they say that it has been "futile" to expect cooperation among companies in developing candidate assays. They even suggest that a "payers' cooperative" in the EU to investigate cost-effective combinations in immune-oncology may be feasible.

This could also feed into efficient mechanisms of withdrawing ineffective drugs from the market, which Hartmann agrees is needed as a balance. "If we have that, we can take more risks, and it could also cut prices."

Indeed, it is the rigour of post-marketing surveillance and regulation that seems to be the major concern of oncologists such as Tannock and Prasad, as they do recognise that surrogate measures are valid means of approving some drugs.

ESMO's clinical benefit scale

This is also where ESMO's Magnitude of Clinical Benefit Scale comes in (one of a number of tools for measuring clinical benefit of cancer drugs – the other main one being ASCO's Value Framework). Elisabeth de Vries, a Dutch medical oncologist and chair of ESMO's MCBS working group, says the scale was developed to address decision making in accessing relevant drugs, especially given limited budgets in certain European countries. "Not everyone was excited about this initially – the outside world was not sure what would happen if oncologists grade drugs and whether it would be good for patients," she comments. But she says it has received largely favourable attention, as most countries have affordability problems.

"The scale's methodology is transparent and anyone can use it to grade cancer drugs"

The scale relies on data from the clinical trials that led to drug approval, and can take into account a range of factors – OS/PFS, hazard ratio, long-term survival, response rate, prognosis, QoL and toxicity. Serious toxicity can downgrade the score, but fewer effects that bother patients can upgrade it. As de Vries says, it is unrealistic to expect all medical oncologists to be on top of the latest papers on all new drugs, so scores from MCBS give them a way to synthesise information for decision

making (and Tannock praises the scale as being easy to use).

It is also the case, she adds, if there is additional data from subsequent publications regarding a given drug – on quality of life or on side effects, for example – the drug is graded again. ESMO is sufficiently confident with field testing to now incorporate the grades into its guidelines, but so far these only include drugs approved since 2016. New data can then mean drug scores can be up- or downgraded.

De Vries says there are misunderstandings about the scale. For example, in the *BMJ* paper that turned the spotlight on approvals (and which used the MCBS to score 48 drugs the EMA approved between 2009 to 2013), she and colleagues say in a reply that it is incorrect to say that the MCBS sets a "threshold for clinical meaningfulness", and that only the highest scores matter (these are grades A and B for treatments of curative intent and 4 and 5 for non-curative). They point out that those with a grade 3 score are mostly approved for example by the Israeli HTA body, but those below mostly not. She adds that what is clinically meaningful also depends on the oncologist and patient. "Three more months may be extremely valuable if you want to see your first grandchild or to attend your daughter's wedding."

© Mauro Ferrero

ESMO is in discussion about the MCBS with the HTA agencies in Germany and France, to see how it can be used in their healthcare systems. Countries outside Europe, including India (for its National Cancer Grid), are also considering adopting the scale, says de Vries. The European Hematology Association is currently testing the MCBS in the non-solid tumour field. As she adds, the scale's methodology is transparent and anyone can use it to grade cancer drugs, while current HTA methodologies tend to be more proprietary.

Could pharma use tools such as MCBS to improve drug development? "We hope it will lead to more relevant clinical trials," says de Vries. An example, although investigator-driven, is the SONIA trial in the Netherlands – an advanced breast cancer study on the CDK4/6 inhibitor palbociclib. "They want to see at least a grade 4 according to MCBS for 1st vs 2nd line therapy, QoL and OS."

But the European Federation of Pharmaceutical Industries and Associations (EFPIA) have lined up with the EMA in criticising the *BMJ* paper, saying that the study

predominantly focused on clinical trials, rather than on real world data on patient outcomes, and quoting Pignatti saying, "Restricting approvals of cancer medicines only to situations where there is indisputable evidence of improvement in OS or QoL will not improve the outlook for cancer patients in the EU. On the contrary, such an approach may deprive patients of early access to effective medicines for patients in urgent need."

A greater role for clinicians and patients?

The idea of putting oncologists and patients much more at the centre of how treatments are developed and deployed is perhaps the most important theme that is emerging from the focus on clinical benefit. As de Vries says, there has been the view that doctors take care of patients, and others decide which drugs are available to them. She notes though that in the Netherlands, there is a longstanding committee where oncologists, especially, can decide that certain drugs are not relevant to give to patients.

This may become more usual – oncologists at Sloan Kettering in New York, for example, made the news when they decided they wouldn't use an expensive new colon cancer drug, although cost was a key factor.

This may well have prompted current moves in the US to follow Europe's lead in investigating value-based pricing for drugs – the more a drug proves effective for a patient, the more a company can charge. Hartmann, for one, says he is glad that de Vries and colleagues are "bringing back oncologists into the story".

Involving patients is harder, but a key goal. Pignatti says his main reservation about the current MCBS is that it needs validation with patients to take it forward as a clinical decision-making tool, apart from use in the HTA field. "This scale was never designed for the purpose of clinical decision making and was mainly constructed on the basis of oncologists' views rather than a systematic evaluation of patient preferences," he has said.

De Vries says the scale has been welcomed by patient advocacy organisations, and that help from patients will certainly guide future versions of the scale, and cautions that it is still early days – "We only launched the first version in 2015." The EMA is also investigating whether patients could be part of the regulatory process – for example in a pilot study on patient preferences (*Clin Pharmacol Ther* 2016, 99:548–54).

Patient advocate, Bettina Ryll, founder of Melanoma Patient Network Europe, who also chairs ESMO's patient advocates working group, is another who takes issue with the *BMJ* paper and the general sentiment that too many drugs are poor. "The absence of evidence is not the evidence of absence," she says.

"In my experience people misunderstand the EMA's remit, even in the oncology community," adds Ryll. "It is not about approving drugs that are necessarily better than before, but drugs that are safe and do what they claim to do. We have HTA bodies to decide on their cost-effectiveness."

Ryll has strong words for the criticism that using surrogate endpoints in trials is not good enough. "These drugs save patients' lives while on trials. If you go back to the Helsinki Declaration, no interest can take precedence over that of a single research individual, so our first premise for any trial must be to save patients' lives. This is the reason why we look at PFS or any other surrogate marker, especially in oncology. However, this does not relieve us of the obligation to collect OS data afterwards and in the real world, not in an idealised trial population. There is an 'ivory tower' debate about the 'ideal' data set, independent of the human cost associated with it, which I find entirely unacceptable."

"There is an 'ivory tower' debate about the 'ideal' data set, independent of the human cost associated with it"

She also points out that the QoL measures are currently too unreliable to draw firm conclusions about lack of benefit (and if there is one point that everyone agrees with, it is that measuring QoL is hard and needs much more work – see also, 'PROMs put patients at the heart of research and care', p54).

New drugs such as checkpoint inhibitors do not necessarily behave like the blockbuster chemotherapy drugs of old, she adds, and it is not appropriate to use basic median measures of survival, when a drug such as ipilimumab has big effects in a small group (as Tannock also points out). "The best drugs can look bad if we don't treat them differently." She also cautions against judging drugs in isolation: "We need

a long-term strategy for survival, as we see now in melanoma where patients cycle between different therapies. Taking a drug out of a treatment landscape can risk the entire enterprise."

Collecting real world data is the answer

The critical stage for Ryll is generating data on drugs when they are in the clinic. "It's an evidence collection problem – the regulators won't fix that for us," she says, adding that she supports the adaptive approach and a move away from traditional RCTs – "We need an approach that enables both access and systematic learning, especially in situations of high unmet need.

"Also, I have people in my melanoma group who simply can't believe it is even ethical to randomise people; today's patients are way better informed and less willing to passively accept what is considered as 'research' by others."

A good example of the way forward, she comments, is the Dutch Melanoma Treatment Registry, set up in 2013 to track the treatments given to all patients with advanced melanoma in the Netherlands (see *EJC* 2017, 72:156–65).

"It's an evidence collection problem – the regulators won't fix that for us"

Ryll and advocate colleagues have run a workshop on the MCBS – she likes the tool as it provides a systematic way to evaluate clinical benefit independent of price. But, as she points out, it works best with mature data sets. "So it is weakest when we need it most, namely in situations of uncertainty, as it is reliant on RCTs. Patients often have to make decisions before that data becomes available, and don't have the luxury to wait. It is still a valuable way of thinking, but I believe we need different approaches to bridge this evidence gap."

De Vries points out that a recent MCBS revision does include single-arm studies aimed at orphan diseases and diseases with high unmet need. She notes also that MCBS can be used as educational tool to help oncologists interpret data from clinical trials and in journal club discussions regarding the efficacy of new treatments. (One of the big issues in the drug debate is indeed about understanding the clinical applicability of the trial results – if most oncologists don't understand hazard ratios, what chance for patients?)

There is probably no solution to all of the problems in trying to rank clinical benefit, as Alberto Sobrero, an Italian medical oncologist who has been on the MCBS taskforce, notes in an ESMO Award presentation (*ESMO Open* – 2017, 2(1):e000157). For example: "A prohibitive task in oncology is finding equivalences between extent of benefit in terms of OS and … other endpoints such as PFS." Clinical benefit is also an integration between efficacy, toxicity and what he calls 'convenience' – trips to hospital, ability to work, etc. Above all, tools need to have a "sound scientific basis, something as close as possible to what patients value most and something easily understandable by all other stakeholders." But he believes the MCBS and other tools are a good start.

If it is true that the current system is not sustainable, the way forward seems to be for a much more open debate about the uncertainties and choices among all parties, as Pignatti advocates, while bringing tools such as MCBS to bear, with the eye on improving trial design and biomarkers.

The way forward seems to be for a much more open debate about the uncertainties and choice among all parties

But the key tension between the regulators and their supporters, and critics such as Prasad, looks set to continue. "It is only because regulators are lax that payers have had to wield the stick," Prasad has said. "The default path to market for all cancer drugs should include rigorous testing against the best standard of care in randomised trials powered to rule in or rule out a clinically meaningful difference in patient-centred outcomes in a representative population."

At stake though is also speed. It can't be right that abiraterone, for example, took some 20 years to enter clinical practice, and as an academically developed drug it could – and should – be far cheaper, which implies a different sort of regulation or industrial policy.

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Value and cancer – this is how we reverse the decline

'Value' is the latest buzzword in cancer: value-based pricing, delivering value for cancer care, enhancing the value offering for cancer technologies... It makes sense, as focusing on the value of interventions we invest in is the only way to stop wasting precious health resources on poor value healthcare interventions and missing out on interventions that could offer particularly good value.

And yet 'value' is among the most misunderstood and misused words in the health policy lexicon. This reflects, in part, an inherent confusion among clinicians and policy makers between the concepts of value, benefit, price, expenditure, and affordability. But it also reflects a perception that the value of a given healthcare technology is not amenable to objective measurement – like beauty, its value lies 'in the eye of the beholder'. This can certainly be the impression given by the many arguments over how value should be defined, as producers of healthcare technologies, healthcare professionals, patients and payers seek to influence the way decisions are made regarding what should be reimbursed and at what price. But the impression is not accurate.

The value of a healthcare intervention can be measured, objectively, in a reliable and meaningful way, by using transparent, fair and robust processes. Here's how.

The value of an intervention is defined as its cost compared to its benefit in terms of improving length and/or quality of life – so the value of a given intervention will be higher the greater the benefit it offers, and the lower its cost.

The benefit of a healthcare intervention is measured, most often, according to its impact on the number of additional years patients live, and the quality of that life, and is expressed in quality-adjusted life years, or QALYs. So the more years of life a given intervention can offer a particular group of patients, and the better the quality of their lives, the higher its QALY.

The idea behind 'value-based pricing', which some suggest would be better described as 'benefit-based pricing', is that, to achieve the maximum impact from limited funds, new products should be priced at the level at which the health benefits they offer (measured in QALYs) are no less than the health benefits that could be achieved if that same money were spent a different way.

The question of what constitutes a 'fair price' per QALY is likely to vary from country to country – in general, wealthier countries will have more money available to spend than poorer ones, and will be willing to pay more for the same health benefit.

Using these basic 'value for money' principles, every country should be able to work out, using a transparent, fair and robust process, what cost per QALY their health systems are able and willing to pay, and apply that process to negotiating prices for new healthcare interventions.

The confusion arises when decision makers start to include additional considerations on top of patient benefit in determining what they are willing to pay for a new intervention.

There are certainly legitimate issues, for instance around fair reward for innovation or for addressing unmet and/or particularly burdensome needs.

But much of the discourse around 'value' has less of a rational basis. Even credible organisations such as US Institute of Medicine are adding in highly subjective areas for

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

consideration in determining value (such as fairness). Moreover, 'value' is increasingly being used as some sort of abstract philosophical term, as in: 'innovation is valuable for patients', which – intentionally or not – further muddies the water.

Many so-called 'innovations' are in reality not innovative at all, because they do not deliver clinically meaningful benefit for their specific marketing indication. For example, 71% of all new medicines in the last five years for lung, breast and GI cancers failed to reach thresholds for delivering clinically meaningful benefit. Study after study has also shown that there is no correlation between the price set for new cancer technologies such as medicines and their impact on patient outcomes.

And if we are to discuss paying a premium for innovation, why is this done only with new cancer medicines but rarely with other types of intervention? And while medicines are at least increasingly being scrutinised by regulators to determine what benefit they offer patients, new technologies such as robotic surgery and new radiotherapy modalities are routinely introduced into cancer care without any attempt to establish whether the impact on patient outcomes justifies the costs.

Perhaps the biggest problem of all is that many countries still have no systems in place that are capable of conducting rational, transparent and evidenced-based evaluations of new healthcare technologies, as was so starkly revealed by the recent EU Commission review of health technology assessment across Europe (bit.ly/EC_HTA).

One result is that decisions on how and where to invest finite healthcare resources can be skewed by hyped marketing campaigns supported by the complicity of the clinical community, who relish the chance to try out and work with new drugs and high-tech equipment. It's little wonder that people end up with the impression that value is all about perceptions and perspectives, and cannot be measured in a rational and reliable way.

The inevitable result is overpriced underperforming cancer care that is becoming inaccessible to an increasing number of Europe's citizens. This does not need to happen.

The riches and creativity of cancer research are extraordinary and deserve to be properly used for the benefit of everyone. But it means we have to be honest about what they can and cannot deliver in terms of patient benefit.

- ***Every country*** needs an equivalent to the UK's NICE, paid from the public expenditure, that is capable of assessing the value of all new health technologies.
- ***Payers*** need to pay a fair price for a clinically meaningful improvement in outcomes.
- ***Countries*** need to put a stop to practices such as the parallel drugs trade, which cheat the system, by exporting drugs bought in countries that have negotiated a lower price on to countries where the agreed price is higher.
- ***The industry*** for its part needs to re-engineer its pricing practices and put a stop to its own tricks for cheating the system, which include widespread use of 'product hopping', 'evergreening', and 'pay for delay' that obstruct competition from generics, as recently detailed by the American Society of Clinical Oncology (bit.ly/ASCO_drugpricing).
- This will require major policy shifts by the ***shareholders,*** most of whom are banks, and an end to the practice of share overvaluation through buy-back schemes, as detailed by Harvard's William Lazonick over many years of research.
- ***Public funders*** – both government and charities – need to stop the slavish alignment of their funding with the interests of the pharmaceutical industry and the private sector in general. It does no one any favours, not even industry. Personalised/precision medicine will only deliver when proper support for research and innovation is given across whole systems – surgery, pathology, palliative care, radiotherapy. And that is a public good. Public research funding needs to be far more balanced than it currently is.
- ***The clinical and scientific cancer research community*** needs to stop designing and running trials that have no chance of delivering clinically meaningful benefit, and
- ***'We' – charities, professional organisations, academic centres and the media*** – need to stop pumping out hype into the public domain, which is presenting a seriously distorted picture of reality.

Somehow we have managed to get ourselves into a vicious cycle where everything new has to be 'management changing' or 'a blockbuster'. Getting ourselves out of this is not rocket science, but nor is it easy, or it would already have happened. The 'system' has to be constantly challenged. The good news is that, in general, everyone now recognises the problems. That's half the battle. We now need to act to deliver cancer research and care of real value.

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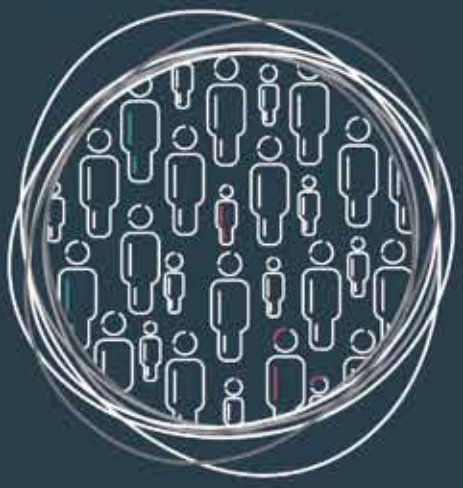

All.Can patient survey

Improving outcomes for patients, focusing on efficiency

You can help shape the future of cancer care

In healthcare, inefficiency is often caused by not focusing on what matters most to patients.

All.Can is gathering patient insights on where inefficiencies occur in cancer care. The All.Can Patient Survey asks where patients feel resources could have been better used to improve their care experience and outcomes. Findings will inform policy discussions on how we can improve the sustainability of cancer care.

The survey will be run in 10 countries, with the pilot beginning in the UK.

For more information and to take part, please visit
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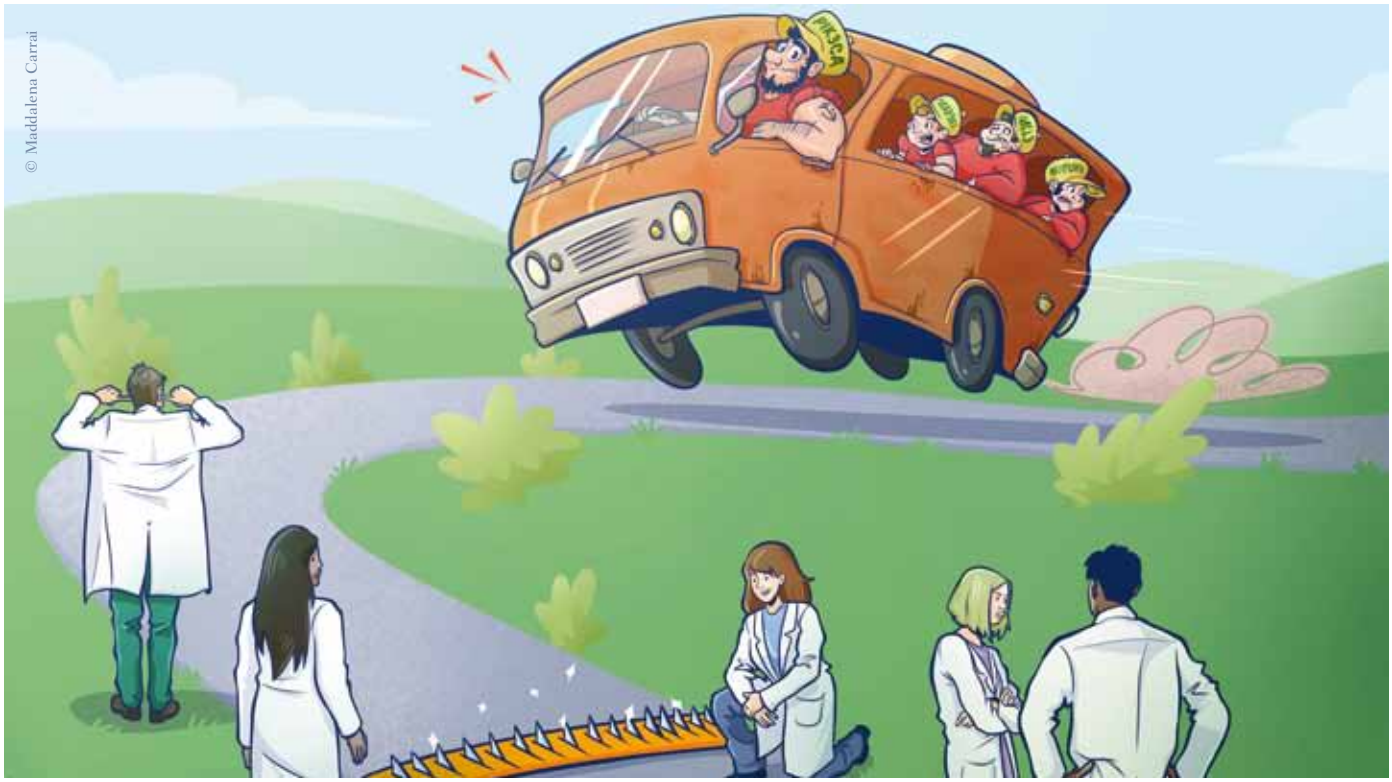
All.Can is a multi-stakeholder initiative involving patient, clinical, academic and industry experts as well as policymakers. We aim to help define better solutions for sustainable cancer care and improve patient outcomes in the future. The All.Can initiative is made possible with financial support from Bristol-Myers Squibb (lead sponsor), Amgen, MSD and Johnson & Johnson (co-sponsors).



