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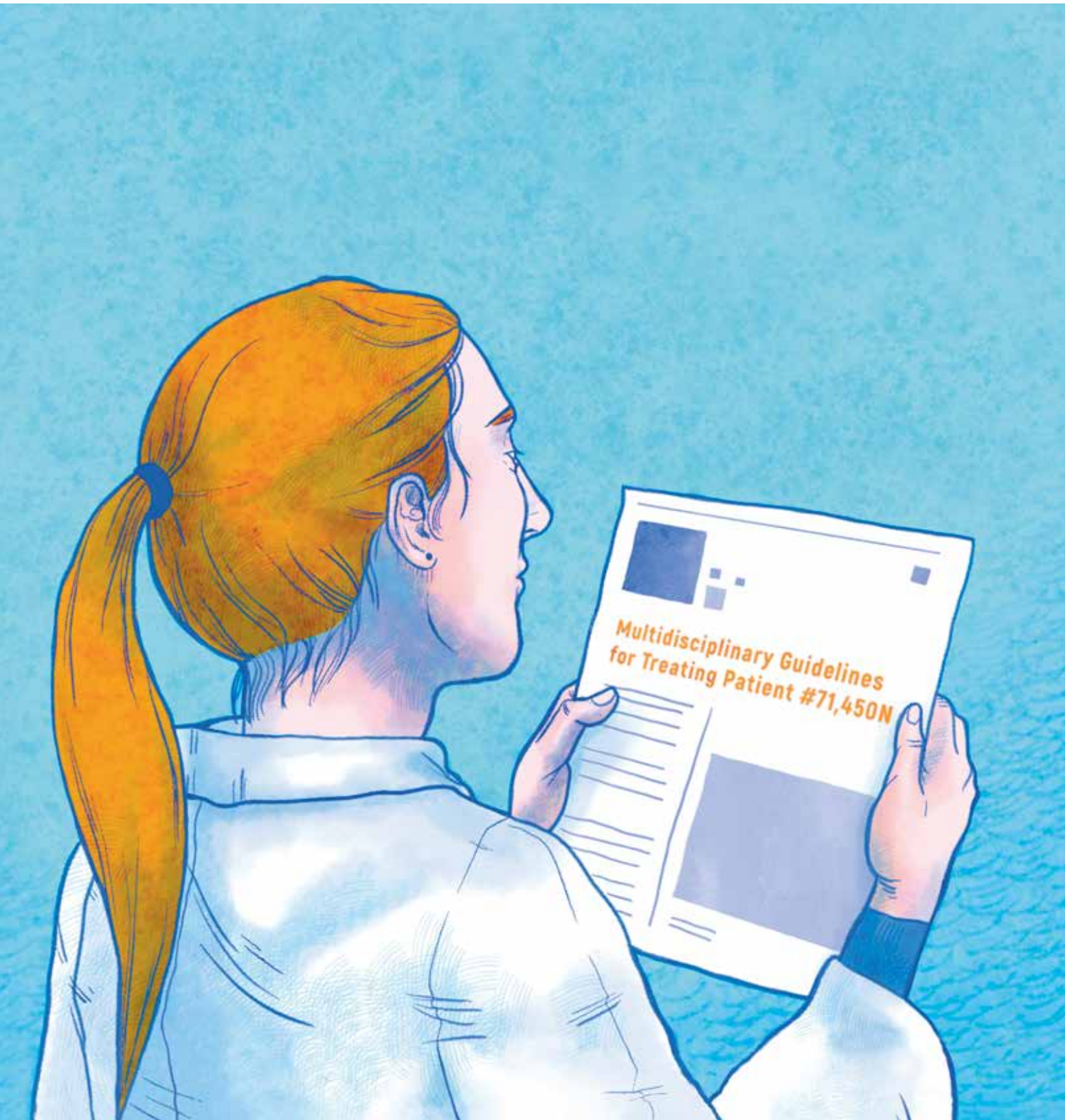

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'Precision medicine?'
by ***Sara Corsi***