Don't shoot the driver!

It's about taxonomy more than targets

Could tailoring treatments to broad taxonomies work where targeting individual – or even multiple – genetic mutations has not? A growing number of researchers working on specific tumour types and/or across tumours believe this integrative approach, involving 'precision classification', could be the way to go. **Janet Fricker** talked to some of the key players.

In a prescient *Cancer World* guest editorial published in 2005, Alberto Costa, breast surgeon and head of the European School of Oncology, wrote, "The whole concept of breast cancer as a single disease is now dead, and we therefore need to make fundamental changes in the way we approach treatment decisions."

The editorial was a response to the 2005 St Gallen conference, which had concluded that breast cancer should be characterised according to eight elements: size, histological type, grading, hormone receptor status, lymph node status, proliferation index (ki67), cErbB2 status, and the presence or absence of peritumour vascular invasion.

In 2018, routine clinical assessment of breast cancer still comprises morphological assessment (size, grade, lymph node status), and testing for oestrogen and progesterone receptors (ER and PR) and HER2. Such information allows pathologists to classify breast

cancer into four subtypes: luminal A cancers (usually ER+ and/or PR+ with a low proliferation index); luminal B cancers (ER+ and/or PR+ and high proliferation index); HER2-amplified cancers (can be either ER/PR positive or negative, but with high levels of HER2); and basal-like tumours (which are 'triple negative', i.e. negative for ER, PR and HER2).

However, it is now widely recognised that this grouping does not reliably predict how tumours behave.

"From our clinic experience we realised that breast cancer patients have very disparate outcomes and that it is a misnomer to call it a single disease, or even one with four subtypes," says Carlos Caldas, who in 2012 published a landmark study demonstrating that breast cancer is an 'umbrella term' for at least 10 separate diseases (*Nature* 2012, 486:346–52).

This new breast cancer stratification was validated in a subsequent paper by the Caldas group (*Genome Biology* 2014, 15:431).

"Personalised medicine is about good taxonomy. When treating bacterial infections you need good classification to know whether you are treating gram-positive or gram-negative infections. In much the same way, for effective treatment of cancer you need proper molecular stratification of tumours," says Caldas, from Cancer Research UK's Cambridge Institute.

A revolution in tumour pathology

In the intervening years the METABRIC project, a joint project between Caldas' group and Sam Aparicio's group at the University of British Columbia, has spurred a revolution in breast cancer stratification. The collaboration has been largely responsible for moving tumour classification beyond examining tissue under a microscope to pinpoint abnormal anatomy, to a system that incorporates extensive molecular profiling.

"Ultimately we hope that our 'iCluster' approach will help doctors treat diseases better based on specific genetic signatures"

In METABRIC (see box, p19), investigators used microarrays to delve into the DNA and RNA of tumours. They also tested each tumour sample for alterations in copy number, because copy number aberrations were known to dominate the breast cancer genomic landscape.

The resultant large-scale, multidimensional dataset, which incorporated samples from 2,000 women with breast cancer, together with data on their clinical outcomes, was navigated using novel high-performance computational and statistical techniques.

In an epic effort, the investigators sifted through gigabytes of information to extract meaningful patterns in an analytical approach known as 'data mining'.

The result was 10 integrative clusters, or 'iClusters' (see table, p19), which were later expanded to 11 clusters, after cluster 4 was further subdivided into tumours that were ER positive and negative (*Nature Communications* 2016, 7:11479).

"The basic tenet of medical practice is that the better you phenotype a disease, the more likely you are to treat it correctly," says Caldas, who initially trained at the University of Lisbon.

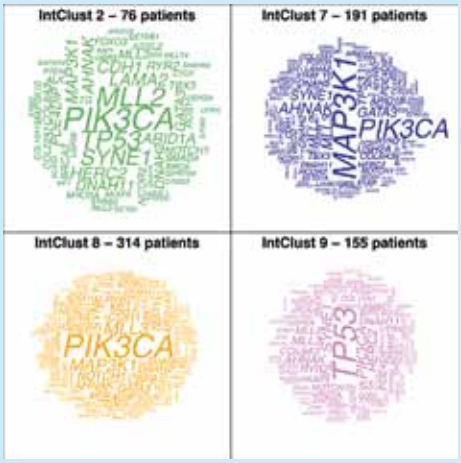
"Ultimately we hope that our 'iCluster' approach will help doctors treat diseases better based on specific genetic signatures."

The iCluster methodology, which has become known as 'integrative medicine' or 'precision categorisation', has since been utilised to explore a range of cancers, including:

- Prostate: divided into five subtypes by the CamCaP project (*EBioMedicine* 2015, 2:1133–44),
- Pancreatic: divided into four subtypes by Andrew Biankin (*Nature* 2015, 518:495–501),
- Colorectal: divided into four groups by Angurah Sadababdam (*Nature Medicine* 2015, 21:135–56),
- Bladder: divided into five subtypes by Seth Paul Lerner (*Cell* 2017, 171:540–556.e25),
- Melanoma: divided into four subtypes by researchers from The Cancer Genome Atlas Network (*Cell* 2015, 161:1681–96).

While the groups stratifying each of these cancer types all took broadly similar approaches, they analysed different combinations of data sets, including DNA and RNA, single point mutations, copy number, whole genomes and other properties of tumours.

Breast cancer integrative clusters (iClusters)



In a study looking at the somatic mutation profiles of breast cancers, Carlos Caldas sequenced 173 genes in samples taken from almost 2,500 patients with breast cancer, and showed that PIK3CA (coding mutations in 40.1% of the samples) and TP53 (35.4%) dominated the mutation landscape (*Nature Communications* 2016, 7:11479). Only five other genes harboured coding mutations in at least 10% of the samples: MUC16 (16.8%); AHNAK2 (16.2%); SYNE1 (12.0%); KMT2C – also known as MLL3 – (11.4%) and GATA3 (11.1%).
These word clouds illustrate the distributions of mutations in the 173 sequenced genes in four integrative clusters, with the size of each word corresponding to the relative frequency of the mutations observed for a given gene in each cluster.

Making sense of complexity

Initiatives like these are helping investigators to 'gain a handle' on the ecosystems involved in growth of tumours, and to start to acquire more of a holistic understanding of the complexity of cancer, by including information about a wider group of genes, says Caldas, who sees it as a pragmatic approach to dealing with massive complexity. "The idea that every tumour is different from all others represents an impossible task. Subdividing cancers into different subtypes provides the closest approximation that we can get to the truth," he says.

Andrew Biankin, from University of Glasgow, who now chairs the International Cancer Genome Consortium, agrees: "The integrative approach allows cancers to be broken down into manageable subtypes that help us to understand similarities and then design drugs against shared mechanisms."

Caldas stresses that the characterisation of breast cancer into subtypes has yet to affect the way patients are managed. However, he firmly believes that the 11 subtypes offer the eventual possibility of a platform to investigate new treatments.

"At the moment trials are more about the drug than the disease. Hopefully studies like METABRIC offer the possibility to change that and start to tailor treatments to the disease," says Caldas.

> "The clusters in effect provide a grouping of biomarkers that can be used to test new treatments"

In a recent paper (*Nature Communications* 2016, 7:11479), Caldas and colleagues investigated the frequency of 173 genetic mutations across 2,500 breast cancer patients, and showed that patients in the same iCluster demonstrated similar patterns of mutations (see above). Since some of these genes are known to be involved in the production of enzymes within human cells, they could provide targets for the development of new anti-cancer drugs.

A guide to diagnosis, prognosis and hopefully treatment

"The clusters in effect provide a grouping of biomarkers that can be used to test new treatments," said Heinz Zwierzina, from Innsbruck Medical University, who chairs the Cancer Drug Development Forum.

Caldas' next goal is to devise a simple molecular test that could be performed on routinely collected paraffin block samples, to prospectively assign patients to one of the 11 subtypes. Once patients have been characterised into the different subtypes it would then be possible to follow these subgroups in clinical trials to explore

The Molecular Taxonomy of Breast Cancer

Integrative cluster group	Copy number driver	Pathology biomarker class	DNA architecture	Dominant PAM50	Clinical characteristics (survival)
1	Chrs 17/ Chrs 20	ER+ (HER2+)	Simplex/firestorm (chrs 17q)	Luminal B	Intermediate
2	Chrs 11	ER+	Firestorm (chrs 11q)	Luminal A and B	Poor
3	Very few	ER+	Simplex/flat	Luminal A	Good
4	Very few	ER+/ER-	Sawtooth/flat	Luminal A (mixed)	Good (immune cells)
5	Chrs 17 (*HER2* gene)	ER-(ER+)/HER2+	Firestorm (chrs 17q)	Luminal B and HER2	Extremely poor (in pre-Herceptin cohorts)
6	8p deletion	ER+	Simplex/firestorm (chrs 8p/chrs 11q)	Luminal B	Intermediate
7	Chrs 16	ER+	Simplex (chrs 8q/ chrs 16q)	Luminal A	Good
8	Chrs 1, Chrs 16	ER+	Simplex (chrs 1q/ chrs 16q)	Luminal A	Good
9	Chrs 8/ Chrs 20	ER+ (ER-)	Simplex/firestorm (chrs 8q/chrs 20q)	Luminal B (mixed)	Intermediate
10	Chrs 5, Chrs 8, Chrs 10, Chrs 12	TNBC	Complex/sawtooth	Basal-like	Poor 5-year, good long-term if survival

PAM50 – breast cancer molecular subtyping in current use; Chrs – chromosome; ER – oestrogen receptor; TNBC – triple-negative breast carcinoma
Source: HG Russnes, OC Lingjærde, AL Børresen-Dale, and C Caldas (2017) *Am J Pathol* 187: 2152-62. © 2017. Reprinted with permission from Elsevier

The Molecular Taxonomy of Breast Cancer International Consortium (METABRIC) undertook an integrative analysis of tissues samples from breast cancer patients that resulted in the landmark definition of breast cancer as a constellation of 10 genomic-driver-based subtypes (*Nature* 2012, 486:346-52).

The project, representing the largest molecular profiling study ever undertaken, was led by Carlos Caldas, from Cambridge University, and Sam Aparicio, from the University of British Columbia, Canada.

For the analysis, investigators obtained 1,000 frozen breast cancer samples from five tumour banks in the UK and Canada. DNA and RNA were isolated from samples and then hybridised to microarrays (state of the art for 2011), which had around two million probes for DNA, RNA and increased copy numbers.

This research was enabled by the biobank infrastructure in both Cambridge and Vancouver, which allowed tumour samples to be linked with detailed information about clinical outcomes and treatment of patients. Remarkably, every patient in METABRIC now has had a minimum of 10 years' follow-up.

Additionally, blood samples from 550 patients were available, allowing the group to compare tumour DNA with normal DNA in individual patients. For individuals with no matched 'normal', their tumour DNA was compared to an average of 500 'normals'. From this approach, the team were able to identify when a copy number was not a tumour aberration, because some people had this pattern in normal DNA.

Investigators used computer algorithms to search for patterns, or integrative clusters, based on similarities in copy number variants, single nucleotide polymorphisms and somatic copy number aberrations, SNPs, and gene expression, and whether they shared similar outcomes. Altogether, the team identified 10 groups of tumours (listed above) that behave consistently. The team went on to validate these grouping with a second cohort of 1,000 biobank breast cancer samples and a third cohort of 7,500 biobank breast samples (*Genome Biol* 2014, 15:431).

More recently, the team have subdivided the fourth group into whether patients are oestrogen receptor positive or negative, providing 11 subgroups (*Nature Communications* 2016, 7:11479). Changes in copy number led to the identification of 40 putative cancer driver genes, including PIK3CA.

which agents work best for each.

To accelerate the drug testing process, Caldas and his team have developed a technique where human breast cells grown in mice can be removed to run further tests using experimental drugs *in vitro* (*Cell* 2016, 167: 260–74). The approach, says Caldas, reflects the biological reality of cancer more accurately than growing cells in plastic dishes, which is known to differ from the way cells grow inside the body. "Testing all the new treatments on patients with the 11 different breast cancer subtypes would take centuries and tens of thousands of patients. We hope this approach will help speed things up," he explains.

In addition to helping drug development, the integrative approach can be used to provide prognostic insights for patients. In breast cancer, for example, Caldas' team have found that 40% of patients with breast can-

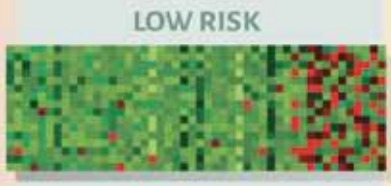
Timeline – Exploring the Cancer Genome

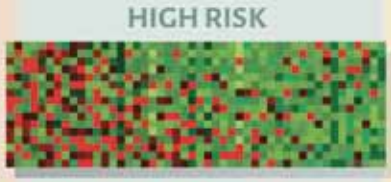
1977

Frank Sanger devised a method of 'sequencing' the four letter genetic code of DNA (Adenine, Cytosine, Guanine, Thymine), laying the foundations for unravelling the human genome. The technique, now known as Sanger sequencing, used specific tags to label each letter, allowing the code to be read out one letter at a time.

2002

Gene expression profiling was developed, allowing simultaneous measurement of all the genes expressed at a single point in time using microarrays (small probes detecting DNA or RNA). Researchers at the Netherlands Cancer Institute used the technology to identify a 70-gene signature that could discriminate between early breast cancers that are at high risk of metastasising, and those where the risk is low. The test was approved by the US FDA in 2007 as Mammaprint, and used in the clinic to help inform decisions on whether women operated for early breast cancer could safely be treated with adjuvant hormonal therapy alone, or whether they needed chemotherapy as well.





2003

The Human Genome Project published the first complete sequence of a normal human genome, consisting of the full set of genetic instructions encoded as DNA within 23 chromosomes. It took 15 years and $3 billion to sequence one genome, using capillary Sanger sequencing machines. The project identified approximately 25,000 genes in the human genome, and has formed the foundation of work investigating how changes in DNA are involved in cancer.

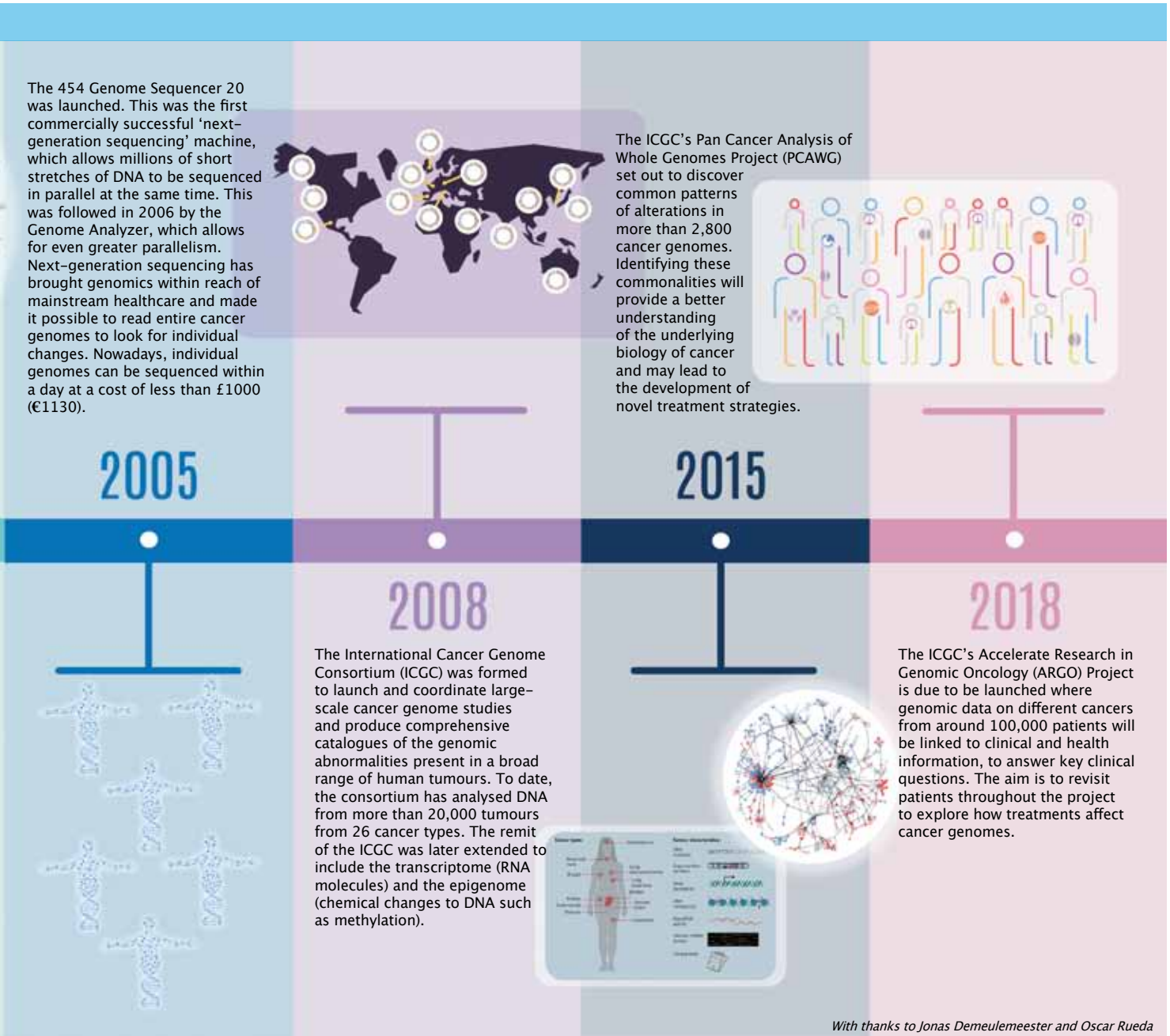
2005

The Cancer Genome Atlas (TCGA) was launched to catalogue genetic mutations responsible for cancer, using genome sequencing and bioinformatics. The project, funded by the US National Cancer Institute (NCI) and the National Human Genome Research Institute (NHGRI), first focused on characterisation of lung, glioblastoma and ovarian cancer, but later extended to characterise 33 cancer types (including 10 rare cancers). The goal was to provide publicly available datasets to help improve diagnostic methods and treatment standards, and to prevent cancer.

cer classified as cluster 2 or cluster 5 are alive 15 years after diagnosis, while 75% of those with cancers classified as cluster 3 or cluster 4 are alive at the same time point.

The same approach can also be used to identify the groups that would benefit from other treatment approaches, including surgery, radiotherapy and active surveillance. "In prostate cancer, molecular signatures associated with the most aggressive disease could be used to provide a rationale for early adjuvant treatment immediately after prostatectomy or for undertaking active surveillance," says Alastair Lamb, a prostate cancer surgeon from Oxford, who led the CamCaP project while training in Cambridge.

Integrative data can also help diagnosis, providing investigators with additional 'flags' to look for in liquid biopsies – an approach that uses



With thanks to Jonas Demeulemeester and Oscar Rueda

tumour DNA shed into the blood to track cancers in real time. "This could change the way we monitor patients and may be especially important for people with cancers that are difficult to reach, as taking a biopsy can sometimes be quite an invasive procedure," says Caldas.

Targeting mutations has been 'a major disappointment'

The integrative approach contrasts to the 'reductionist' approach of cancer personalised medicine, where investigators have focused on treating one component of the tumour, such as an aberrant enzyme or protein. "The successes of imatinib in CML, crizotinib in NSCLC and trastuzumab in breast cancer gave the impression that targeting single molecular alterations was easy," says Vassilis Golfinopoulos, Medical Director at EORTC, Europe's largest cancer clinical trials organisation. "However, the reality is that these agents represent only a tiny percentage of targeted drugs, with many more having failed to show significant efficacy in clinical trials."

Leif Ellisen, Program Director at the Massachusetts General Hospital Center for Breast Cancer and Professor of Medicine at Harvard Medical School, agrees, and says the reason why the approach of targeting a single gene or mutation has been so disappointing is because cancer has so many ways to subvert the effects of inhibiting one pathway.

He cites as an example the transitory impact BRAF inhibitors have in melanoma patients with the BRAF V6000 mutation, due to the ability of the cancer cells to get around the inhibited BRAF through activating the MAPK pathway.

Hopes of fixing the problem by targeting multiple pathways are largely failing in practice, he adds "because the toxicity is additive, with the result that combinations aren't tolerated."

"By exploring complex data we can identify potential common denominators that would not be so open to developing resistance"

"Taking into account the heterogeneity of cancer, it's highly unlikely that many tumours would be regulated by a single driver," says Jan Brábek, a cell biologist from the Charles University, Prague, with a special research interest in cancer cell invasiveness and metastasis. "It's only by exploring complex data that we can hope to find patterns of drivers and identify potential common denominators that would not be so open to developing resistance."

The new 'integrative' paradigm

To explain the potential of integrative medicine, Brábek uses the analogy of a 'getaway' car in a bank robbery. "If you shoot one of the drivers it's all too easy for another to take over the wheel, which is in effect what happens with resistance. However, if you target more fundamental mechanisms, such as shooting the wheels, you can prevent the possibility of anyone else being able to take over. This enables you to stop the car completely."

Possibilities for more fundamental agents that could be explored in the 'iCluster' subgroups, he suggests, could include anti-invasive and anti-metastatic agents and drugs targeting tumour metabolism.

Integrating new types of data into the taxonomy

New concepts and approaches to exploring the cancer genome are continually becoming available, which could further refine the iCluster classifications

One concept is that the tumours could in theory contain a number of different iClusters side by side. The evidence for this comes from Charles Swanton, now at the Francis Crick Institute, London, who analysed the entire genomes of seven individual samples taken from a single renal tumour, and found that only around one-third of more than a hundred separate mutations he identified were present in all samples (*NEJM* 2012, 366:883–92).

As point mutations and copy number aberrations tend to change over the course of the illness, account also needs to be taken of how cancer gene expression evolves with time and whether iCluster definitions might change.

Serena Nik-Zainal, from the Wellcome Sanger Institute, Cambridge, has been characterising patterns of mutations, known as 'mutational signatures', which include base substitutions, small insertions/deletions, rearrangements and copy number changes.

"Whole genome sequencing allows

us to read every single mutation in a cancer genome, which includes not just 'drivers' but also passenger mutations as well," says Nik-Zainal, who adds that, while passenger mutations may not have caused the initial cancer they can have significant effects on the biology of tumours.

In the first paper, Nik-Zainal explored the whole genome sequence of 21 breast cancers and created a catalogue of more than 200,000 different mutations that had occurred over the course of the patient's life (*Cell* 2012, 149:994–1007).

In a second study of the genomes of 560 women with breast cancer, Nik-Zainal found five new genes associated with breast cancer and 13 new mutational signatures influencing tumour development. (*Nature* 2016, 534:47–54*; Nature Communications* 2016, 7:11383).

"New concepts and approaches to exploring the cancer genome are continually becoming available"

Nik-Zainal is now working with Caldas, Jean Abraham and others in the Personalised Breast Cancer Project, launched in Cambridge at the end of 2016, to combine the mutational signatures obtained from a highly detailed DNA profile of 2,250 breast cancer patients with the iCluster subgroup classifier (to date more than 200 patients have been recruited into this clinical molecular study). "In effect we are combining two integrative approaches to provide further integration, to see if we can split patients into yet smaller cohorts to better inform treatment decisions," Nik-Zainal explains.

Unfazed by the prospect of future subdivisions making his 11 subgroups obsolete, Caldas draws comparisons to plant taxonomy. "Each subtype can be considered as a type of tree. One subgroup is composed of olive trees, another of pine trees, and another of beech trees. While all olive trees are not identical, the pattern of their branches, leaves and flowers are similar and very different from those of pine. We can be confident that the olive tree will not evolve into the pine tree," he said.

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METASTATIC BREAST CANCER POLICY ROADMAP

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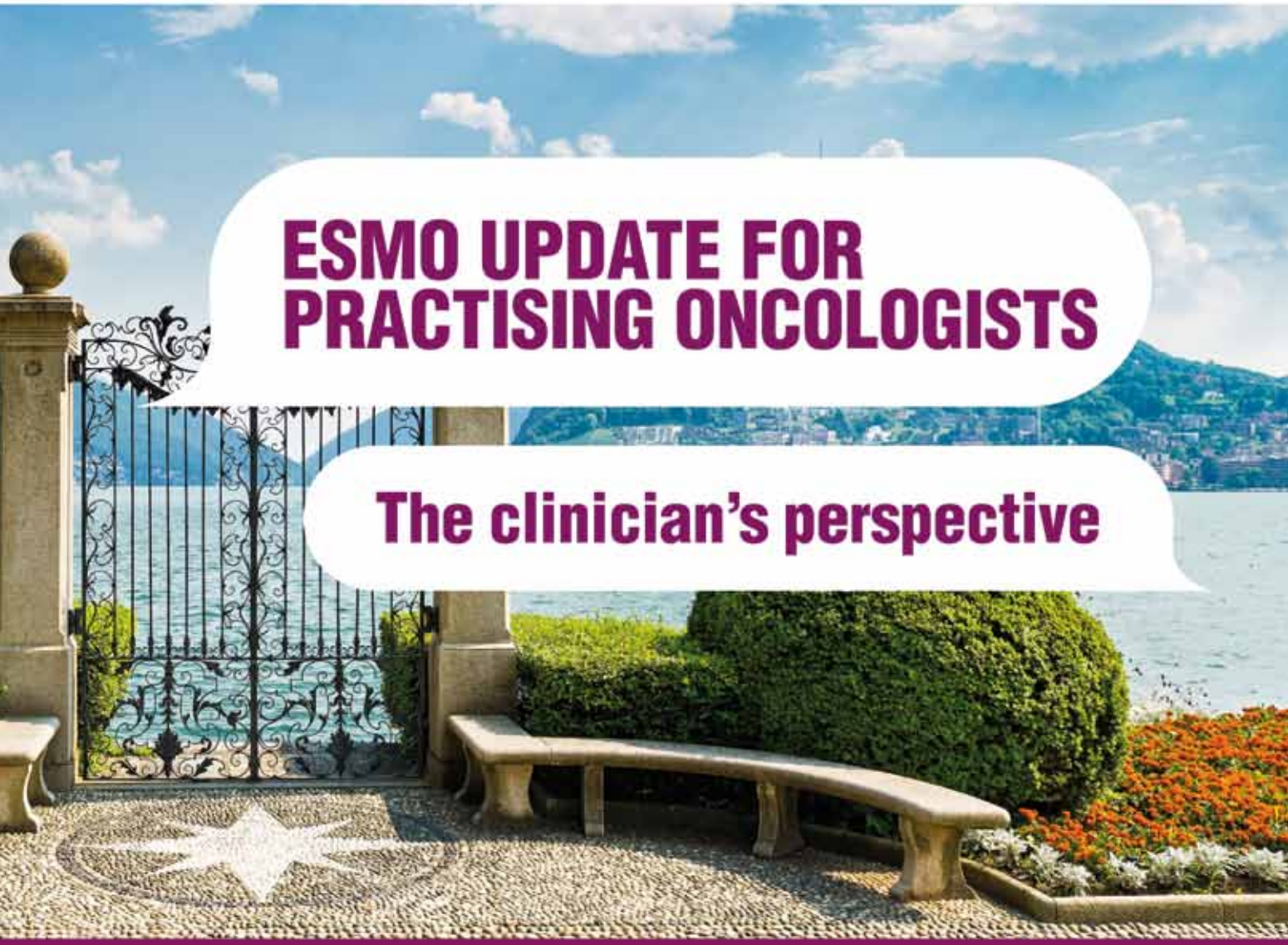

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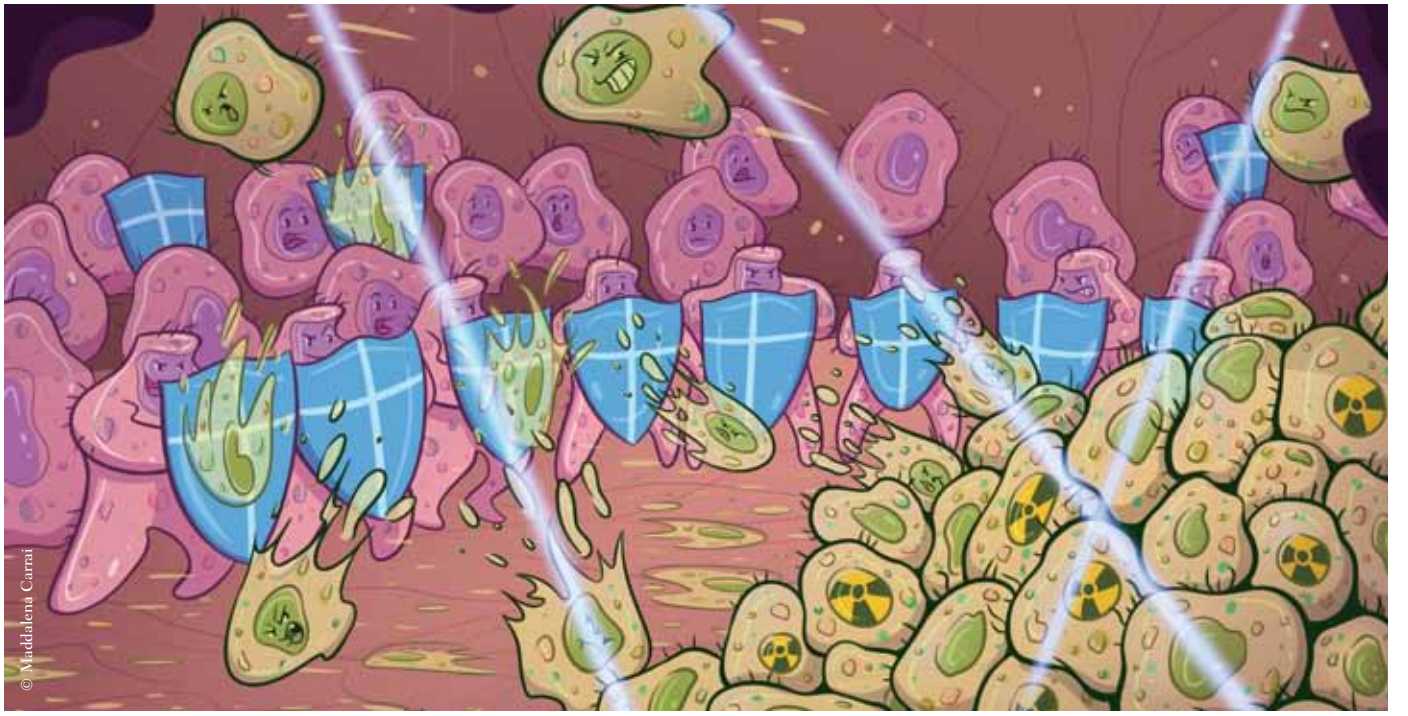


Collateral damage

How does treating the primary affect risk of a secondary?

Most solid tumours will prove fatal if they are not treated with surgery and/or radiotherapy and medical therapies. But evidence is building to show that treating the primary may raise the risk of metastatic spread. **Sophie Fessl** looks at the evidence and the implications.

Even after treatment, patients with seemingly locoregionally defined solid tumours frequently die from metastases that may only appear several years down the line. These may arise from so-called micrometastases – clinically undetectable remote tumour growths that formed even before treatment began. Or they may arise after treatment, in cases where the treatment failed to control the primary tumour. But clinicians and researchers have been aware for some time now of a third, somewhat paradoxical, possibility: that cancer therapy, intended to treat and cure the disease, may set in motion a cascade of events in the patient that supports the formation of distant metastases. As the evidence for this process extends from surgery to include other types of therapy, questions are beginning to be asked about just how much of a danger is posed by this process, and what can be done to mitigate the risks.

Circulating tumour cells (CTCs)

have been used as a prognostic factor in different cancer types, indicating a correlation between tumour cells in the bloodstream and disease progression. In cancer surgery, evidence points to CTCs as potentially causative factors in metastasis: surgical interventions have been reported to be linked to an increase in CTCs, and levels of CTCs during an operation can predict the likelihood of disease recurrence. Tumours can, rarely, form along the needle track left during biopsy. Changes in technique during and surrounding surgery are even being implemented to reduce the risk of metastases forming.

But a causative link between CTCs and cancer therapy may not be limited just to surgery. Research led by Michael MacManus, a radiation oncologist at the Peter MacCallum Cancer Centre in Victoria, Australia, has shown that radiotherapy in patients with non-small-cell lung cancer can mobilise CTCs. MacManus explains the rationale behind the study. "We wondered: What happens to the cellular debris when radiotherapy rapidly kills off a large tumour? As large numbers of cells may flood the lymphatic system during a course of radiotherapy, might tumour cells spill over into the circulation? To our great surprise, in our study we found that radiation therapy in non-small-cell lung cancer patients can indeed mobilise viable tumour cells into the circulation. We were the first to show that this mobilisation can occur during a course of radiotherapy."

Radiotherapy can promote circulating tumour cells

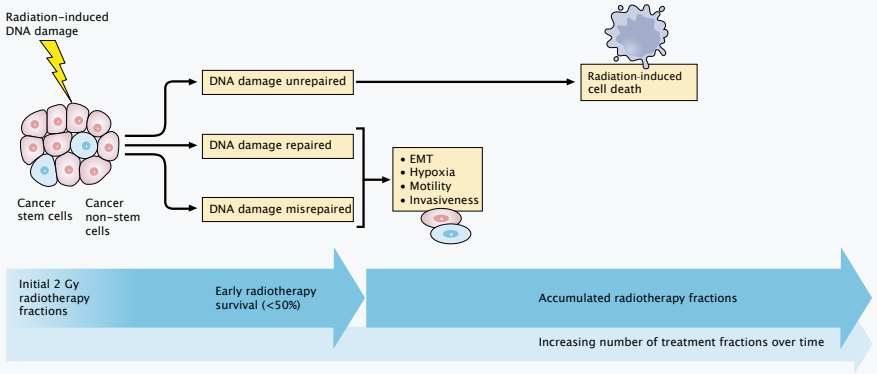
In a recent review on how therapeutic interventions might affect the risk of metastasis through circulating tumour cells (*Nat Rev Clin Oncol* 2017, 14:32–44), MacManus proposes several ways in which radiotherapy may enable tumour cells to acquire properties that allow them to spread more easily and subsequently form metastases. In the later phase of fractionated radiotherapy, if treatment is successful, the high cumulative dose of radiation means that tumour cells cannot reproduce any more. But in the early stages of radiotherapy, up to one half of irradiated tumour cells survive and may escape to the circulation.

This may happen through the impact of the radiation in disrupting the tumour architecture, leading to tumour cells entering the circulation either directly into the draining veins, or indirectly via the lymphatic system.

Preclinical studies show that radiotherapy can make irradiated tumour cells more aggressive than non-treated cells. In animal models, changes in gene regulation in irradiated cells are seen in genes associated with radioresistance, tumour aggressiveness, hypoxia, motility, invasiveness and epithelial-to-mesenchymal transition. Radiotherapy can also stimulate the irradiated primary tumour to self-seed from CTCs. It may also modulate angiogenesis, and so indirectly affect metastasis.

So far, the only clinical evidence directly indicating that localised radiotherapy mobilises CTCs comes from the study by MacManus and colleagues, which reported increased numbers of CTCs, both singly and in clusters, in the bloodstream of

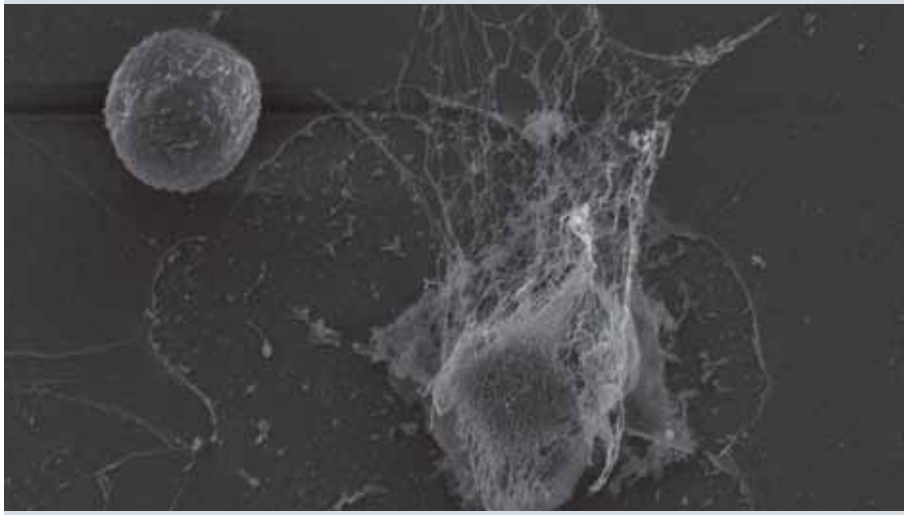
Progressive effects of fractionated radiotherapy on tumour cells *in vivo*



Up to 50% of the malignant cells in an irradiated tumour can survive the first radiotherapy fractions; they can subsequently acquire a more-aggressive phenotype, becoming circulating tumour cells that are detectable during the course of radiotherapy. Radiotherapy affects the regulation of genes associated with radioresistance, tumour aggressiveness, and enhanced metastatic potential, including signatures associated with hypoxia, invasiveness and motility, and epithelial-to-mesenchymal transition (EMT).

Source: OA Martin et al (2017) Does the mobilization of circulating tumour cells during cancer therapy cause metastasis? *Nat Rev Clin Oncol* 14:32-44, reprinted with permission © Macmillan Publishers Ltd

Mitigating metastatic risk



Neutrophil extracellular traps (NETs) like this one, can trap circulating tumour cells, offering a foothold in the blood vessel barrier. The use of deoxyribonuclease after tumour surgery has been proposed as a way to mitigate the risk this could pose for metastatic spread.

Source: ©Stephen Hearn, CSHL/Egelbad Lab

patients with non-small-cell lung cancer early in the course of radiotherapy. These mobilised CTCs were better able to grow in culture, a characteristic that can be associated with worse patient outcomes. However, there is no evidence for a direct link between radiotherapy-induced CTCs and a worse patient prognosis.

Surgery and inflammation as factors for metastasis

While the potential for radiotherapy to mobilise viable tumour cells into the circulation came as a surprise to MacManus and colleagues, evidence for a similar phenomenon occurring in relation to surgical treatment has been known about for some time. In animal models, experiments show that removing a tumour is followed by accelerated tumour growth, both at the local tumour site and at distant sites. Clinical evidence that surgery can increase both the establishment of new metastases and the growth of micrometastases is mounting. "Surgeons are aware of potential links between surgical procedures and metastasis," says MacManus, "and are implementing changes to operating techniques to make metastasis less likely."