Contents

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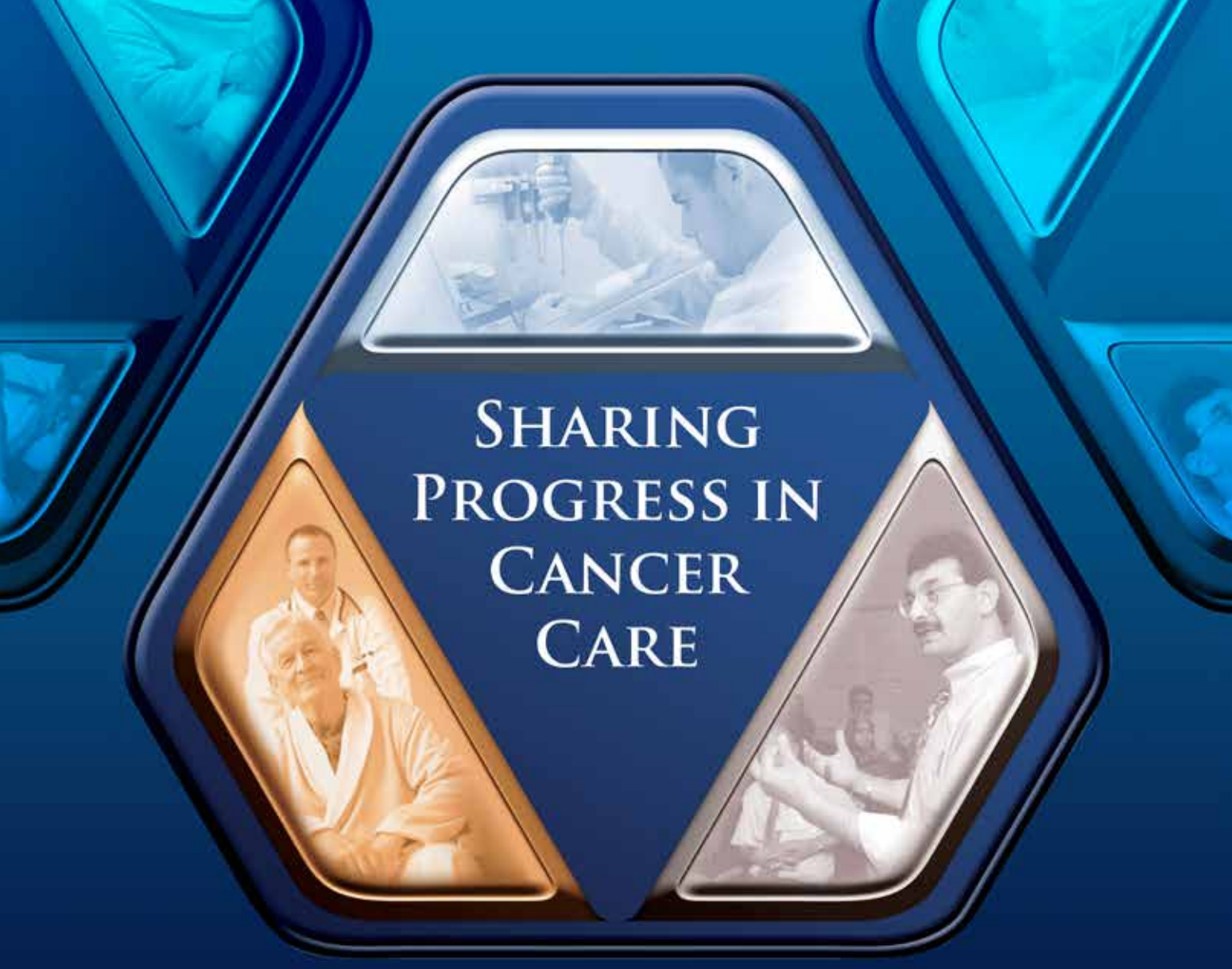

Sharing Progress in Cancer Care (SPCC) is an independent, non-profit association based in Switzerland. It works in the fields of cancer education, care improvement and innovation, focusing on areas where collaboration between various stakeholders including industry and academia is the key for success.

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Tackling cancer in interesting times

Adriana Albini *– Editor in chief*

Being Venetian by birth, I am a keen visitor to the Biennale – the contemporary art exhibition that is hosted by the city every two years. In 2019, reflecting this period of tumultuous change, the Biennale adopted the theme: "May You Live in Interesting Times".

The phrase could be interpreted as a wish or a curse. It can evoke a sense of challenge or even menace, but it can also be an invitation to consider the turn of human events in all their complexity.