Understanding more about the mechanisms that could link cancer surgery with CTCs and metastasis is a special interest of Allan Tsung, a surgical oncologist at the University of Pittsburgh School of Medicine, who co-authored a recent review on cancer surgery as a trigger for metastasis (*Cancer Res* 2017, 77: 1548–52). "The inflammatory response to surgery may play an important role in enhancing the risk of tumour recurrence," argues Tsung, adding that "patients with bigger operations and those who suffer from complications and infections, have, stage-by-stage, a worse prognosis."

In their review, Tsung et al. point to studies showing that manipulation and handling of the tumour during surgery can lead to a release of tumour cells into the circulation, and that the level of CTCs before and during an operation is a strong predictor of whether disease recurs. Inflammation and trauma, they argue, may provide an ideal environment both for capturing CTCs and promoting their growth. This point is also highlighted by MacManus et al., who describe how, after surgery, the surgical bed contains not only tumour cells, but also blood, extracellular fluid, inflammatory cells and cytokines, and suggest that this may promote the entry of CTCs into lymphatic vessels and the peripheral circulation (*Nat Rev Clin Oncol* 2017, 14:32–44).

The cascade of inflammation even has the potential to capture cancer cells and promote their growth, argue Tsung and colleagues in their paper, pointing in particular to the role played by neutrophil extracellular traps (NETs) – extrusions of DNA coated with pro-inflammatory proteins that are spewed out by neutrophils in injured tissues.

After surgery, the number of neutrophils and NETs in the blood increases. NETs can capture bacteria and promote their killing, but they have also been shown to trap CTCs, says Tsung. "Through NETs, the circulating tumour cell gets a foothold in the blood vessel barrier, allowing its invasion." In their review paper, Tsung et al. highlight a study showing that, in patients whose colorectal metastases to the liver have been surgically removed, the greater the evidence of NETs forming in the serum, the higher the risk of disease recurrence. Inflammation may also play a

role in the growth of micrometastases, Tsung believes. "Inflammation after surgery may augment occult disease, so that initially dormant tumour cells grow after surgery," he says.

Radiofrequency ablation and CTCs

A group of researchers from the departments of thoracic radiology and thoracic surgery at the Harefield Hospital in London report that the use of radiofrequency ablation can also lead to an immediate increase in CTCs (*Anticancer Res* 2015, 35:2823–6). Radiofrequency ablation, which uses heat generated by an electrical current to kill cancer cells, is increasingly used as an alternative to surgery in patients with surgically unresectable lung tumours. The study, by Dimple Chudasama and colleagues, measured CTCs in blood samples taken before and immediately after treatment with radiofrequency ablation in a series of nine patients. They report a general increase in CTCs in seven of the nine, noting that the largest increases were found among patients with metastatic disease, and they call for further studies to investigate the implications.

What about systemic therapies?

Clinical evidence linking systemic anti-tumour therapies with a potential for inducing metastases is lacking. However, preclinical evidence does suggest such a link could be worth investigating, in particular as part of efforts to understand why some systemic cancer treatments do not lead to the results expected.

Anti-angiogenic therapies are a case in point. This class of therapy aims to block the growth of blood vessels the tumour needs in order to survive, but its impact in patients has not lived up to the hopes and expectations initially held by many in the oncology community. John Ebos, Assistant Professor of Oncology at Roswell Park Cancer Institute, thinks that unintended effects of this class of treatment, including inducing metastases, may be part of the explanation. "Based on initial preclinical studies, it is somewhat surprising that the treatment response with antiangiogenic agents is so limited in patients," he comments. "However, further studies in mice have generated some provocative hypotheses, and based on these further studies, this limited response is not necessarily unexpected."

"Although inhibition of angiogenesis reduces the growth of the primary tumour, it can also promote invasion and metastasis"

Two such preclinical studies, including one led by Ebos, have shown that, although inhibition of angiogenesis reduces the growth of the primary tumour, it can also promote invasion and metastasis by inducing a hypoxic environment in the residual tumour mass. In the wake of these studies, members of the board of the Metastasis Research Society wrote an open letter to the (US) FDA and other regulatory agencies, calling for preclinical drug development to consider a cancer drug's impact on metastasis (*Clin Cancer Res* 2009, 15:4529).

Other systemic therapies shown to promote metastasis in preclinical models include the BRAF inhibitor vemurafenib and cytotoxic chemotherapy agents such as cyclophosphamide. Animal models have clear limitations, however. The apparent pro-metastatic effects of some anti-angiogenic treatments in experimental systems are controversial, and probably depend on variables such as dose, the tumour system and the specific inhibitors used.

As MacManus points out, "These are very artificial models, and we do not know how to extrapolate to humans." Ebos argues, however, that these models do have a value in studying the mechanisms of treatment-induced metastasis. "We need to make preclinical models relevant to patients. Studies in mice have uncovered biological phenomena, such as treatment-induced metastasis, that are otherwise very difficult to observe in humans."

Clinical implications

If disturbing a tumour and its environment – particularly through surgery and radiotherapy – might, under some circumstances, promote metastasis, what impact if any should this have on clinical decision making? Does it tip the scales of benefits and risks that guide if, when and how to intervene?

Probably not, according to the current consensus. All interviewed experts agree that current standard of care therapies remain the best way to treat cancer. "This is not a reason to be worried. Cancer treatments allow many patients who would otherwise die from progressive disease to be cured," MacManus emphasises. "It

has not been proven that the mobilisation of CTCs by therapy actually causes metastasis. We need more studies to see if tumour cells circulating after cancer therapy are an important factor determining patient outcome – or if it is just a scientific curiosity. But it is a subject worth studying, and we need more clinical studies looking at how the different parameters of treatment affect patient outcome."

Treatment-induced metastasis may, he feels, turn out to be rather similar to toxicity: an unwanted side effect that hampers the efficacy of an otherwise good therapy. Like toxicity, treatment-induced metastasis could then be taken into account when developing or choosing therapies.

One of the hopes, says Ebos, is that studying treatment-induced metastasis may ultimately improve existing therapies: "The strong benefits of cancer therapy may actually be reduced by reactive mechanisms that permit metastatic growth. Taking this into account, if we can limit this effect, we might take a good therapy and make it great."

"Studying treatment-induced metastasis may enable us to take a good therapy and make it great"

Steps to improve therapy in the light of potential treatment-induced metastasis have already been taken in cancer surgery, says Tsung, including using keyhole surgery to limit the trauma. More direct measures are also used, he adds. "Small trials have shown us that using agents to block the inflammatory response affects cancer development. Deoxyribonuclease, which is used for treating cystic fibrosis, could be used to inhibit NETs after tumour surgery." Attention is also paid to factors around surgery, such as the anaesthetic agents used, which may alter aspects of the immune response and affect tumour spread.

If MacManus' finding that radiotherapy releases CTCs indeed has prognostic value, he suggests that strategies to either target CTCs or ensure that they are critically damaged before they even enter into the circulation would be appealing. "These strategies could include larger or more-frequent fractions of radiotherapy, or modulating the immune system to eliminate CTCs, among others."

Getting the message right

How should a potential link between treatment and metastasis be communicated, both to the patient and the wider community? MacManus admits concern: "I'd hate the message to be that patients shouldn't have conventional therapy. In reality, if a carcinoma spreads to the lymph nodes, the patient will die without surgery and/or radiotherapy. But the patient may fare better if we improve the available treatments."

Bernhard Albrecht, a German journalist and former doctor, who has investigated the way alternative therapists promote their services to cancer patients (see, for instance, Dangerous Healers, *Cancer World* Nov–Dec 2015), flags up the risk that this sort of research will be abused to lure people away from evidence-based treatments. "Alternative healers have a very selective view of science, and pick out anything critical. When medicine is – rightly – self-critical, the arguments get adopted and generalised."

Scientific arguments get distorted, says Albrecht, so that they fit into the worldview of alternative therapies. "While the intention of looking into surgery-induced metastasis is to bring this phenomenon to light and address it, a homeopath I talked to simply said: 'See, this is how dangerous cancer surgery really is!' No amount of corrections or reactions by the original authors of the scientific publications is able to change this misappropriation."

"Strategies to either target CTCs or ensure that they are critically damaged before they enter into the circulation would be appealing"

There is no magic formula to stop people cherry-picking evidence in this way. It certainly should not stop researchers, clinicians and patients alike from participating in honest discussions and carrying out further research to clarify the complex relationship between cancer treatments and metastasis. Indeed pursuing this research is vitally important, argues MacManus. "If we can take a link between treatments and metastases into account in our therapies, there may be some patients that could be cured who are not cured now."

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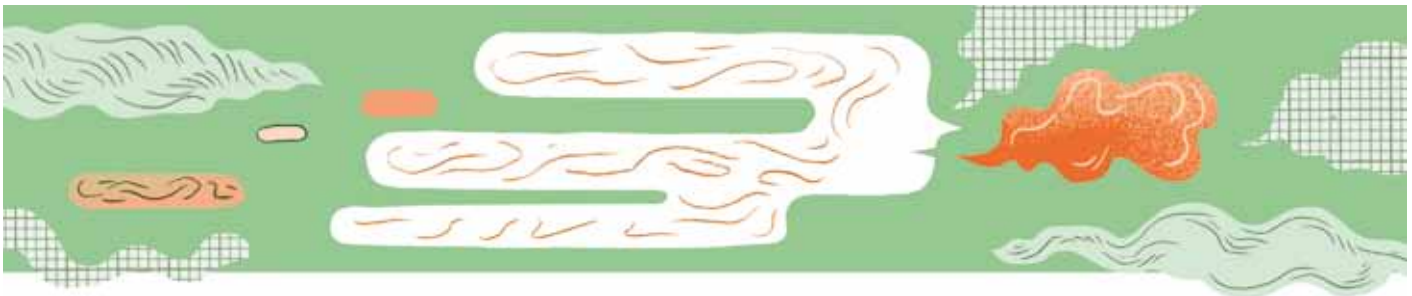

Anastassia Negrouk: fixing the system

Legislators and policy makers could do a lot more to promote cancer research if they understood that improving treatment strategies is not all about new drugs, and that patients and health budgets pay a high price for failures to coordinate across Europe. Anastassia Negrouk tells **Sophie Fessl** about her efforts to get those messages across.

"When you look at society and see something is wrong, you can either just complain about it, or you can get involved and fix it," says Anastassia Negrouk, Head of the International Policy Office at EORTC. Her decision was to get involved and try to fix it.

EORTC, the European Organisation for Research and Treatment of Cancer, is Europe's largest non-commercial sponsor of academic clinical trials. The job of Anastassia Negrouk and her team is to analyse how regulations affect patients, and how they affect Europe as a clinical trials location. "A number of regulations are relevant to our activities in clinical cancer research, from clinical trials regulation to data protection. I follow up on these key dossiers, to see they are drafted and implemented in the right way."

A major point on Negrouk's agenda was and still is the EU Clinical Trials Regulation. This regulation will replace the controversial 2001 Clinical Trials Directive, which, for all its good intentions, is widely believed to have paved the way for a drop of up to 25% in the rate of new trials being registered.

Negrouk was part of the attempt to turn this around: "When the new Clinical Trials Regulation was in development, I wrote articles to welcome the rethink and drafted position papers. Now, I'm involved in its implementation as part of the multi-stakeholder group at EMA [the European regulatory agency]."

The original Clinical Trials Directive turned clinical trials in Europe into a nightmare of red tape, requiring trials sponsors to negotiate separate procedures often with multiple bodies in each country where patients would be enrolled. But Negrouk is happy with the new legislation: "The Clinical Trials Regulation is a very good example of what Europe can do when things are worked out in a transparent and cooperative way," she says. "Most added value is given by the coordinated assessment of trials, and the single submission portal for clinical trial applications and authorisations. The transparency that this portal will ensure is key to public trust."

From lab to legislation

It was personal experience that first led Negrouk to train as a biologist – and then later led her to swap the laboratory bench for a job in cancer policy. "My grandfather, who I loved dearly, passed away from cancer when I was three years old.

Photo: Jennifer Jaquemart/POLITICO

Replacing the Clinical Trials Directive. Negrouk argued for greater harmonisation of rules at this workshop hosted by European Voice (now POLITICO) in 2012

I was then always interested in cancer, and studied biology at University of Louvain in Belgium. For my end-of-studies work, I investigated the toxicities of cancer drugs on cells *in vitro*. I continued working in the lab for a few more years, developing a new anti-cancer drug derived from doxorubicin, aimed at reducing toxicities.

During these years, Negrouk gained an insight into the research process – the logistics of the job and the battle for funding – that was to prove invaluable in informing her later policy work. But she soon realised that life at the lab bench was not for her, and started looking for other ways to help the research effort.

Working for a pharmaceutical company did not appeal. "I was not sure about working for industry, as I'm very 'not-for-profit' in my ways. By chance, I met a doctor whose wife worked at EORTC, and he told me about the organisation. When my contract at the lab ended, I saw a position as data manager at EORTC, applied and was accepted."

From there, Negrouk "slipped" into working on regulations: "I started working on intergroup cooperation, in which I set up the cooperation between different cancer research organisations. Part of this work is looking at regulations, which of course differ between countries and continents. And when you learn about regulations, you become somehow frustrated. When I become frustrated, I want to fix it. This is how I came into working on policy."

With a staff of three, the EORTC Office of International Policy is quite small. But this gave Negrouk a unique vantage point. "I look at all the different regulations at the same time, and can see when regulations are not consistent, or even contradict each other. These divergencies do not help patients, they just make research more expensive without any added value. A major plea of EORTC is to have more harmonised and consistent regulations at the European level."

These divergencies may directly affect Europe's competitivity in clinical trials, explains Negrouk, who cites as an example the way transparency obligations are applied to novel diagnostics. "In the Clinical Trials Regulation, transparency is very important. Information entered in the clinical trial portal is public, unless you have commercially confidential information, in which case the publication may be postponed. But this [let-out clause] applies only to information related to the drug itself," she says. In the Regulation on *in vitro* diagnostic medical devices, by contrast, the demands for transparency are less stringent, she says. "I wonder – what will be the result if a company has very confidential information on *in vitro* diagnostics, in the scope of a phase III clinical trial?... Without putting in question the general need for transparency, if companies have doubts about their obligations regarding what they consider confidential information, they may well decide not to come here."

From Negrouk's work as EORTC's data protection officer, she also sees potentially negative impacts on research of the Data Protection Regulation (DPR), which will be

implemented from May 2018 onwards: "The amount of paperwork needed to comply with the DPR is overwhelming. I am not sure that it provides any additional favours for patients, or just adds costs. I'm much more aware about privacy scandals around primary healthcare institutions, such as medical files that are released in a non-appropriate scope. But I do not recall any scandals about a misuse of research data. Also, while the healthcare area is one of the biggest targets of hacking, the research area is not. There is no information about the risks associated with the sort of pseudo-anonymous data we hold. It is questionable if all of this is proportionate to the risks – I think the DPR is overshooting."

The reason for this cautious approach, Negrouk suggests, may be a disconnect between regulators and health research: "Regulators may not always be knowledgeable of the realities in the field. The regulation is very general, speaking about scientific research, which is much larger than health research, and overall does not operate in the strict legal environment that we in health research do. As there was no quick consensus, a lot was delegated to the member states, which almost completely annihilated any interest to have a regulation. Harmonisation in data protection is worse than before the DPR."

Not just another bureaucrat

Negrouk has now worked at EORTC for 17 years, and sees the risk of becoming a pen-pusher. "When you work on your computer all the time, the notion of patients can become a bit theoretical. You risk becoming just one more bureaucrat." But in 2011, EORTC decided to involve the patient community in its activities in a structured way – a responsibility that Negrouk's unit took on. "Working with patients and patient organisations, I discovered a whole different world – and it is a part of my work that I really love," Negrouk enthuses. "When confronted with the patient community, you recall why you are doing your work, why it is important. I find it extremely inspiring that the patient community – whether patients themselves, advocates, or family members – have the strength to overcome difficult situations and use their anger at dysfunctions in the system in a very constructive way."

EORTC's activities involving patients range widely. "Every two years, we organise a patient advocacy course, which I chair. We also have patient representatives on our panel on the protection of research subjects. We exchange opinions and work on position papers on policy with patient organisations." EORTC also involves patient advocates in reviewing their clinical trial concepts. "They give us input on whether the trial design would be acceptable to patients. It is better to involve patients from the start, because from one type of disease to another, and from one treatment consequence to another, a trial may be more or less acceptable."

But some difficulties persist: "It is challenging, as we work in an extremely regulated environment. We are creating the interface between a caring patient community who have a lot at stake, and the clinical research community, where timelines are important, and where they have a very structured and somewhat distant style of communication and working."

And as input from patient advocates is sought from increasing numbers of organisations, there is a growing problem with finding patients with the necessary expertise and the time to spare. "Those who are willing to contribute are overbooked. If the community wishes to continue with patient engagement, patient advocacy groups will need more people to be involved and more structural support to enable this."

Clinical research ≠ drug development

EORTC's mission is to improve standards of cancer treatment for patients. Yet a review of therapies approved for solid tumours between 2002 and 2014 showed that the median gains in progression-free and overall survival have been 2.5 and 2.1 months, respectively (*JAMA Otolaryngol Head Neck Surg* 2014, 140:1225–36). Does Negrouk believe this is OK?

"We should not say 'we don't accept these little advances,' we should demand that these little advances are built upon"

"What are two additional months of life worth? If we discuss this on the level of society, it is a very dangerous debate. I personally don't believe that society can decide this, as opposed to individuals," argues Negrouk. "The real debate is slightly different. We should not say 'we don't accept these little advances,' we should demand that these little advances are built upon. We should not forget that childhood leukaemia is pretty much treatable now because little advances were steadily built upon."

But Negrouk doesn't rush to blame the system: "With maintenance treatments, which we now see more frequently, we have a clear conflict of interest from the perspective of industry. This is not attributing blame, it's just a fact, and we need to have a counterbalance in society. This could be a role

played by academic institutions. Once the drugs are on the market, they could look at the exact treatment length. Does it really have to be forever? It would be in the interest of health-care systems to support such academic work, as it would save them a lot of money."

Denis Lacombe, Director General of EORTC, recently wrote a piece titled, 'Let's be honest – our research centres on drugs not patients" (*Cancer World* Winter 2017/18). Negrouk agrees that he has a point. "We need to get away from the idea that it will be a new drug that saves the patient. In cancer, this is so not true. It is the combination of treatment strategies that saves lives. We need to create a system that is complementary, with industry discovering new molecules and making drugs available to patients and the academic community, and on the other hand an academic community that fine-tunes how to optimally use those molecules."

Fixing the problem of drug-centred research will not be easy, as the problem is essentially political, argues Negrouk: "The system is drug-centred because the pharma industry is there to develop new molecules and will always think in relation to their molecule portfolio. If we want society to think from the patient angle, we need to start from the patient."

What this means in practice, she argues, is to start by finding the exact nature of the patient's disease, and then go on to see what the available optimal treatment is. "But this is not easy – doctors do not necessarily have a full picture of all emerging treatment opportunities," says Negrouk.

Clinical trials registries, such the EU's EudraCT or clinicaltrials.gov, run by the US National Institutes of Health, are of course a step forward in helping doctors and patients access information about potentially relevant trials, she says, but the problem is that these only concern drugs.

"You might like to have a full picture of what is available to your patient, also including interventional trials with or without drugs, such as surgery, radiotherapy, or a combination." This has so far proved impossible, says Negrouk. "EORTC tried to put in place a register for all clinical research carried out, not just clinical trials. But when we speak to EU parliamentarians, they say, 'We have just put this in place – it's the drug trial registry.' They still do not realise that clinical research is not just a means to develop a new drug."

Fixing the system

Don't just complain, fix it, is Negrouk's motto. One way to fix the system, she suggests, would be to set up clinical trial infrastructures that can address most of the common regulatory problems in one go: "Such infrastructure helps us carry

out projects more efficiently, and is the basis for EORTC's partnership with other scientific and leading organisations in conducting complex international research projects."