We who work in oncology are living in 'very interesting times'. The field has been undergoing a permanent revolution over the past three decades. Molecular diagnosis and new imaging modalities have transformed clinical practice. We have seen the implementation of hormonal and targeted therapy, immunotherapy, CAR T cell technology, genetic engineering, enhanced radiation therapy and nuclear medicine – all of these with great advantages but also non-negligible toxicities.

The digital revolution has brought us big data and eHealth Technology. We now interrogate our genetic background, and sequencing and 'omics are in day-to-day use. We measure our health using a proliferation of smartphone apps – not all of them endowed with the same quality or reliability.

Costs have risen progressively, leading to therapies becoming less affordable and wide disparities in access emerging along geographic, ethnic, gender, age and socio-economic lines. Living longer frequently entails many years of poor health in later life, and often also loneliness – cancer is a disease of the whole body: organ, microenvironment, and soul.

In my own research, alongside the patient there is always the 'non patient' – the healthy person who is at risk of cancer. We need to ask: what does it mean to be truly 'healthy'? And how can we learn about what stops healthy people tipping into sickness? Prevention studies are notoriously difficult as they seek to explore a non-event.

The term 'chemoprevention' was defined by Michael Sporn in the late 1970s as the use of natural, synthetic, or biologic agents able to delay, reverse, or inhibit tumor progression. *Cancer World* editor Alberto Costa was heavily involved in early clinical applications of the prevention concept in breast cancer in the 1980s and '90s.

A recently emerging concept is 'cancer interception', a sort of early-adjuvant approach, introduced by Nobel laureate Elizabeth Blackburn, which strives to actively interrupt the growth of a tumour mass at its earliest stages. Craig Jordan's tamoxifen studies, which are described in this issue, can be seen as an early example of using the interception approach in relation to secondary tumours.

We know that the health, wellbeing and happiness of cancer patients depend on many factors beyond diagnosis and therapy. Our approach should be not only Predictive, Preventive and Personalised Medicine (PPPM), but also Participatory, and with a Psycho-oncology dimension.

We need specialist nursing care, rehabilitation, good food and exercise, serenity. We need to think more deeply about what the 'end of life' and palliation should be.

These times are interesting: it is both a wish and a curse. "In times of great change," observes Biennale President Paolo Baratta, "we must pay attention to the evolution of the world," and we should ask ourselves, "How have we reacted?" He suggests that successfully navigating the complexity requires not reducing "to schemas and formulas – something which, by its very nature, is manifold."

From its birth in 2004, *Cancer World* has sought to address all the many and complex aspects of cancer that matter to patients and where oncology professionals have a role to play.

I see it therefore as an honour and a responsibility to take over as editor of *Cancer World* to address new challenges for these 'interesting times' in oncology.

Evidence-based medicine and precision medicine – irreconcilable or inseparable?

How do you build an evidence base to inform treatment choices that are tailored to the unique genomic profile of each patient and their disease? **Sophie Fessl** talks to some leading clinical researchers and statisticians who are trying to find answers.

"Medicine cannot be learned quickly, because it is impossible for there to exist any established method in it, as for example when someone who has learned to write in one way that is taught then understands everything. Medicine from one moment to the next does things that are opposite, and it does opposite things for the same person, indeed, even things that are self-contradictory."

The writer of the Hippocratic treatise *On the Places in Man* – written around the mid-fifth century BCE – articulated a dilemma of medical thought that has prevailed until today: How can a framework for medical theory and practice be built? Should medicine proceed based on the differences between patients or on their similarities?

The tension between the general and the specific continues in oncology today. In the past century, considering the general was the norm. Large trials generated evidence for treatments, under the brand of "evidence-based medicine", the results of which were then applied across the patient population. But not everyone is the same. In the past twenty years, personalised medicine, with its premise of tailoring treatment to a patient's individual profile of mutations, entered oncology. The hype and hope with which personalised medicine – variously also called precision medicine or stratified medicine – has been greeted suggested it may revolutionise cancer treatment. But will it?

Hype or hypothesis?

One of precision oncology's most prominent critics, Vinay Prasad, haematologist-oncologist and Associate Professor of Medicine at Oregon Health and Science University, has called precision oncology "a hypothesis in need of verification," (*Nature* 2016, 537:S63). Damian Rieke, oncologist at the Charité University Hospital in Berlin, Germany, expresses his reservations more cautiously: "I do believe that precision oncology has a future and that it makes sense to continue to pursue this approach. But we have to be careful not to throw evidence-based medicine overboard, just because we can now sequence our patients."