She is a strong supporter of two of the new, more holistic, data collection infrastructures launched in recent years by EORTC. SPECTA is an integrated and shared European platform that collects biological material and correlates relevant clinical data to learn more about how cancer develops, but also to see which treatment protocols may be proposed. YOU, Your Outcome Update, is a platform for long-term follow-up, beyond the usual five-years disease-free survival looked at by most companies (see also 'Gathering long-term data on what happens next', p62).

"With YOU, we have the opportunity to go back to patients who participated in the original trial, and ask whether they would contribute to discovering something, for example, about late toxicities. In collaboration with registries, we can build a comparison between how cancer patients do in clinical trials compared to in real-life treatment, and develop new methodologies."

Battling red tape on a daily basis would frustrate most people. But not Negrouk: "I have a very analytical mind, and do not find legislation frustrating. What I do find frustrating are all the little differences between member states, which complicate organising pan-European research a lot. These are usually just cultural or historical preferences. Europe must recognise that they need to unite if they want to offer their citizens the prospect of high-quality and affordable healthcare, underpinned by high-quality pan-European research."

To comment on or share this article go to bit.ly/CW81_anastassia-negrouk

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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

Quality in cancer care: making it a European habit

Aristotle said, "quality is not an act, it is a habit". On becoming President of the European CanCer Organisation (ECCO), I think of this advice when considering how to deliver ECCO's mission: improving outcomes for cancer patients through multidisciplinarity.

The ECCO mission is expressed well via the Essential Requirements for Quality Cancer Care. These new charters for improvement, created for specific tumour types, set out in clear terms the checklist elements required to be in place to achieve quality cancer care, including:

- membership and role definitions within the core and extended multi-disciplinary team;
- organisation of the cancer patient pathway;
- timelines for care and interventions;
- quality assurance processes; and,
- articulation of rehabilitation and survivorship needs.

Covering the entire patient journey, they speak to the reason why ECCO was established: to be the place where professions and others involved in cancer care (not least the patients themselves), can meet to discuss, agree and advocate for the changes required to improve cancer care in Europe.

So remembering Aristotle's words, we need to recall that the act of agreeing what quality cancer care means does not represent its achievement. That is represented by what healthcare systems do on a daily basis – as habit.

For quality cancer care to become a habit, change must be promoted. Specifically, we need to:

- **ensure understanding** by all involved in delivering cancer care as to what quality cancer care is made up of, and
- **measure more effectively** how healthcare systems are performing when it comes to quality cancer care.

So while ECCO, its members, and its Patient Advisory Committee will continue to articulate new Essential Requirements documents (this year, for melanoma, oesophageal-gastric cancer, breast cancer and prostate cancer), we will also be launching a new communication action, 'Quality Cancer Care Week' (5th–11th March 2018), to increase public understanding of the topic.

Additionally, we invite you to join us at the ECCO 2018 European Cancer Summit (7th–9th September) in Vienna, to contribute to the formation of consensus resolutions on how quality cancer care should be achieved.

More than two millennia after Aristotle, management scientist William Demming recommended, "Quality is everyone's responsibility". Indeed it is.

Therefore, I hope *Cancer World* readers will join us in spreading the messages of Quality Cancer Care Week and help us to create a united plan in Vienna for how to make quality cancer care a true European habit.

To find out more about Quality Cancer Care Week and the European Cancer Summit please go to www.ecco-org.eu/Events

The ECCO Essential Requirements for Quality Cancer Care manuscripts were published in *Critical Reviews in Oncology/Hematology* (110; 2017) and are freely available online at http://bit.ly/ECCOpublications

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Cancer surgery: the key factors that influence outcomes

Cancer patients are put at risk unless the surgeons who operate on them understand the principles of the disease, work closely with other oncology disciplines, and know which patients need to be referred to high-volume specialist centres. This grandround looks at the key surgical factors that influence cancer outcomes, and how to optimise them.

This grandround was first presented by Charles M Balch, MD, FACS, FASCO, Professor of Surgery at the University of Texas MD Anderson Cancer Center, in Houston, Texas, as a live webcast for the European School of Oncology. It was edited by Susan Mayor. Charles Balch is Past-President of the Society of Surgical Oncology and Editor-in-Chief of the Annals of Surgical Oncology.
The webcast of this and other e-sessions can be accessed at e-eso.net

Access to surgery is a key issue affecting outcomes in a wide range of conditions, including cancer. The *Lancet Commission report on Global Surgery 2030* pointed out that, "Access to surgical care is essential for reduction of mortality and morbidity from surgical conditions" (*Lancet* 2015, 386:569–624). A subsequent paper on global cancer surgery estimated that 45 million surgical procedures would be needed worldwide by 2030 (*Lancet Oncol* 2015, 16:1193–224), "Yet, less than 25% of cancer patients worldwide actually get safe, affordable or timely surgery," warned the authors.

The Commission identified factors associated with poor access to quality cancer surgery, including: lack of investment in public surgical systems; low investment in research and training in surgery; and widespread educational gaps. Recommended solutions included:

- better regulated public systems, particularly regarding the training and certification of surgeons,
- international partnerships,
- super-centralisation of surgical services,
- novel surgical clinical trials, and
- new approaches to improving quality and scale-up of cancer surgical systems through education and training.

The Commission acknowledged that achieving good outcomes in modern cancer surgery is technically demanding, and noted that outcomes improve when surgery is performed by specialised teams working in high-

Key Points

A team approach. Almost all cancer patients in the US now receive more than one treatment modality, making contemporary cancer care a team approach combining the collective wisdom of surgeons, medical oncologists, radiation oncologists and pathologists.

Managing chronic disease. Developments in effective systemic treatment mean that cancer is becoming a chronic or curable disease, requiring measures to optimise survivorship, manage second primaries, and promote adherence.

Continuing education. Oncology is one of the most rapidly advancing specialties in medicine, underlining the importance of validating advances through well-conducted clinical trials and the need for high-quality training and education throughout a surgeon's career.

Specialists and telemedicine. Surgeons who carry out higher voumes of a given procedure achieve better outcomes in patients with complex or advanced cancers, and there is patient and public demand for getting optimal cancer care from specialists and multidisciplinary cancer centres. However, this does not mean that all cancer patients need to be treated by specialists, particularly if they are diagnosed early and their treatment is simple. Innovations such as telemedicine can enable patients to be treated in local hospitals with input from specialists, where required.

Supporting standards in general surgery. Surgical oncology specialists should provide educational and research leadership within the general surgery community. Professional societies have a central role in defining the standards for treating surgical patients with cancer and providing education and training to achieve optimal cancer care. Partnerships between societies and medical institutions, including at an international level, will accelerate progress, advance the specialty and improve patient care.

volume centres, particularly for complex patients and more complicated operations.

Access to high-quality training is essential, with suitable accreditation and quality control for aspiring cancer surgeons. However, this has yet to be achieved by regulatory authorities in many countries. High-income countries, including the US and many in Europe, are driving greater specialisation, but general surgeons also need wider training.

The Commission recommended that surgical professional societies take a lead role in this. It also advised that high- and middle-income countries expand their educational offerings on cancer surgery to low-income countries through bilateral exchanges and greater use of technology-enhanced learning and partnerships, and by including specific curriculum content on cancer in general surgery residency training programmes.

Several organisations, including the US Society of Surgical Oncology, the European Society of Surgical Oncology, the British Association for Cancer Surgery, the European Society for Medical Oncology, the American Society of Clinical Oncology and the (US-based) Health Volunteers Overseas, are all contributing to developing global programmes in cancer surgery.

Why surgeons who treat cancer need to specialise/subspecialise

There have been rapid and substantial advances in cancer research, with new diagnostics and biomarkers, and new systemic therapies including chemotherapy, hormone therapy, targeted therapy and, more recently, immunotherapy. This has led to new combinations and sequences of cancer treatment, including use of neo-adjuvant and adjuvant therapies in surgical patients.

There have also been major advances in surgical technologies in the operating room, such as laparoscopic surgery, robotic surgery and intraoperative imaging techniques. The challenge now is to remove cancer with better results, better local-regional control, improved safety and lower incidence of complications. In addition, there is greater recognition of the importance of rehabilitation and restoring function to patients after surgery.

There have also been many changes in the delivery of cancer care, with the development of regional cancer centres and multidisciplinary teams of oncology specialists. This includes surgeons who spend part of their time working as part of a multidisciplinary team, participating in treatment planning with

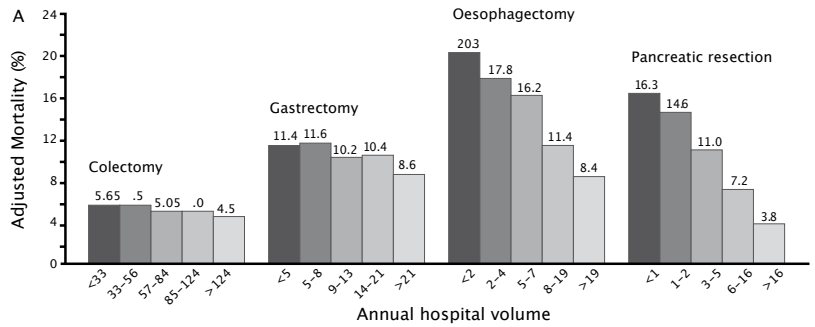
colleagues from medical oncology, radiation oncology, pathology and radiology.

Evidence of better outcomes in specialist cancer centres

Well-trained general surgeons can achieve good outcomes in cancer surgery, but it is important they have the judgement as to when complex cases will achieve better outcomes with surgery performed by specialists working in high-volume centres. One example of this was reported in a UK study of breast cancer, which showed that the risk of inadequate treatment of the breast among patients treated by specialists was half that of patients treated in non-specialist units (24% vs 47%, $P<0.001$), where 'inadequate treatment' was defined as treatments where breast-conserving surgery was performed for tumours larger than 30 mm, or if resection margins were positive, or if radiotherapy was omitted (*Br J Cancer* 2004, 90:1920–5).

The same study showed that treatment by specialists was also associated with a five-fold lower risk of inadequate axillary staging (8% vs 40%, $P<0.001$) and a nine-times lower risk of inadequate axillary treatment (4% vs 38%, $P<0.001$). The local recurrence rate, which is a metric of surgical outcome, was 57% lower at eight years (13% vs 23%, $P<0.001$), and the risk of death from breast cancer was 20% lower for women treated in specialist units, after allowing for case mix and adjuvant therapies. The authors concluded that adequate surgical management in breast centres is fundamental to improving the outcome of patients, irrespective of where it is delivered. This study was conducted in 2004, and since then the UK National Health Service has developed much better cancer centres.

Hospital volume and operative mortality



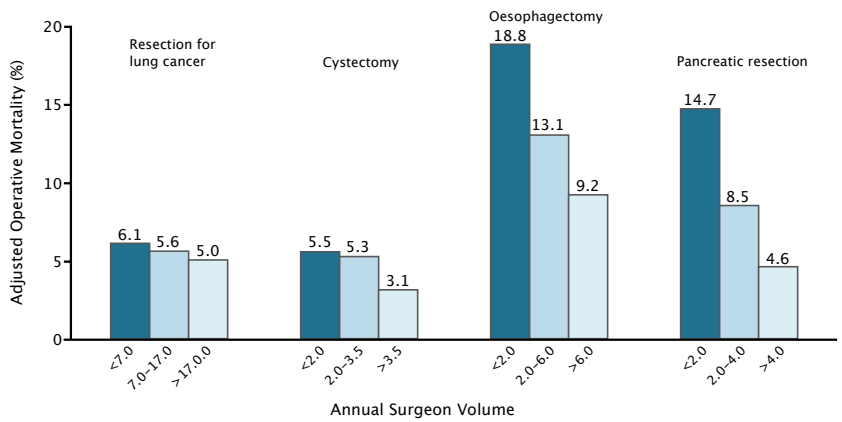
For certain types of cancer surgery, the risk of operative mortality, defined as death before hospital discharge or within 30 days after the index procedure, is significantly higher for patients treated at hospitals with lower annual caseloads for those procedures

Source: JD Birkmeyer et al. (2002) *New Engl J Med* 346: 1128–37, © Massachusetts Medical Society, Reprinted with permission

US studies have also shown that surgical volume (i.e. patient caseload) and surgical specialisation both impact, independently, on survival. A breast cancer study showed that surgeons who performed more than 15 breast cancer surgeries per year achieved a five-year survival of 84%, compared with 75% for those who performed 1–5 breast cancer surgeries per year. Risk of death at five years was more than one-third (36%) lower among patients treated by a surgical oncologist compared with a general surgeon, even after controlling for both hospital and surgeon volume, as well as hospital, age, stage, and race (*Ann Surg Oncol* 2003, 10:606–15).

Several US studies have also shown the relationship between hospital volume (the hospital's annual caseload of patients requiring a particular treatment) and surgical mortality (defined as the rate

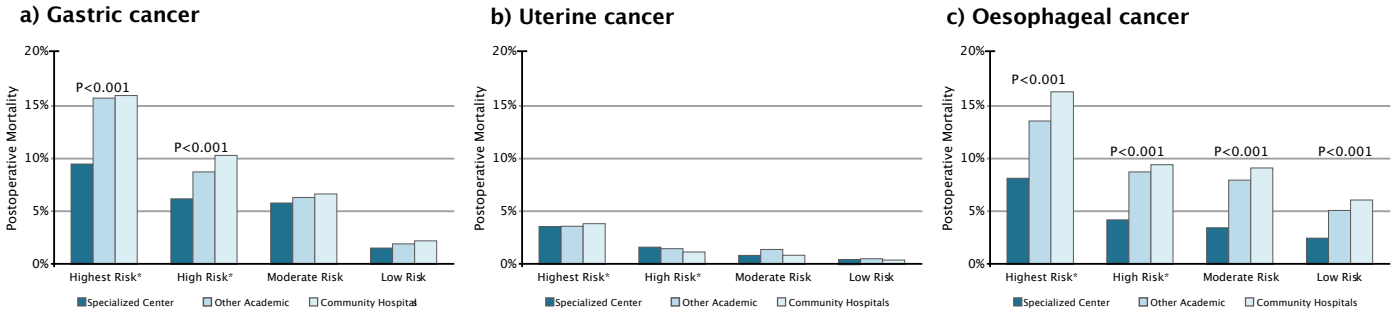
Surgeon volume and operative mortality



For certain types of cancer surgery, the risk of operative mortality, defined as death before hospital discharge or within 30 days after the index procedure, is significantly higher for patients treated by surgeons who do fewer operation of that type each year

Source: JD Birkmeyer et al. (2003) *New Engl J Med* 349: 2117–27. © Massachusetts Medical Society, Reprinted with permission

Outcomes for different cancers by risk and hospital type



Patients with gastric cancer (fig. a) do better in specialist centres if they are at high risk; patients with uterine cancer (fig. b) do no better in specialist centres regardless of whether they are at high or low risk; all patients with oesophageal cancer (fig. c) do better at specialist centres. Patients with bladder, colon, liver, lung, rectal and renal cancers have a similar pattern of outcomes to those shown in fig. a. Patients with breast, melanoma, ovarian prostate and thyroid cancers have a similar pattern of outcomes to those shown in fig. b. Patients with pancreatic cancer, like those with oesophageal cancer, all do better when treated in specialist centres

Source: K Bilimoria et al. (2010) *Ann Surg* 251:708–16. https://journals.lww.com/annalsofsurgery/. Reprinted with permission

of death before hospital discharge or within 30 days after the index procedure) varies by type of surgery. Results showed no difference by hospital volume in adjusted mortality for colectomy, which is a more standard operation. However, there was a significant difference by hospital volume in treatment-related mortality after gastrectomy, oesophagectomy or pancreatic resection, (see figure p41 *top*).

Another study, this time looking at the surgeons' annual caseload (*NEJM* 2003, 349:2117–27), found that for some procedures, including resection for lung cancer or cystectomy, there was little difference in adjusted operative mortality between surgeons with different annual caseload volumes, but for others, including oesophagectomy and pancreas resections, the difference was highly significant (see figure p41 *bottom*).

A further study showed highly significant differences in 30-day surgery-related mortality in patients undergoing pancreatectomy in relation to both hospital volume and surgeon volume (*NEJM* 2003, 349:2117–27). Mortality was 18% in hospitals managing fewer than one case per year, compared to 4% in hospitals with more than 16 cases each year. Mortality was three times lower in patients treated by surgeons with more than four cases a year compared to those with one case per year (5% vs 15%).

Patient risk factors

Stage at presentation and comorbidity, particularly in older people, are more important influencers of cancer outcomes than the annual number of similar patients treated by their surgeon or at their hospital.

Studies comparing postoperative mortality in specialised centres with other academic centres and community hospitals in the US have shown that treatment at specialist centres is particularly important for 'high-risk' patients with some cancer types, but not others (see figure above).

High-risk patients with bladder, colon, gastric, liver, lung, rectal and renal cancers had improved outcomes when surgery was performed at specialised centres compared to community hospitals, but there were no differences for moderate- or low-risk patients (*above left*). However, no such difference in outcomes was seen for high-risk patients with breast, melanoma, ovarian, prostate, thyroid and uterine cancers (*above centre*).

For patients with cancer of the pancreas or oesophagus, treatment at specialist centres was associated with lower postoperative mortality compared to other hospitals, regardless of the patient's level of risk (*above right*).

Training of oncologic surgeons and general surgeons in cancer surgery

The US Society of Surgical Oncology and the European Society of Surgical Oncology recently published two important papers on the training and education of cancer surgeons. The first showed very large variations in the training of surgical oncologists around the world (*Ann Surg Oncol*

2016, 23:1769–81). The second proposed a global curriculum in surgical oncology that can be used both for training general surgeons and also as curriculum recommendations for training surgical oncology specialists, who are very important at the national level for managing complex patients and for leading training programmes for general surgeons (*Ann Surg Oncol* 2016, 23:1782–95).

Both the US and the global curriculae defined the distinguishing features of a surgical oncologist as an excellent surgeon who:

- can safely manage cancer patients through complex operations, and has the judgement to know which operations to select
- knows how to integrate surgical treatment as part of a multidisciplinary team, including the type and timing of surgery after preoperative systemic therapies and/or radiation therapies
- participates as an oncologist in long-term disease management of cancer patients.

How preoperative treatments are changing the role of cancer surgery

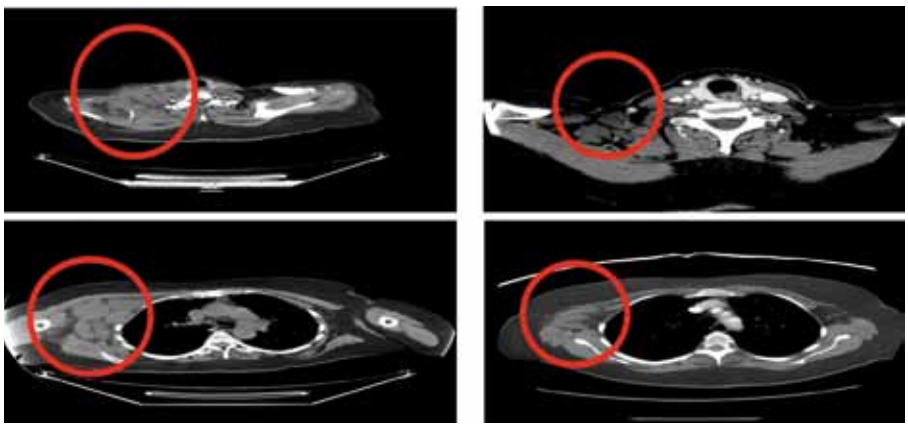
An important part of the surgical management of patients who present with stage 3 disease is the increasing preoperative use of medical therapies including chemotherapy, targeted therapies and immunotherapies. This is going to change how we manage patients surgically. For the majority of US patients with stage 2–3 breast cancer, and in many centres in Europe, systemic therapy is now the first treatment, and surgery the second. This requires a lot of planning with medical oncology colleagues around the timing of surgery and the role of the sentinel node, which is different in this setting. This approach represents the future of treatment for many cancers, for which breast cancer is the prototype.