The starting signal for precision oncology was the development of imatinib as a treatment for chronic myeloid leukaemia, CML. Imatinib inhibits the bcr-abl kinase, the aberrant protein driving CML. In the phase I trial of imatinib, 53 of 54 patients went into complete haematological response. This created a new paradigm of targeted treatments that take aim at driver mutations. But with the benefit of hindsight, commentators point out, imatinib and its effectiveness in CML turned out to be an exception. In fact, imatinib is one of the very few targeted agents that achieve a long-lasting benefit, even when administered on its own. For many other precision oncology agents, this success was not repeatable. Tumour heterogeneity and clonal evolution usually give cancer multiple escape routes from targeted therapy.

Hence, treatment response and prognosis is much less predictable by genetic tests than was expected based on the imatinib-CML paradigm. And while the course of illnesses with a clear, identifiable, singular genetic alteration, such as CML, may be altered dramatically, it is much less clear whether this promise holds true for other cancers (*Lancet Oncol* 2016, 17:e81–86). In 2016, Prasad noted that, "When patients with diverse, relapsed cancers are given drugs based on biological markers, only around 30% respond at all and the median survival rate is just 5.7 months." He estimated that "precision oncology will benefit around 1.5% of patients with relapsed and refractory solid tumours" (*Nature* 2016, 537:S63).

Making sense of complexity

The main difference between evidence-based medicine and precision medicine is the depth of data, says Rieke. "When a patient comes to the clinic, we try to gather as much data as possible – diagnosis, stage, previous treatments, lifestyle, allergies – and then decide what the best therapy is, based on the currently available data… When [in addition] we sequence 10,000 genes, we have many more datapoints and a higher complexity. In both approaches, we personalise treatment based on the patient, but in precision oncology, we have the added genetic datapoints."

Molecular tumour boards attempt to make sense of this complexity. "At the Charité, two to three doctors work full time to look at patients' genetic data and comb through the literature. This information is collected and assessed, based on study design and the level of evidence. The aim is to make the recommendation for which there is the best evidence", explains Rieke.

Rieke led a study comparing the treatment recommendations made by molecular tumour boards (MTBs) worldwide (*JCO Precision Oncology* 2018, 2:1–14). The team sent genomic information of four fictional patients to MTBs. Although all MTBs received the same information, the recommendations of the five MTBs that replied

differed substantially for some patients. This is a problem, says Rieke. "On the one hand, it means we create a lot of evidence which is not optimally retrievable for the individual patient. On the other hand, we have no standards for how to handle genetic data."

All MTBs received the same information, but the recommendations of those that replied differed substantially for some patients

One step towards harmonising recommendations is to make genetic evidence more readily accessible. A dozen knowledge bases store evidence on genetic mutations, of which Rieke estimates only a few to be useful, "but each database also holds unique information – this shows us just how much data we have."

A framework for aggregating and harmonising clinical interpretations of detected variants has now been developed using data from six prominent cancer variant knowledgebases *(biorxiv.org/content/10.1101/366856v1.full.pdf)*. The framework aims to provide access to concise, standardised, and searchable clinical interpretations (therapeutic, diagnostic, prognostic and predisposition) of detected variants drawn from across multiple institutions that gather and store that data. The harmonised interpretations from those six knowledgebases have been published on an open and searchable website *search.cancervariants.org*.

Therapeutic freedom versus treatment algorithms

How to handle genetic data and make treatment decisions based on – eventually harmonised – genetic evidence is a different debate. Rieke advocates giving oncologists freedom to decide.

"I think we are far removed from assigning optimal treatments using a computer. We shouldn't treat patients according to an algorithm, but based on experience – taking into account, for example, previous therapies. Oncologists should have a certain therapeutic freedom, but the available evidence should be the same – which it isn't."

Developing treatment algorithms is hard, not least because statistical considerations have to be taken into account. Jan Bogaerts, Scientific Director at Europe's largest independent cancer research organisation EORTC, explains the dilemma: "I'm concerned about which methodology we will use to tease apart the changes we make for patients, and worry about the multiplicity of testing. The more research claims to be personalised, the smaller the subclasses of analysis will become. One idea is to solve this with AI, but these methods are very data hungry – I'm not sure that will work with the data we have available."