The figure above shows an example of a patient with a bulky and unresectable advanced melanoma in the groin and pelvis, treated with anti-PD1 immunotherapy. Tumour shrinkage after immunotherapy facilitated surgery. The patient had a pathological complete response, which could not have been staged without surgical resection of the tumour masses that were originally detected.

The increasing number of effective systemic therapies will impact on the management of surgical patients. Many of these are administered orally, and many are less toxic than traditional chemotherapies. Examples of new oral and subcutaneous agents that are available for a variety of cancer types include: anastrozole, capecitabine, gefitinib and sunitinib. More than 1,000 new cancer drugs are in various stages of clinical development. Some dramatic examples of tumour shrinkage have been seen with agents such as the targeted BRAF inhibitor vemurafenib in metastatic melanoma with V600E mutation. Another major advance is the development of immunotherapy such as immune checkpoint inhibitors, which have now been shown to be active in more than 17 different types of cancer. These agents will be used increasingly in surgical patients, and the sometimes dramatic treatment responses achieved in patients with advanced disease indicate that they will translate into benefits in patients with earlier disease.

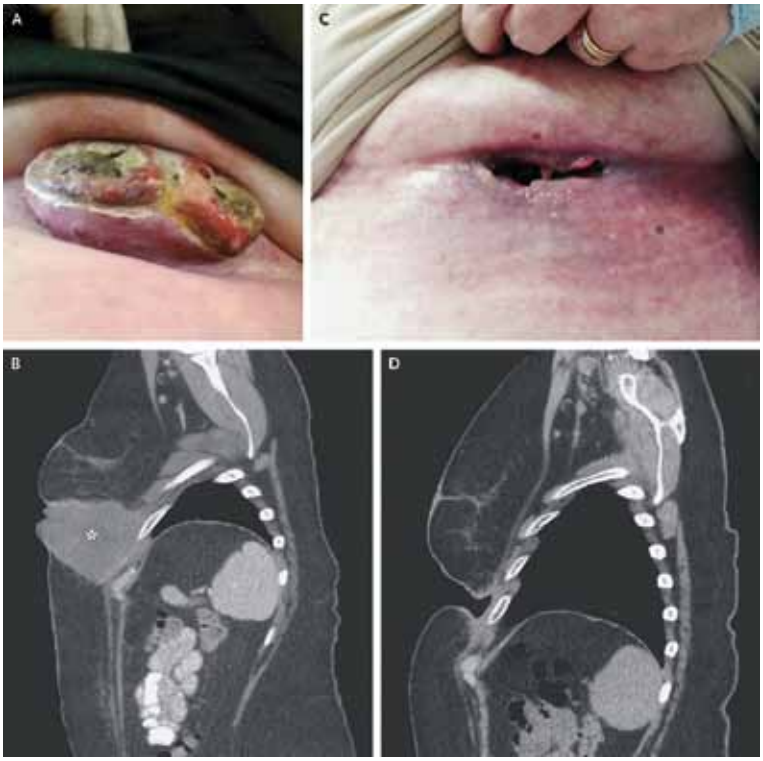
An example illustrating the future of how these new therapies impact on cancer surgery is shown in the figure overleaf, which shows the response of a very large melanoma metastasis after a single dose of combination immunotherapy. The patient had a pathological complete response demonstrated by surgical excision of the remaining tissue (*NEJM* 2015, 372:2073–4). A more famous example, former US

Preoperative immunotherapy in advanced melanoma



Increasing use of preoperative systemic treatments is changing the role of cancer surgery, requiring ever closer team work between disciplines
Source: Images courtesy of Dr Merrick Ross, University of Texas, MD Anderson Cancer Center

Response of melanoma to immunotherapy



A single dose of ipilimumab plus nivolumab resulted in complete pathological response of this large metastasis in the chest wall of a patient with melanoma
Source: PB Chapman et al. (2015) *New Engl J Med* 372:2073–4. © Massachusetts Medical Society
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president Jimmy Carter, has been in complete remission for more than 14 months [as of July 2017] after treatment with a single dose of an anti-PD1 checkpoint inhibitor, following presentation with liver and brain metastases from metastatic melanoma at the age of 92.

How surgeons can keep up with advances

Continuing education for practising surgeons is essential. There are a variety of ways that this can be provided, including live meetings such as those run by the US, European and British surgical oncology societies, SSO, ESSO and BASO, and also through affiliations with tertiary centres, such as the one between community hospitals and the MD Anderson Cancer Center. There are also continuing medical education (CME) initiatives led by journals such as the *Annals of Surgical Oncology* and the *European Journal of Surgical Oncology*, both online and in print versions, and training initiatives conducted by live webinars such as those provided by the European School of Oncology. The US Society of Surgical Oncology now runs a compulsory self-assessment programme, to help surgeons keep up with the field.

Telemedicine is increasingly being used both for medical education, especially for physicians in community settings and rural areas, and for specialist consultative services, particularly in supporting shared decision making about individual patients between doctors working in different locations and even in different countries.

Telemedicine is increasingly being integrated into the operations of US hospitals, speciality departments, home health agencies, private physicians' offices and, in some cases, even for educational purposes in the patient's home or workplace. The technology enables the sharing of X-ray, pathology and even ultrasound images, in real time and in high resolution, between locations.

Telemedicine specialist consultations and virtual tumour boards can bring together specialists from different countries to discuss complex cancer cases anywhere in the world. A study reported at ASCO 2016 showed that 91% of participants in virtual tumour boards found it very helpful in managing their patients; 100% felt quality of patient care was improved; and 100% considered their own confidence improved (*JCO* 2016, 34:211).

International relationships with individuals and organisations can be of assistance in consultations, reviewing complex patients, and in the education of surgeons in local communities and nationally.

Impact of quality improvement programmes on surgical quality

The National Surgical Quality Improvement Program (NSQIP), run by the American College of Surgeons, now operates in most US

hospitals (*Ann Surg* 2009, 250:363–76). An evaluation of the impact of NSQIP demonstrated what a difference this type of programme can make at a national level.

Results showed that two out of three hospitals (66%), including community hospitals, reported lower mortality rates, and more than four out of five (82%) reported lower morbidity rates.

The poorest-performing hospitals, with low volumes at surgeon or hospital level, were more likely to improve, but even high performers improved. The number of low outliers (with low mortality/morbidity) increased, and the number of high outliers (with high mortality/morbidity) decreased, which is very encouraging for a programme initiated nationally. It was estimated that the programme was associated with each hospital avoiding an average of 250 complications per year.

Advocating for quality cancer surgery

Professional bodies, together with governments in each country, need to insist that their citizens receive high-quality care. This includes ensuring there are well-trained surgeons, that cancer care is well organised nationally, for instance with regional specialist cancer centres, and that relationships are developed internationally with individuals and organisations that can be of assistance.

Surgeons working in communities should facilitate sharing of knowledge, and support young surgeons working in cancer, encouraging them to engage with leading specialists and networks in the field. Governments should raise expectations for high-quality and timely care, working within their resources to achieve that over time.

To comment on or share this article, go to bit.ly/CW81_surgery-outcomes

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HOW TO ESTABLISH PATIENT-CENTRED QUALITY STANDARDS FOR VARIOUS TYPES OF CANCER NETWORKS

Paris
April 19th 2018

OECI
Organisation of European Cancer Institutes

An initiative under the OECI Accreditation and Designation Working Group

In collaboration with:

Institut Marie Curie

Under the auspices of:

Rare Cancers of the Adult Joint Action (JARC)

Innovative Partnership for Action Against Cancer (iPAAC)

OECI Invitational meeting to debate on governance and organization supporting and enhance Comprehensive Cancer Networks which encompass care, education and research.

PROGRAMME

Host welcome and introduction to the "Comprehensiveness model" - ***Thierry Philip*** *(15 min.)*

Introduction - ***Wim H. van Harten*** *(30 min.)*

Principles of OECI A&D approach to quality evaluation and how this might apply to Networks
Simon Oberst *(15 min.)*

SESSION 1
The added value of Cancer Networks around a University Medical Centre
Chairperson: ***Wim van Harten***
Case 1: Lyon: a Comprehensive Cancer Centre Network based on a university hospital
Gilles Freyer *(20 min.)*
Case 2: Cambridge University Hospitals and the CRUK Comprehensive Cancer Centre
Simon Oberst *(20 min.)*

SESSION 2
The added value of, and quality criteria for, regional cancer networks
Chairperson: ***Tit Albrecht*** *(10 min.)*
Case 1: The Czech Regional Network - ***Ladislav Dusek*** *(20 min.)*
Case 2: The Cancer Centre and University hospitals in the Rhône-Alpes Région
Pierre Biron *(20 min.)*

SESSION 3
The added value of, and quality criteria for, national cancer networks
Chairperson: ***Paolo Casali*** *(10 min.)*
Case 1: Danish Comprehensive Cancer Centre concept - ***Cai Grau*** *(20 min.)*
Case 2: Quality in Research and in Clinical Studies: the UNICANCER experience - ***Pierre-Henri Bertoye*** *(20 min.)*
Case 3: The development of Cancer Networks in Germany - ***Simone Wesselman*** *(20 min.)*

Discussion: **Outcomes from the presentations: how can we move towards Europe-wide quality standards for Cancer Networks?**
Chairpersons: ***Wim van Harten, Thierry Philip*** *and* ***Dominique de Valeriola***

The meeting is launched to stimulate a debate and provide material to define a position on quality criteria, effectiveness and patient centeredness of different types of Cancer Networks. Ultimately this should lead to a decision of the OECI whether or not to expand our Accreditation & Designation Programme to Comprehensive Cancer Networks which meet certain quality criteria.

The meeting is open to OECI Member Organisations, representatives of other key Organisations, particularly patient bodies, and those presenting case studies and project leaders involved in such a debate.

REGISTRATION

OECI makes no charge for participating in this meeting, but representatives will pay for their own travel and accommodation.

Registration is mandatory before March 31st at:

Secretariat:
OECI Liaison Office
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Four cities, three continents, 12 million people

Can the City Cancer Challenge succeed where others have failed?

When it comes to developing capacity for tackling cancer, all too often the best intentions founder because key players are not engaged, costings are not done, sustainable funding is not secured, visiting experts dispense their wisdom and fly off home. **Peter McIntyre** reports on a new initiative designed with those pitfalls in mind.

Four cities with a combined population of more than 12 million people are pioneering a global campaign to build sustainable cancer services in low- and middle-income countries.

The City Cancer Challenge was launched in January 2017 by the Union for International Cancer Control (UICC) and is supported by 40 partners including the World Bank, the World Economic Forum and the Access Accelerated consortium of pharmaceutical companies targeting non-communicable diseases.

The aim is to galvanise a global network of cities with more than a million inhabitants to focus on the quality and coverage of cancer care, identify and fill in gaps and reduce mortality.

A total of five 'key learning cities' will lead the way. The first four are Cali in Colombia (pictured above, population

2.4 million); Greater Asunción Metropolitan Area, Paraguay (2.2 million); Yangon, Myanmar (5.2 million); and Kumasi, Ghana (2.6 million).

They have embarked on a three-year programme to develop, cost and implement a plan to tackle cancer as a priority health issue, in a context of the Sustainable Development Goal global commitment to reduce premature deaths from non-communicable diseases (NCDs) by one-third by 2030. Cities will receive support from UICC and international partners.

As the programme rolls out, they will be joined by cities with a population greater than one million that are committed to improving access to quality cancer care for their citizens, and meet the requirements and opt to become a 'C/Can 2025 Challenge City'. The fifth 'key learning city' will be announced during 2018, along with up to five challenge cities.

The central thrust is to bring public, private and civil society stakeholders from the cities together with regional and national governmental bodies, to identify gaps and set priorities for cancer detection, treatment and care. The city authorities and the national governments must sign commitments to back the project, with particular emphasis on determining sustainable financing solutions to ensure ongoing delivery of cancer treatment services. Progress in developing services and reducing cancer mortality will be monitored, but there will be no single service model. Each city will set its own course.

Each city establishes an executive committee and a series of technical groups to identify gaps and priorities in areas of cancer diagnosis, treatment and care, with support from a C/Can 2025 city manager and consultant technical experts. As well as local and national government bodies, the multisectoral model brings together cancer societies and networks, patient support groups, professional bodies, private sector bodies and foundations.

Susan Henshall, director of C/Can 2025, says that it is important that city executive committees bring together leaders in the city, region and government "who are able to take decisions and drive the process forward".

"This is a multisectoral group and it is imperative that they work as a collective. They will tell you openly it is challenging, but when they commit to putting the patients first, a lot of the issues are put aside."

Melissa Rendler-Garcia, C/Can 2025 director of regional operations, says that it is the growing collaboration and sense of mission that have excited her most about the City Cancer Challenge. "It has been one of the first opportunities for people who work in different institutions to look beyond what they are doing day to day, and envision what an optimal cancer care and control system would look like for their city. Initially it is challenging to begin to use this type of multisectoral approach, but once they start, they really see the value and enjoy the process."

UICC president Sanchia Aranda recalls that the city challenge grew out of discussions during the 2015 Istanbul World Cancer Leaders' Summit. "We were lamenting the fact that national cancer control plans tend to sit on the shelves and don't really mobilise action. They certainly don't mobilise investment and, because they are government led, they don't grab the imagination for a range of other players. We identified that governments in low- and middle-income countries tend to have limited capacity to work with the not-for-profit sector, and when they work with the private sector it is often a vested interest relationship, with the private sector wanting to capitalise on rising wealth."

The C/Can 2025 approach has been modelled in part from the C40 network of cities committed to partnerships to address climate change, with the added understanding that creating sustainable health programmes requires investment from the national government and buy-in from a wide range of stakeholders.

Sanchia Aranda, who is also CEO of Cancer Council Australia, says, "City investment is a missing piece, but is not enough. You need ongoing commitment to sustainable funding from governments to build sustainable health delivery systems."

The idea quickly blossomed. "It seemed to engage the imagination of the mayors, the non-profit sector and the private sector. Everyone quite quickly wanted to come to the table."

Cali and Asunción lead the way

The greatest progress has been made in Latin America. Cali and Asunción have completed needs assessments, and both presented draft implementation plans at the World Cancer Leaders' Summit in Mexico in November 2017. Both cities are supported by regional and national governments and international networks.

Cali began the C/Can 2025 process in March 2017, selected in part because the Cali Cancer Registry (CCR) is the longest-serving cancer registry in Latin America, having been in continuous operation since 1962. The Cali registry analyses incidence and mortality trends,

Bringing everyone to the table. A meeting of the Cali city stakeholders C/Can 2025 technical forum

and has carried out long-term survival analysis for the five leading causes of cancer and for all cases of childhood cancer.

Public awareness in Colombia has been heightened by the fact that President Juan Manuel Santos had surgery for prostate cancer in 2012 and resumed treatment in 2016, and has been very open about his condition. The Valle del Cauca department, of which Cali is the capital, has identified high rates of prostate cancer deaths, high incidence of childhood cancer and an increase in cervical cancer deaths as specific challenges for cancer control.

"The initiative helps demonstrate that investing in access to timely and accurate cancer diagnosis and quality treatment is cost-effective"

Key gaps identified by the C/Can 2025 city executive committee in Cali include: continuing and specialist education for cancer; slow authorisation processes holding up diagnosis and treatment; lack of operational procedures, treatment protocols, guidelines, and quality assurance programmes; gaps in access to essential oncology medicines; lack of radiotherapy equipment; and weaknesses in pathology.

Cali is receiving support from the American Society for Clinical Pathology (ASCP) to implement improvements in quality control and lab processes. One of the ASCP volunteer experts is herself originally from Cali. Rendler-Garcia says: "For her it was very exciting to be able to go back to her own city and work with pathologists, some of whom she knew because she had trained with them."

In Paraguay, the Ministry of Public Health and Social Welfare recognises cancer as a health priority, and it has adopted a national action plan to prevent and control NCDs. Vaccination against human papillomavirus and hepatitis B have been introduced to the national immunisation programme, and there are programmes to reduce tobacco exposure. Action has been taken to screen women for cervical cancer and for the early detection of breast cancer.

Cancer care is delivered by 18 public and private health care providers across Greater Asunción, and the municipality believes that C/Can 2025 will bring about greater integration and collaboration. Local authorities in Paraguay are working to educate senators in the national Parliament that they need a new law to ensure an effective long-term cancer control programme.

Ivan Allende, Director of Social Services for Asunción Municipality, says, "Civil society organisations need to play a leading role in advocacy actions to position cancer as a top priority in the political agenda. Initiatives like C/Can 2025 can help us to build the case to demonstrate to decision makers that investing in improved access to timely and accurate cancer diagnosis and quality treatment is cost-effective."

Gaps identified by the Asunción assessment include a need for trained medical professionals, external quality assurance programmes and standard treatment protocols; a need for greater involvement of multidisciplinary teams in treatment decisions; an updated list of essential oncology medicines and easier access to these drugs; limited capacity of radiotherapy services; and low availability and use of opioids for cancer pain management.

"A lot of expats from both Cali and Asunción who have heard about this project from their peers or from their friends, and are in the health profession and want to help, and are already starting with technical assistance," says Rendler-Garcia. An oncologist from Paraguay now practising in Valencia, Spain, is working with UICC to try to develop long-term fellowships, exchanges and research projects between Paraguay and Spain.

Increasingly there is interaction between the two cities and more broadly across Latin America. The head of planning and evaluation at the National Cancer Institute

in Colombia has been helping the team in Paraguay to construct their implementation plan. The President of Uruguay, Tabaré Vázquez, who is a radiation oncologist by training, has agreed to become Ambassador for C/Can 2025 and to co-sponsor a regional meeting in 2018 to focus on costing and budgeting and attract investors.

Financing the action plan

Financing the action plan is identified as a major challenge at the point when a city or country signs a memorandum of understanding.

Rendler-Garcia says, "We explain to the key stakeholders that within the next five years our goal is to assist them in developing a cancer control system and cancer care services at the highest standard possible in their context and sustainable in the long term. They do the costing for the next five-year cycle, but we really want them to go through to 2025 to ensure that the solutions proposed are fully owned by the stakeholders, and that city and national governments are empowered to find mechanisms to sustain financing.

"We are here to lead the process and guide them through it, but they develop the solutions – they are the ones who do the assessment. We will help them with the costing, we will help them find support in certain areas, but for larger budget issues – for capital investments – they are going to have to work with the financing community, with the international and regional banks, and come up with leverage for financing options."

C/Can 2025 will be launching a 'City Health Financing Lab' during 2018 to provide tools, services and networks to help cities cost implementation plans, conduct feasibility studies, and identify and attract new sources of financing.

Director Susan Henshall says, "Our commitment is to support them to deliver a fully costed implementation plan and help cities to identify avenues for financing that plan."

Yangon and Kumasi

Yangon signed up as a key learning city in July 2017; the Ministry of Health and Sports and Yangon Regional Government signed a memorandum of understanding in October. Findings from the city needs assessment were presented to the city executive committee in January 2018.

In 2014, almost six in ten deaths in Myanmar were attributed to NCDs, with more than one in ten attributable to cancer. Factors in the selection of Yangon as a key learning city were the launch of a National Health Plan in December 2016, aimed at delivering Universal Health Coverage (UHC), and the creation of a Myanmar National Comprehensive Cancer Control Plan (2017–2021).

Kumasi, the second city of Ghana, serves as a hub for cancer care and treatment for the country's northern and central populations, and has been selected as the first key learning cty in Africa. Breast, cervical, and liver cancer are the most common, but there is a large undiagnosed cancer burden. Late-stage diagnosis and associated challenges for treatment are top priorities. The first official meetings of the C/Can 2025 city executive committee and the international team were scheduled to take place in February 2018.

"Our commitment is to support them to deliver a fully costed implementation plan and help cities to identify avenues for financing that plan"

One of the aims of UICC is to broaden the base of support for the City Cancer Challenge so that it will eventually become a self-supporting initiative, as new cities join and share experiences.

Princess Dina Mired was for 15 years Director-General of the King Hussein Cancer Foundation in Jordan, and takes over from Sanchia Aranda as President of UICC in October 2018. She says that C/Can 2025 offers new hope in tackling the rising tide of cancer in low- and middle-income countries.