Several years ago, Bogaerts was asked to comment on an idea of comparing several treatment assignment methods in parallel – but this approach had to be abandoned as the statistical requirements were too complex. "If we try to compare two or more gene-based methods of deciding which patient gets which treatment, and want to answer the question of which one of ten drugs should be given to a patient, we have a very difficult problem. In our answer, we would mix the relative efficiency of drugs tested and the way of assigning patients to them. In reality, we would only be able to give a pragmatic answer, that one method of assigning patients gives a somewhat better survival, without being able to identify the reasons why that happened."

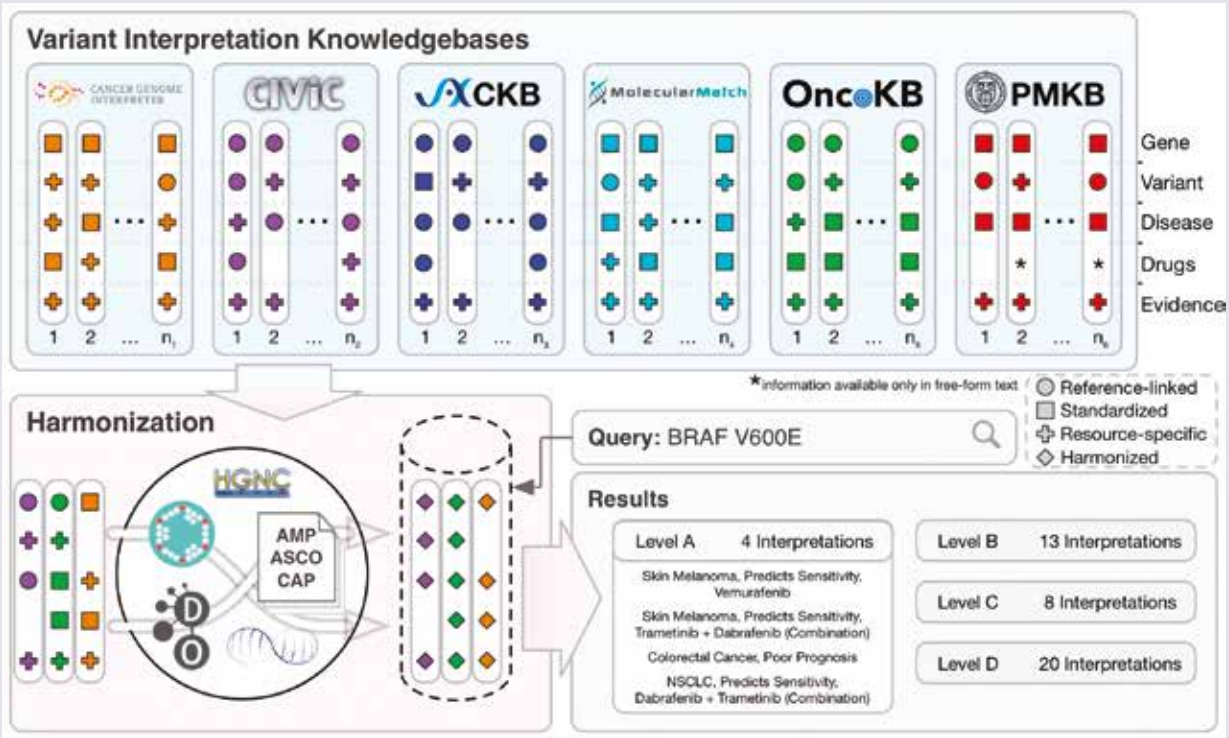
"An approach in which we do within-patient experimentation before deciding on a treatment would improve the situation a lot"

From a statistician's point of view, Bogaerts sees a protocol in which each patient serves as her or his own control as ideal. "For statisticians, an approach in which we do within-patient experimentation before deciding on a treatment would improve the situation a lot. But this is totally utopian in most situations in cancer."