"I believe in it very much. When I become President of UICC, I will put all my weight behind it because I have been through the experience of how to implement cancer control in my country, and I have seen all the struggles and trials and tribulations and the resistance."

She would have welcomed an initiative like C/Can 2025, she says, "... this amazing organisation coming to give you free expert consultancy and then hand-hold for several years until you reach the point where you can do it on your own – how amazing is that?"

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Sergio Sandrucci, Vice-Chair of ESSO's Education and Training Committee, and head of the Sarcoma and rare visceral cancers unit, S. Giovanni Battista Hospital, University of Turin, Italy

Inadequate nutritional support for cancer patients is ethically unacceptable

Malnutrition is a frequent problem in cancer patients, the prevalence and degree of which primarily depend on tumour stage and site. Preoperative malnutrition in surgical patients is associated with prolonged hospital stays, more postoperative complications, higher re-admission rates and a higher incidence of postoperative death.

Given the focus on the cancer and its cure, nutrition is often neglected or under-evaluated, despite the availability of international guidelines for nutritional care in cancer patients and the evidence that nutritional deterioration negatively affects survival. Many malnourished patients still do not receive adequate nutritional support from health professionals.

Patients undergoing multimodal oncological care are at particular risk of progressive nutritional decline. It is essential to minimise the nutritional/metabolic impact of oncologic treatments and manage each surgical episode within the context of an enhanced recovery pathway. Enhanced Recovery After Surgery (ERAS) is a multimodal perioperative care pathway that is designed to achieve early recovery by decreasing the surgical stress, with a significant (30–40%) reduction of postoperative complications and of length of stay in hospital. Nutritional management is a key component of ERAS.

In Europe, ERAS and routine nutritional assessment are part of routine practice in only a minority of cases, or are only partially implemented, with limited advantage for the patients. This may be related to insufficient awareness of nutritional problems among health professionals and/or a lack of structured collaboration between surgeons and clinical nutrition specialists, old dogmas, or the absence of dedicated resources. In view of the above considerations, nutritional support and ERAS pathways may still represent a neglected right for cancer patients.

ESSO and the ERAS Society opinion leaders dedicated to Enhanced Recovery After Surgery have come together to promote nutritional assessment and perioperative nutrition, with and without enhanced recovery programmes. They have produced a White Paper to improve awareness in the surgical oncology community and at institutional level, to modify current clinical practice and identify optimal treatment options.

The full scientific paper, 'Perioperative Nutrition and Enhanced Recovery After Surgery in Gastrointestinal Cancer Patients. A position paper by the ESSO Task Force in collaboration with the ERAS Society (ERAS Coalition)' will be published in the *European Journal of Surgical Oncology* in the coming months, and is already available online at www.ejso.com. This paper has been endorsed and shared by the European Federation of the Associations of Dietitians.

It is time for inadequate nutritional support for cancer patients to be considered ethically unacceptable. Prompt nutritional support must be guaranteed to all cancer patients and incorporated into daily practice, to give rise to many clinical and economic benefits.

Prof. Sergio Sandrucci will be hosting a Meet-the-Expert Session on Principles of Enhanced Recovery at ESSO 38. The Congress will take place on 10-12 October 2018 in Budapest, Hungary.
For more information on registration deadlines or to follow details of the programme as they are announced, visit the congress website: www.essoweb.org/ESSO38, or follow the conversation on
Twitter: @ESSOnews #ESSO38 or
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PROMs put patients at the heart of research and care

The need to give greater weight to patients' own assessments of treatment impacts is increasingly accepted in principle. Putting it into practice will require a lot of hard work, developing tools that work for specific conditions and treatments, are easy to use, and command an international consensus. **Simon Crompton** talks to some of the people who are determined to make it happen.

The answer to the meaning of life, the universe and everything is 42, according to celebrated science fiction writer Douglas Adams. Roger Wilson, founder of Sarcoma UK and one of the most prominent cancer advocates in Europe, says he has found his 42: patient reported outcome measures.

He believes that these measuring tools of quality of life could put patient experience at the centre of research, clinical decision making and treatment availability – life, the universe, everything.

Patient reported outcome measures (PROMs) use patients' own assessments of their quality of life, capturing subjective experience through questionnaires. They have long been used in clinical practice and research to monitor patients during treatment, looking to measure physical symptoms, psychological problems and general quality of life.

But their use is patchy, inconsistent and uncoordinated. Wilson – who has advised the UK's National Cancer Director and was honoured in 2011 for services to healthcare – is on a mission to change that. He wants systematically gathered information about what gives patients a good quality of life to guide everything – research into drug treatments, clinical decision making, health technology assessments, cancer policy.

His vision is about to be spelled out in a far-reaching piece in the journal *Research Involvement and Engagement* – a rare example of a patient sole-authored paper in the peer-reviewed medical press. Wilson argues that the development of new cancer treatments is guided not by the value they add to patients' lives but by convoluted surrogate endpoints. Equally, treatment choice is informed by clinician opinion rather than patients' past experience of what works. Patient quality of life data, he says, must be standardised and gathered on a massive scale, so that whole pathways of care in every disease can be guided by what has actually helped patients live fulfilled lives.

"We need to measure and describe the pathways experienced by patients in terms that they understand," he says. "This would be done by bringing together quality of life data from a range of clinical and research sources, and aggregating and analysing it, to describe stages in the disease pathway."

Wilson's own experiences of can-

cer over 18 years demonstrate current gaps – and the potential of PROMs to fill them. Since being diagnosed with soft tissue sarcoma in 1999, Wilson, a former producer at the UK broadcaster the BBC, has had ten operations, chemotherapy and radiotherapy. These included a lower leg amputation in 2007.

It was his experiences when diagnosed with lung metastases in 2013 that truly convinced him that a change had to come. He was presented with several options: surgery, different types of ablative therapy, chemotherapy and palliative care. But the right choice was far from clear. There was no evidence about outcomes from each option for someone in Wilson's circumstances, and no quality of life data apart from one palliative care study. All he had to go on was clinical experience and informed opinion.

"I was at a branch point in my pathway," says Wilson. "And there were between four and seven routes I could follow, and the chosen one would unfold as my pathway from that decision point. In my own non-curative situation, all the pathways available would probably collapse into one at some future point. But I wanted the pathway which offered the fullest and longest life, and currently the data isn't there to inform the answer. Only information from patients can answer that question."

"I wanted the pathway which offered the fullest and longest life, and currently the data isn't there"

Having taken the best advice he could, from all the contacts he had, Wilson opted for innovative laser knife surgery. But he acknowledges that if he had had more information about patient experience along each of the treatment pathways, he might have taken a different decision.

How might this be achieved? The vision is that patients' own reports of quality of life are comprehensively recorded in every trial of every treatment and in every clinical intervention. This doesn't just have benefits in terms of monitoring patients as they undergo treatment. It produces a vast pooled database of experience

that can be used to assess outcomes and inform decision making at every point: drug approvals, clinical guidelines, treatment availability and health policy decisions.

"What I'm after, ultimately, is that anyone with a smart phone can report just one piece of data every day," says Wilson. "They could be reporting on pain one day, fatigue another, psychological feelings another. And even if you had a rare disease such as sarcoma, 100 patients feeding back on surgery by a particular surgeon, or a particular treatment over a year, you get extremely useful feedback."

Integrating PROMs into cancer care

It's not just patient advocates who are enthusiastic about PROMs. The Centre for Patient Reported Outcomes Research at Birmingham University aims to optimise the use of PROMs in clinical trials and routine care, to improve outcomes and ensure that the patient perspective is at the heart of health research and decision making. Patient partners, including Roger Wilson, are closely involved in the work.

Melanie Calvert, Director of the centre, says PROM data should be integral to cancer care. "Introduction of PROMs into a healthcare system can have a number of benefits and has the potential to tailor care to individual patient needs."

The immediate benefits in terms of monitoring patients are already clear. Recent work by Ethan Basch from the University of North Carolina shows that clinicians miss around half the symptoms experienced by chemotherapy patients. Using electronic systems where patients can continually record their quality of life allows a mechanism for early detection of symptoms and rapid response. Basch's team has shown electronic PROM use reduces hospitalisation and improves survival.

A recent review of evidence by Cancer Care Ontario in Canada found that use of PROMs in routine cancer care is popular with patients, enables earlier detection of symptoms and aids communication between clinicians and patients. Many PROMS are already used for monitoring – for example PROMIS (Patient Reported Outcomes Measurement Information System) and the QLQ-C30 quality of life questionnaire, developed by the EORTC. The Ambuflex telehealth system of patients reporting their symptoms and life quality via online questionnaires has been widely implemented in Denmark.

"PROMs data should be integral to regulatory and commissioning decisions"

But the potential benefits go way beyond monitoring. "In cancer care, patient reported outcome data collected in clinical trials can help future patients make informed choices," says Calvert.

"In addition, the data can be used to inform clinical guidelines and health policy. In my opinion these data should be integral to decisions made by drug regulators and commissioners, alongside survival and safety data."

Guiding approvals and access

Never has the need for this been clearer, as increasing evidence emerges that current decisions on treatment development and availability are skewed by commercial priorities rather than reflecting patient need. A systematic evaluation of oncology drug approvals by the European Medicines Agency (EMA) in 2009–13, published in the *British Medical Journal* last year, found that most drugs entered the market without evidence of benefit on survival or quality of life. Of 68 cancer indications with EMA approval, only 35 showed significant survival or quality of life improvement after three years.

An analysis of FDA cancer drug approvals in 2016, by Canadian researcher Christopher Booth in *Nature Reviews Clinical Oncology* last year, found that many approved agents offer only marginal value to patients, judged by the ESMO Magnitude of Clinical Benefit Scale.

Roger Wilson believes that drug approvals – and decisions about availability – are too far removed from patient experience. He points to research by Ian Tannock, presented to the National Cancer Research Institute in 2014, which reviewed major randomised controlled trials in breast, lung and colon cancer since 1975. He found evidence of smaller and smaller benefits from new drugs, researchers using complex surrogate endpoints, under-reporting of side effects and under-researching of quality of life.

"The analysis suggests that data are garnished to claim fancy conclusions, that a few weeks' added life is hyped as significant benefit, and that data on outcomes that patients really worry about – like the day-to-day effect of

their treatment – are missing," says Wilson. He worries that the situation could get worse, as excitement about immunotherapy, pharmacogenomics and precision medicine threatens to obscure realities for patient – such as new types of side effect and the need for regular biopsies on relapse.

For patient advocates like Wilson, it's part of a bigger picture of cursory patient involvement in running trials. For all the patient 'representation' on committees, how often do patient perspectives on quality of life guide assessment of outcome? If they are included as an endpoint, it tends to be secondary rather than primary.

Types of PROM

There are two main types of PROM, measuring different measures of quality of life:

Generic measures of quality of life

- enable easy comparisons across diseases,
- measure general functioning and quality of life over time.

The most commonly used generic measure is EQ-5D.

Disease-specific measures of quality of life

- are responsive and clinically useful
- measure frequency and severity of specific symptoms (e.g. nausea, fatigue).

Some patient reported outcome surveys integrate questions measuring disease-specific symptoms with questions measuring general quality of life. Together, generic and disease-specific PROM questionnaires allow patients to record both symptoms and their impact on their everyday functioning.

Slow progress

The University of Birmingham's Centre for Patient Reported Outcomes Research says there is evidence that patient-reported quality of life information is often omitted, poorly collected or badly reported in trials. In a major new study called EPiC, funded by Macmillan Cancer Support, the centre has joined with international collaborators to investigate how well – or poorly – PROMs are being used in UK cancer trials. Lead researcher Derek Kyte says that if PROM data is not being effectively collected and reported, "it is less likely to effectively inform patient and clinician decision making at the point of diagnosis and beyond, and represents a waste of limited healthcare and research resources."

One of the EPiC collaborators is Fabio Efficace, Head of the Health Outcomes Research Unit at Fondazione Gimema, Adjunct Professor at Northwestern University, Chicago, and Chair of the EORTC Quality of Life Group. He's pleased that, over the past 20 years, more and more trials have included a PROM component, reflecting patient perspectives rather than solely physician views on adverse events.

"The major evidence we have now is that the adverse events reported by clinicians typically represent an underestimation of the real symptom burden perceived by the patient themselves," he says. "Well-validated PROMs are the only way to translate the patient voice into clinically meaningful data that should better inform clinical decisions."

The need is clear. But if Roger Wilson is to see his vision realised, a multitude of barriers and limitations need to be overcome.

Making PROMs usable

It isn't just the problem of PROMs being poorly applied. There's also the problem of making sure that patients regularly provide information about their life quality over long periods. There's the problem of making sure that comparable PROM data is collected consistently across health systems – so that it becomes a genuinely useful big data project. And there's the problem of making sure that all that data, whether collected in trials or in everyday clinical practice, is actually used – in drug approvals, health technology assessments and treatment choices.

For Calvert, at Birmingham University, one of the main challenges to address is the multiplicity of PROM data capture systems being used to address different stakeholders' needs. "We are currently working with patients, clinicians and other stakeholders to understand their needs, and are developing systems for efficient PROM data capture in the UK National Health Service," she says.

To achieve consistency, the Centre for Patient Reported Outcomes Research is recommending that all clinical trials use its new international PROM protocol guidance, which was developed with international collaborators (SPIRIT-PRO). PROM data would more easily inform patient care if PROM reporting guidelines,

PROMS in cancer: the main players

The European Organisation for Research and Treatment of Cancer (EORTC)

- EORTC has long been involved in producing quality of life questionnaires for people with cancer.
- The most commonly used PROM in oncology is the QLQ-C30, which was launched by EORTC in 1988.
- QLQ-C30 is largely a generic quality of life tool, but has bolt-on modules for specific cancers and their symptoms (see box p 60).
- QLQ-C30 was designed to be used mainly in the context of clinical trials.
- EORTC supports the routine use of PROMs in manuals and guidelines.
- EORTC's SISAQOL project is developing an international set of data standards so that PROM data gathered in cancer research can be better compared and interpreted.

The Centre for Patient Reported Outcomes Research, Birmingham University, UK

- CPROR is researching how PROM use can be optimised in trials, applied research and routine practice.
- It is looking at the PROM guidance available to clinicians and study developers.
- It has been involved in the development of CONSORT-PRO and SPIRIT-PRO guidance – extensions of the CONSORT and SPIRIT guidance on methodological rigour and transparency in trials – to encourage high-quality reporting of PROMS.
- It works closely with patient partners.

John Ware Research Group, Boston, US

- The John Ware Research Group aims to standardise PROMs so that data from treatment outcome studies, individual patients, and populations can be compared, making information about outcomes more useful.
- Founder John Ware developed the SF-36 – an internationally used patient reported health survey.
- It recently developed new tools to: standardise PROM content and scoring across diseases; adapt to multiple chronic conditions in disease-specific measures; and integrate disease specific and generic measures.

Drug regulators

- The European Medicines Agency (EMA) and Food and Drug Administration (FDA) have issued guidance to researchers on the use of PROMs.
- The EMA has indicated that it is acceptable that quality of life and efficacy should be co-primary endpoints.
- The FDA has highlighted the importance of patients informing PROM content.
- Both the EMA and FDA are supporting EORTC's SISAQOL initiative to standardise PROMs analysis.

such as CONSORT-PRO were used, according to Calvert.

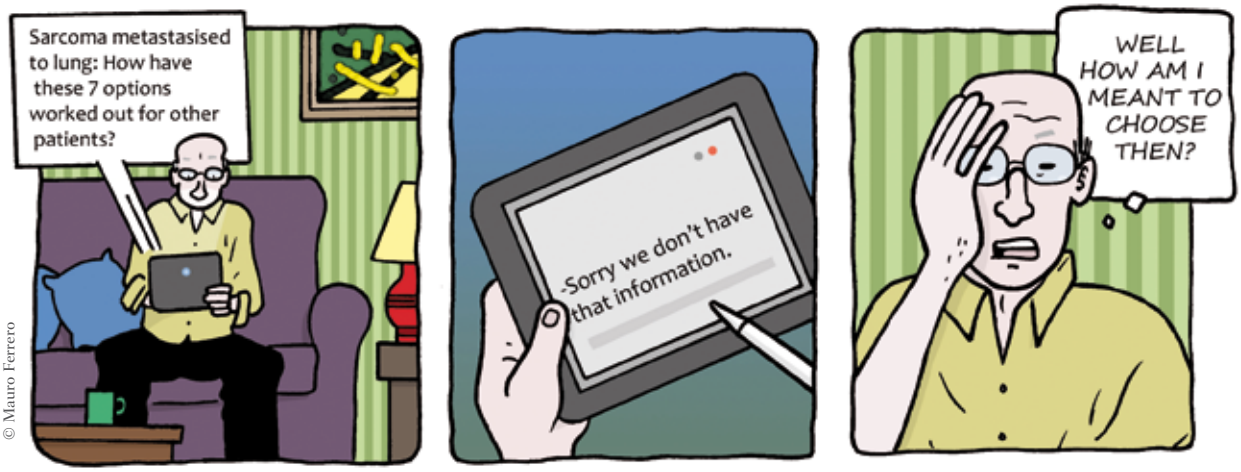
The other big challenge is to make the act of capturing data as easy and effective for the patient as possible. "There's a risk of over-burdening patients," she says.

Completing quality of life questionnaires can often be time-consuming – and sometimes frustrating to patients if the questions don't allow them to reflect what's actually happening to them.

Asking the right questions

This is an issue that has been preoccupying John Ware, Professor of Quantitative Health Sciences at the University of Massachusetts, who runs a research group aiming to standardise PROMs so that they can be used effectively to improve services. He is clear about the need for questionnaires that cover a broad range of domains and disease types, but which also allow the patient to zoom in and drill down into specific areas that are of concern to them at a particular time – and provide a "barometer" to their general wellbeing.

Ware's team have developed 'short-form' digital questionnaires, reducing dozens of questions to less than ten by directing patients to respond only about the disease, symptoms and issues that matter to them at a particular time. He has demonstrated that, through the use of apps, gathering detailed actionable data without



overburdening the patient is feasible.

The challenge now, he says, is to harmonise PROM tools on an international basis, so that all the data collected is comparable and useful. The harmonisation will involve incorporating already well-established generic PROMs with disease-specific PROMs, which provide the detailed data that cancer patients and clinicians really need. The measures produced by EORTC's Quality of Life Group have already provided a good basis on which to build, says Ware. Its QLQ-C30 questionnaire to assess the quality of life of cancer patients has been validated in more than 100 languages and is used in more than 3,000 studies worldwide. It is supplemented with modules for specific types of cancer (see box overleaf).

"It's the best generic tool, and what needs to happen is for it be more efficient and part of the move towards harmonisation," says Ware. Roger Wilson agrees they are a good basis on which to build. "The EORTC QLQ-C30 and the range of tools developed alongside may be the best generic PROMs we have at the moment. The extensions cover different tumour types, and patients are engaged in their development."

Making PROMs count

The potential is clear to Efficace, Chair of the EORTC Quality of Life Group. He says that, in the past, lack of methodological rigour and statistical consistency in trials has been a major impediment to PROM information being used to guide clinical decision making. But things are changing.

He has shown that gathering detailed actionable data without overburdening the patient is feasible

"Performing research well, and presenting it well to the scientific community, is essential. But it is not yet sufficient to make a difference in the real world," says Efficace. "The next step is to make sure that patient reported outcome data is considered by health policy makers and regulatory stakeholders, and actually influences future clinical decisions.

"I don't have all the answers for how you make that happen, but what I can say is that, in Europe, it helps a great deal that the EMA has recently issued a document stating how patient reported outcome tools should be implemented in clinical trials. These kind of official endorsements from regulatory stakeholders help clarify a number of aspects that could guide future studies."

EORTC too has a leadership role to play – both in keeping its tools relevant as cancer treatments and their side effects change, and in standardising data and its analysis. In 2016, it launched its SISAQOL initiative (Setting International Standards in Analyzing Patient-Reported Outcomes and Quality of Life Endpoints Data). This aims to develop recommendations for standardising the analysis and interpretation of PROMs and quality of life data in cancer randomised trials.

Efficace believes the initiative is an important one: the challenge will be to make sure it is implemented, among all the other guidelines that researchers and clinicians are supposed to abide by. "We in EORTC

An example of PROM scales: the QLQ-C30

The QLQ-C30 patient questionnaire consists of both multi-item and single scales. These include:

- **Functional scales**: Physical, Role, Emotional, Social, Cognitive;
- **Symptom scales**: Fatigue, Nausea and vomiting, Pain;
- **Global health status/QOL scale**;
- **Other items**: Dyspnoea, Insomnia, Appetite loss, Constipation, Diarrhoea, Financial difficulties.

should play a major role in raising awareness of the value of PROMs," he says, "both with regulatory stakeholders and with the public in general. We are fully committed to this, and will continue to push it over the coming months."

PROMs development starts with patients

For Roger Wilson, change needs to go even deeper, and the perspective needs to change more completely towards the patient. Impressed as he is with validated tools such as EORTC's, patients of all types – not just 'professional advocates' – need to be involved in revising and widening them. The work of updating and standardising PROMs needs to be truly multidisciplinary.

"The idea that you can have patient reported outcomes without patient provided inputs to inform methods and processes is irrational and probably unethical," he says.

For tools used specifically within cancer, the focus also needs to shift away from what researchers need to something that is used and valuable for every patient and in every clinic. "One of the problems with existing tools is that they have been developed in the context of randomised controlled trials. And although there is a growing library of tools covering specific cancers, they tend to be tumour specific, with a treatment focus," says Wilson.

"There are fewer tools available for use in specific situations, apart from palliative care," he adds. He cites the example of amputation, which is associated not just with cancer – as in his case – but also diabetes, vascular disease, and motorcycle accidents.

"Seven years ago I was involved in a project with palliative care sarcoma patients at the Royal Marsden. We used QLQ-C30 and several other instruments – getting a mix of generic and specific tools was the best we could do, because there was no sarcoma specific tool. There still isn't, although one is in development."

Will that kind of detailed development happen more widely? What will it take for Roger Wilson's 42 to be more than science fiction?

It is achievable, he insists. And, like Efficace, he believes the key is increasing awareness and changing mindsets. "The big issue is people thinking, 'Why do we need to do that?' So it's going to require a lot of willpower – a lot of real energy to get the word out and accepted. Nationally, PROMs need high profile leaders or organisations to provide credibility." Governments, he fears, are unlikely to impose anything from on high, or provide cash for blue sky projects.

John Ware shares his scepticism: "Personally, I'm tremendously disappointed that governments, which are spending huge proportions of GDP on the maintenance of human health, are not taking a lead on standardising its conceptualisation and measurement," he says.

So it may be down to the cheerleaders. And maybe the galvanising role of Roger Wilson, a man who will be spreading the word about PROMs at cancer events across the world during 2018 and 2019, will in the end prove crucial.

"Patients – and not just 'professional advocates' – need to be involved in revising existing tools"

"Across all the areas that people talk about for improving cancer survival – better diagnostic techniques, faster routes to diagnosis, new drugs and treatment techniques – lies the issue of quality of life," he says. "All the buzz and hype is about drugs, particularly in advanced disease, and what's friendly to the patient gets forgotten. It's about redressing the balance."

And by prioritising the patient experience, it also happens to be rather revolutionary? "Oh yes, I love that," says Wilson. "I'm all for a bit of revolution."

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Gathering long-term data on what happens next

'Survivorship' is a rapidly growing field of research, as more cancer patients live longer, and require different types of support to get their lives back on track. Typically such research has been disconnected from clinical trials, but this may be starting to change, as **Anna Wagstaff** reports.

Survival is a necessity after a cancer diagnosis, but 'getting one's life back' is what everyone aspires to after treatment. Yet the literature on long-term outcomes reveals very little evidence about some of the things that matter most.

Does the pain, fatigue, sickness or neuropathy reported during clinical trials abate or continue, and if it continues, how severely and for how long? How does the experience of having that cancer and undergoing that treatment affect people's confidence, wellbeing, the ability to fulfil roles as parent, partner, carer, friend? What's the success rate in terms of capacity to have children, to work, to enjoy sex and enjoy their leisure time, to travel and to make plans, take out loans or mortgages and generally carry on normal life?

As advances in early detection and treatment lead to more cancer patients being cured or living longer with cancer, these aspects of long-term outcomes are giving rise to a new field of 'survivorship' research.

However, such research is fragmented and has diverse aims: defining

and meeting the needs of survivors, assessing the efficacy and value for money of different interventions and pathways of care, and/or looking for ways to mitigate the economic burden of growing numbers of survivors. Research is typically conducted within different academic settings, looking at different sets of indicators for different cancer populations and usually without any reference to the specifics of their diagnosis or treatment.

Step forward the EORTC, Europe's oldest and largest academic cancer trials organisation, which has been coordinating clinical trials across a wide range of cancers for the last 56 years.

EORTC recently committed to developing and implementing an infrastructure designed to "optimise long-term follow up among patients treated in clinical trials" and promote data sharing with cancer registries and other "data owners", with a view to reducing wasteful duplication and fostering "scientific collaboration on long-term outcome research".

The clinical trials group will shortly be piloting its new YOU (Your Outcome Update) protocol, designed for collecting long-term data from patients who participate in EORTC-supported trials. Lifang Liu, coordinator of the YOU protocol, explains the thinking behind it. "Currently long-term outcomes research is quite scattered and normally it is done by academic centres. Pharma are not very interested in long-term follow up – after their drug is approved, they are done with the whole business. At EORTC we are independent, academic and not for profit, following patients for their care and late adverse effects. That is our tradition, and we want to follow up in this tradition. EORTC is working with multiple international tumour groups. The YOU protocol is really built on this collaboration across tumour types. We don't do breast only. We don't do Hodgkin lymphoma only. We just do research for all types of cancers, common and rare. And EORTC has this ability to do so."

EORTC has a long tradition of conducting long-term follow up, including its first ever trial, started in 1964, which looked to optimise treatment of patients with Hodgkin lymphoma, and is still being followed to this day.

"It is our responsibility as oncologists to make sure these patients don't have to go through a second ordeal to get back to normal life"

What's new, says Liu, will be the inclusion of highly specific questions about long-term effects that are tailored to the specific treatment protocol each patient received. "So far, evidence on long-term side effects mostly comes from observational data, without prospective randomisation. With the EORTC data, we know the randomisation, we have all the clinical data related to each patient's treatment, so we can see which treatments cause the long-term effects."

Liu mentions immunotherapies as a prime example where such research is urgently required. This is an entirely new class of drugs, for which very little is known about long-term toxicities, and where use is beginning to spread from the relatively rare cancers where they first showed their value, to more common cancers where their benefit may be less pronounced. Generating reliable data on the long-term effects associated with different regimens will be essential to ensuring patients get the best evidence-based care – and the EORTC's YOU protocol, says Liu, will be seeking to provide that evidence, using outcomes measures specifically tailored to the treatments under review (see also 'PROMs put patients at the heart of research and care', p54).

More generally, she adds, generating reliable data on long-term outcomes of different therapeutic strategies will offer a unique resource for healthcare providers and payers to see where they need to intervene.

Prejudice and discrimination

The decision to invest so heavily in researching long-term outcomes can be attributed in no small part to Françoise Meunier, who was Director General of the EORTC between 1991 and 2015, and now leads special projects, with a focus on survivors. She is particularly pleased that the YOU protocol will gather evidence on socio-economic outcomes, such as access to financial services and employment.

"This is something totally new. We may have collected follow-up data for 25 years on breast cancer patients treated with radiotherapy, but we have never collected societal issues."

This is important, she argues, because one of the biggest obstacles survivors can face comes not from the impact of the cancer and treatment

Loans and insurance: new strategies for access

© Niccolò Assirelli

Over the past three years, France and Belgium have adopted laws to help survivors of cancer and chronic diseases improve access to financial services, such as mortgages and insurance. It has taken time for the new systems to get up and running, so details on who is benefiting remain unclear. Françoise Meunier, who leads the EORTC's survivorship work, believes the two laws offer possible templates that other European countries could follow. She is determined to see similar rights extended to survivors across Europe before she retires.

Under the French law of *droit à l'oubli* – right to be forgotten – people applying for loan-related insurance need not mention any history of cancer if at least 10 years has elapsed since the end of their active treatment – five years in the case of childhood cancers. Shorter time periods are specified for certain adult low-risk cancers, such as early stage breast or skin cancer, or cancers of the thyroid or testicles, as defined in a reference table. This is updated annually by a commission including representatives from insurance companies and banks as well as the Department of Health and patients, based on data provided by the French National Cancer Institute (INCa).

Another approach, adopted in Belgium, requires companies to justify any decision they make to refuse insurance to people deemed at additional risk or to quote a premium more than 75% above the standard. Risk assessment is done at the individual level, and applicants have the right to appeal to a body

on themselves, but from the prejudice and discrimination they face from others: employers who assume that someone with a history of surviving cancer is a liability rather than an asset, insurers who evaluate risk based on the word 'cancer' rather than the evidence of a personal prognosis.

Meunier believes that, as a clinical research organisation, EORTC is not only uniquely placed to gather this sort of information, but it also has that responsibility. "I have fought for 44 years as a doctor to improve survival and quality of life of patients with cancer. We have reached a point where we cure 90% of children with leukaemia, 99% of testis cancer, 85% of Hodgkin and so on. So I think it is our responsibility now as doctors and oncologists to make sure these patients don't have to go through a second ordeal to get back to their normal life."

She believes robust data on long-term outcomes can help remove unfair barriers in a number of ways. It can be used to shape policies designed to give survivors the support they need and protect them from unfair treatment and prejudice. It can support advocacy to raise awareness of the growing proportion of the population who are living fulfilling lives with or after cancer, and challenge the negative assumptions about survivors that give rise to discrimination. It can also provide insurers with accurate prognostic data on which to personalise risk assessments.

Meunier is keen to work with patients' organisations, employers, insurers and policy makers to pursue all of these avenues. But it is on the specific question of removing unfair barriers to financial services required

composed of representatives from patient groups and the industry, which will base their ruling on data in the literature. Where an additional premium is very high, the bureau can rule that it is paid from a funding pool to which all insurers have to contribute.

"A good start"

Marie Mesnil, a lawyer who has been working with the EORTC, says that both systems fall short of what survivors hope for, but are "a good start". The French *droit à l'oubli* works well for the patients who qualify for the shorter time periods for their diagnoses to 'be forgotten', she says, but "for other people it is quite disappointing as they have to wait for 10 years." As time goes by it is expected that additional groups of patients will be added to the reference table, she adds, but how far and how fast that happens remains to be seen.

The good point about the Belgian system, by contrast, is that, "each refusal or severely raised premium has to be assessed with a second opinion," says Mesnil. However, survivors have been disappointed at how seldom the original decision is overturned, she adds. "In 2016, the appeals body upheld the original decision in 77% of cases of elevated premiums, and 85% of refusals."

Feedback from one of the insurance company representatives on the appeals body does, however, indicate that the law has forced a change in the mindsets of companies, says Mesnil. "They have to be more accurate in risk assessment and take into account the most recent data, and they have to justify their decision in regard to the anti-discrimination legislation."

Mesnil has started mapping legal frameworks for financial services across Europe. No other country has the level of protection that France and Belgium have introduced, she says, though a small minority, including the UK, have niche providers that cater specifically for populations with added risk factors.

> "Feedback indicates that the law has forced a change in the mindsets of companies"

Meunier has spent frustrating years trying to convince European insurance companies to make use of the available data as a basis for risk assessment. She now believes the anti-discrimination legislative approach implicit in the French and Belgian frameworks is the way to go.

She is also encouraged by what seems to be stronger signals coming from the EU about discrimination on the grounds of health. A 2016 recommendation from the European Council (Committee of Ministers) on the processing of personal health-related data for insurance purposes – CM/Rec(2016)8 – includes a section on Provisions on Risk Assessment, which embraces the key principles adopted in France and Belgium.

to buy a house, start a business or even travel, that Meunier is most determined to force through progress for survivors across Europe. It's a goal she has been pursuing for many years, and which she believes now has a realistic chance of success (see panel).

Back to work

The EORTC's decision to focus more on long-term impacts on patients' lives has been broadly welcomed by the European Cancer Patient Coalition (ECPC), which has affiliates in every country in Europe, representing patients from across the spectrum of cancers.

ECPC President, Francesco de Lorenzo, says, "We know from a study conducted by the Italian Association of Cancer Registries that 800,000 people who were treated for cancer in Italy can be considered cured, i.e. they have the same life expectancy as other people of similar age and socio-demographic characteristics who have not had cancer."

He believes, however, that the biggest problem for survivors, both socially and financially, is not so much access to financial services, but getting back to work. "Fifty percent of people who can be considered cured of cancer are living with some kind of disability," he says, and he argues that the priorities must be to fight for access to rehabilitation, and for more protection for survivors against being forced out of their jobs.

Above all, he says, they need action. "It is important to have state-of-the-art cancer research on long-term outcomes, such as that conducted by

EORTC. But patients and survivors also need policy right now for survivorship care and social issues to support them with rehabilitation, tertiary prevention and generally assist 'cured' people in getting back to work and a normal life. So we cannot hold off until we have more long-term data. We are fighting for that now."

ECPC is campaigning on many fronts, says de Lorenzo, including working on guidelines for national cancer plans to improve care and support for survivors, as part of CanCon, the European Joint Action on Cancer Control. It is also collaborating with the European Society for Medical Oncology and the International Psycho-Oncology Society on a Patient Guide on Survivorship and a Survivorship Plan, intended to become an integral part of the patient discharge instructions. ECPC also developed a White Paper on Cancer Carers, in partnership with EuroCarers, which set out the principles, framework and policies needed to give people with cancer and their carers a decent quality of life. This was published in October 2017 in the context of a forthcoming Directive to "support work–life balance for parents and carers".

EORTC's Meunier understands that survivors don't want to wait for data before securing change. She argues, however, that high-quality data linked to specific cancers and protocols will be essential to enabling patients and doctors to make informed choices in the future that take into account the overall long-term impact on lives.

Data can also be used to guide service providers towards providing survivors with the right mix of services and support to help them get all aspects of their lives back on track as fast and effectively as possible.

Key to this will be feeding into health technology assessment (HTA) and reimbursement processes, says Meunier. "So far, in discussions with HTA bodies and payers, they are aware of the importance of long-term outcomes, but the problem is that no one wants to [gather the data]. Pharma are not interested, and even if they were forced to do it, they would not have the ability or authority to access the data. EORTC will have this unique contribution. It takes time for people to realise how important this sort of data will be."

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INSIDE TRACK CONFERENCE

Agnès Buzyn

French Minister for Solidarity and Health

A professor of haematology, specialising in bone marrow transplants and leukaemia, with a career that has spanned clinical practice, research, policy making and now political office – Agnès Buzyn has an unrivalled breadth of experience in tackling cancer. In 2017, after five years at the head of the French National Cancer Institute, INCa, she was appointed Minister for Solidarity and Health. *Cancer World* asked Agnès Buzyn how her time at INCa prepared her for her new responsibilities, and what tips she can offer those of us trying to influence government policy on cancer care.

Cancer World: *What are the most valuable lessons you learned during your time leading the French National Cancer Institute that you can draw on in your present job as Health Minister?*

Agnès Buzyn: When I was the head of the French National Cancer institute, I had the privilege of drawing up the Third Cancer Plan, which was very ambitious both in its scope and its goals.

Today, I continue to believe that the only way to really move the boundaries is to be ambitious and politically courageous.

CW: *What are you learning in your new position that might offer helpful insight for leaders of Europe's cancer community about how to influence policy makers and politicians at national and European level?*

AB: In trying to influence policy makers, it is important to stress that cancer is a big concern for citizens,

and it causes a lot of anxiety. It takes a toll on people's social and economic wellbeing. But some cancers can be avoided by prevention policies, which must be considered as key elements in the fight against cancer.

When you are arguing your case to policy makers, I think it is very important to start from the scientific evidence, and to demonstrate the social consequences of cancer. You need to encourage them to see beyond the aspect of the public health expenditure resulting from this disease.

CW: *All ministers have to balance competing priorities. How effectively are you able to coordinate policy with other ministers in relation to decisions that impact on cancer and health?*

AB: French Cancer Plans have a somewhat unique governance, which involves the highest institutions of the State. The President receives an annual report drawn up by the committee leading the Plan. Ministers for Research and Health co-chair the committee, but other ministers are also involved – including Ministers of Education, Labour, the Environment. This guarantees that a wide range of aspects of the fight against cancer are taken into account.

The current Cancer Plan was launched in February 2014. This committee also integrates the chief executive officer of the French National Health Insurance Fund, the chairperson of the French National Cancer Institute, and associations representing patients and users of the health system.

This enables us to take into account different perspectives and points of view regarding our strategy, and prevents us from taking one-sided decisions.

Finally, the decisions are implemented through coordination by the National Cancer Institute. At the regional level, it is the regional health agencies that are responsible for the implementation of the Cancer Plan in their region. This is very important to enable our health system to adapt to all the specificities of our territories, which is essential in order to guarantee equal access to health care.

CW: *If you had to name one thing, in terms of French cancer policy, that other countries could learn from, what would that be?*

AB: We must open up our perspectives. We have to look for a cross-disciplinary approach, to use all the levers of actions: prevention, health care organisation, research.

The French National Cancer Institute carries out all these missions, and French Cancer Plans have always covered all these aspects. This, I think, is where the strength of our Cancer Plans lies.

CW: *And if you had to name one aspect of cancer policy that another country gets right that you would like to introduce to France, what would that be?*

AB: We can learn a lot from Northern countries. They have a strong capacity for mobilising their citizens regarding healthcare issues. They offer a good example, for instance, on prevention and healthly lifestyle interventions, such as vaccination coverage and promoting health through physical activity.

To comment on or share this article, go to bit.ly/CW81_agnes-buzyn

French Health Minister Agnès Buzyn is Professor of Haematology at the University Pierre-and-Marie-Curie in Paris. She spent a large part of her career as an academic haematologist and clinician at the University Paris Descartes – Necker Hospital, where she headed up the adult haematology intensive care and bone marrow transplant unit.

She spent several years as director of a research team on tumour immunology at the National Institute of Health and Medical Research (INSERM). Buzyn has also served on the boards of many national organisations, including as Chair of the Executive Board of the Radioprotection and Nuclear Safety Institute (IRSN) – a role which first brought her to public attention, during the Fukushima crisis.

She was President of the French National Cancer Institute INCa between 2011 and 2016, during which time she oversaw the development of the third iteration of France's flaghsip national cancer plan (bit.ly/ThirdCancerPlan_fr), and became a familiar figure on the European cancer scene. Agnès Buzyn was profiled in 2013 in a Cover Story for Cancer World bit.ly/Buzyn_CWCoverStory

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E. Senkus-Konefka (Eds.)
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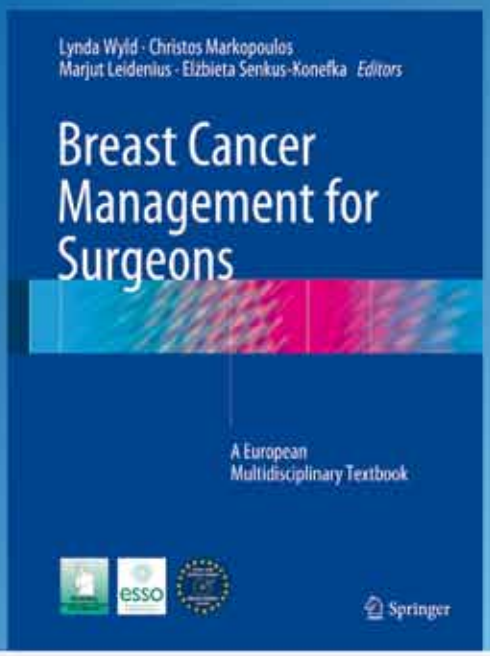

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