Precision oncology on trial

Clinical trials put precision oncology to the test. The French SHIVA01 trial was the first, and so far only, randomised trial of therapy directed at pathway mutations. In this study, patients with metastatic or refractory solid tumours who had already received the approved line of treatment, including molecularly targeted agents, were randomly assigned to either receive treatment aimed at the pathway in which their molecular alteration fitted,

The VICC Meta-Knowledgebase



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The Variant Interpretation for Cancer Consortium (VICC) meta-knowledgebase is a harmonised collection of clinical variant interpretations and related variant information informing of the clinical significance of variants observed in human cancers.
The meta-knowledgebase was created to evaluate the disparities in variant interpretation content and structure across established resources of clinical interpretation knowledge. It harmonised information from six prominent cancer variant knowledgebases: Cancer Genome Interpreter (cancergenomeinterpreter.org), CIViC (civicdb.org), CKB (ckb.jax.org), Molecule Match (molecularmatch.com), OncoKB (oncokb.org) and PMKB (pmkb.weill.cornell.edu).

The VICC meta-knowledge base is searchable using its associated web interface: search.cancervariants.org

or to receive treatment as per clinician's choice. The primary endpoint in the study was progression-free survival. The results showed that treating patients according to the molecular pathway did not improve median progression-free survival.

For Rieke, the design of the study is partly to blame. "SHIVA01 was too simplistic, it targeted only the signalling pathways in which a genetic alteration is placed. However, there are more specific inhibitors that target the exact mutations causing a pathway activation. While thinking in terms of pathways is already more personalised than conventional therapy, the assignment of therapy was obviously not good enough."

Prasad, too, readily grants that these results do not mean that precision oncology *per se* will fail, just that the tested strategy failed. But he warns that "… because the tested strategy is consistent with the growing off-protocol use of these drugs, results of the SHIVA trial should serve as a powerful deterrent against the off-protocol use of unapproved targeted drugs…" (*Lancet Oncology* 2016 17:e81-e86).

Concerns about the extent to which these drugs are being used off protocol were highlighted in a recent article that looked at 'Early Returns from the Era of Precision Medicine', principally from a cost-effectiveness standpoint (*JAMA* 2020, 323:109–110). "Off-label use has

been estimated as high as 30% of use for some anticancer agents," notes the author. A key issue, he says, is that anticancer drugs tend to be tested in metastatic cases first, "because clinical trial recruitment is easier and the time from initiation of therapy to a meaningful end point is shorter." However they are then sometimes used off-label to treat earlier-stage cancers or certain other cancer types, he notes, "even before clinical trials are conducted or completed".

Maud Kamal, scientific manager in charge of precision medicine project coordination at the Institut Curie, in Paris, and scientific coordinator of the SHIVA01 trial, sees validation in the trial's secondary endpoint. "As a secondary endpoint, we used patients as their own control. We compared progression-free survival of patients undergoing targeted therapy as compared to conventional therapy and see that a subpopulation of patients does better if they are treated based on the altered pathway. So treating based on alteration works in a subpopulation of patients."

Kamal acknowledges room for improvement. "We reassessed the SHIVA01 results by classifying the alterations used in the SHIVA01 algorithm according to the ESCAT scale, which classifies the association between a molecular alteration and a specific targeted therapy. We found that the majority of alterations in the algorithm were tier 3 alterations, for which there is only moderate evidence. We may need to refine the algorithm to give better treatments to our patients."

Kamal will keep looking for a proof for the precision oncology approach. "We will need more trials with different types of design to have clinical proof. As for the treatment algorithms, we need to be precise. While one mutation may be actionable, another mutation in the same gene but not at the same position might not be actionable and targetable to the same degree. We know clinical evidence is important, so we should not just stick our treatment decision on a gene or signalling pathway, but go beyond and look at the specific alteration."

Real world data cannot replace RCTs

What can be done to increasingly tailor cancer treatment to the patient, but maintain the "safety in numbers" given by large trials? The collection of so-called real world data after drug approval may not cut it, says Bogaerts. "I'm worried that, guided by hype, and without sufficient certainty that the precision oncology method will work, we will give up parts of randomised clinical research and bank a lot on real world data.

"But this data is not necessarily geared towards answering our questions. If precision oncology doesn't come through as promised, we will have big gaps in our knowledge in the future."

In January 2019, the EORTC launched its 'Manifesto for establishing treatment optimisation as part of personalized medicine development', (bit.ly/EORTC_Treatment-Optimisation-Manifesto, see also p9). This envisages an approach in which relevant questions for patients outside the, often-limited, patient group included in a trial are answered before approval, Bogaerts explains. "In the current model, we test a restricted number of almost ideal cases and then approach all the other cases – often the majority – by hand waving, saying 'we will see in the clinic how we will solve this small problem.' Then a cancer patient comes to the clinic who doesn't exactly fit the description of patients in the trial for which the drug was approved. What do we do with this patient?

"We should move to a situation where we have broader research into how a drug is going to be used once it is approved"

"The manifesto asks drug developers to research this question up front. We should move to a situation where we have broader research into how a drug is going to be used once it is approved, and talk about the practical problems clinicians will have when applying this drug later on."

Rieke echoes this caution. "Just because we now have genetic datapoints, we shouldn't throw overboard everything we've learned in the past fifty years. We shouldn't think that this method is better *per se* – because it isn't, not yet."

And he offers an answer to the age-old question of: What would you do, doc? "If I had a tumour, I would probably have it sequenced. But if we don't find anything for which there is good evidence, I would decide on having a conventional therapy that is well understood. In this case, evidence beats biological hope."

EORTC
European Organisation for Research and Treatment of Cancer

The future of cancer therapy

Denis Lacombe - Director General,
European Organisation for Research
and Treatment of Cancer

EORTC calls for the interests of patients to take centre stage in the development of new treatments

With the arrival of precision medicine, the days of the old 'one size fits all' treatments seem long in the past. Precision oncology and new approaches to clinical research have meant a dramatic change in the field of cancer treatment. But precision medicine, promising as it is, brings its own challenge – how can we be sure that these targeted treatments are used optimally to the benefit of the individual patient?

New treatments now become available based on solid scientific rationale, thanks to our understanding of molecular biology and immunology. However, optimal use of new anti-cancer treatments remains poorly documented. Optimal patient population and cut-off values of biomarkers, treatment duration, sequence and combination are rarely informed, leaving patients, doctors and society facing many questions. In addition, all this is exacerbated by the often very high cost of new treatments. It is therefore essential to find an equilibrium between the interests and needs of all stakeholders, and define it around patient-centredness.

A newer version of the Clinical Trial Regulation will soon be implemented in Europe. However, it is not yet known whether it will address the issue of the qualification of studies designed to answer questions centred on patient care. On the contrary, it raises the risks that all Member States could adopt a position not necessarily based on medically informed criteria, and risks making therapeutic strategy trials yet more challenging to perform in the EU.

The current drug development paradigm has been criticised for being too drug-centred, and not focusing sufficiently on the patients who will eventually be consumers of the new therapies. A recent EORTC manifesto aims to try to find the balance between the interests and requirements of stakeholders (bit.ly/EORTC_Treatment-Optimisation-Manifesto).

The EORTC consulted academic clinicians, representatives of patient organisations, regulatory and payer authorities, health technology assessments agencies, and industry. We now have much greater clarity on what is needed to put patients at the centre of the drug development process, and we were pleased to find that all stakeholders considered treatment optimisation tools to be valuable to address current gaps in evidence.

Treatment optimisation is a process intended to enhance the long term efficacy, adherence, safety, convenience and affordability of a therapy. Its ultimate goal is to expand access to effective treatment to all of those it will benefit. Currently, European patients and the healthcare system are penalised rather than aided by the regulatory hurdle. We need greater independence in assessing the role of treatments. Urgent reform is needed to assess interventional clinical research based on purpose and treatment modalities, not necessarily through the rigid application of inappropriate frameworks.

For more information visit: www.eortc.org

Chiara Gasparotto – winning the case for better access to radiotherapy

A quarter of cancer patients who could benefit from radiotherapy do not receive it. As head of policy and partnerships, Chiara Gasparotto is positioning the European Society for Radiotherapy to make the case for better access and to alert policy makers and the public to the unmet need in their own countries. **Peter McIntyre** reports.

Radiotherapy has a compelling story to tell about its potential in cancer treatment and about significant unmet need across Europe.

Almost half of patients diagnosed with cancer would benefit from treatment that includes radiotherapy, yet almost a quarter of these patients do not receive it. As the number of European citizens diagnosed with cancer rises, the number of patients who would benefit from radiotherapy will also rise, reaching around 2 million by 2025 – a 16% increase in demand since 2012.

And with improvements in skills and technology and imaging now allowing more personalised and precise treatment that can target tumours more effectively, while doing less damage to healthy tissue, the need to improve access to radiotherapy is ever more urgent.

As Director for Policy and Partnerships at the European Society for Radiotherapy ESTRO, Chiara Gasparotto has responsibility for getting that story heard by people who can deliver on the needed investment in skills and technology. For the past seven years, she has been helping the Society to become more outward looking and to build partnerships that strengthen understanding of the potential for radiotherapy among policy makers and within the cancer community.

When she started in that role, says Gasparotto, it was clear that ESTRO lacked the level of public visibility that other oncology societies enjoyed. "For sure there is no difference in importance within the disciplines, but historically the other disciplines started to grow in terms of public knowledge much earlier than radiotherapy."

The turning point came in 2012, she says, when the then ESTRO President Vincenzo Valentini launched the Society's vision for 2020, with the aim that "Every cancer patient in Europe will have access to state-of-the-art radiation therapy, as part of a multidisciplinary approach where treatment is individualised for the specific patient's cancer, taking account of the patient's personal circumstances."

The vision was that other specialities would recognise radiation oncology as a major contributor to cancer cure and ESTRO as a strategic driving force in the multidisciplinary fight against cancer. As part of that, ESTRO aimed to become the pre-eminent educational and scientific society in radiotherapy and oncology.

Gasparotto, who had been managing courses at the ESTRO School for the previous three years, was tasked with establishing the public affairs unit and became its director. With her help, ESTRO began to focus attention on translating clinical and epidemiological data into information that health policy makers can understand and use. And it used facts about unmet need, costs and benefits to achieve greater recognition among the cancer community of the contribution of radiotherapy to curing and palliating cancer.

"When the process started of looking into ESTRO's place with other stakeholders then yes, you did feel a difference," says Gasparotto. "The Society began to feel a growing interest in partnership and in reaching out towards external stakeholders, including other oncology societies.

We started to look into what it means for ESTRO to engage in public affairs."

Making the economic case

One of her roles has been to support the HERO project (Health Economics in Radiation Oncology), launched by ESTRO to develop a European knowledge base and a model for health economic evaluation.

"The role of the HERO project was of paramount importance looking at the health economics of radiation oncology. It started to look into the availability of radiotherapy in terms of staffing, machines and guidelines. Then it looked at the need for radiotherapy – how many patients need the treatment and how many patients are not getting the treatment. It was really looking at the whole healthcare system. We were sitting on data that were and still are extremely important from the point of view of organisation of care."

HERO has delivered a cost-accounting programme as an online tool for use by country-level societies to support data driven decision making.

Changing public perceptions

The Marie Curie Legacy Campaign was launched in 2018 to change public perceptions. An initiative of the ESTRO Cancer Foundation (ECF), developed by ESTRO and corporate partners, it promotes a clear message that radiotherapy could save one million more lives a year by 2035 if used to its full potential.

"The Marie Curie campaign was and still is a beautiful adventure," says Gasparotto. "For the first time we decided to talk a sort of different language and reach out to media and lay public and include decision makers as well.

"We started this adventure without knowing what would be the level of response from the media and we were positively surprised that it caught on. It means there is a hunger for information and understanding more and better what kind of treatment patients can have."

Gasparotto worked with colleagues to draw out essential data from the HERO project and distil it into media friendly messages while retaining the confidence of doctors and scientists. "Science definitely has a different pace from media – much slower," she notes. "It is not always easy to keep up the attention of the media and to make sure that what you are telling them is always newsworthy and relevant."

The Marie Curie Legacy Campaign has been embraced

Credit: David Plas

by ESTRO national societies, which added their own data and backed national media campaigns, notably in Belgium, Poland, Spain, Germany, Italy and Portugal. "The role of the national society was extremely important to be the bridge towards what ESTRO is developing and the different national circumstances," says Gasparotto.

Advocating on the European stage

This initiative was quickly followed by a White Paper, 'Radiotherapy: seizing the opportunity in cancer care,' which makes a pitch for governments, policymakers, healthcare professionals, patients and professional societies to become 'radiotherapy ambassadors'.

The White Paper, presented at the EU Parliament in Brussels in January 2019, highlights a need to deal with inequalities and presents a five-point plan to close the gaps in radiotherapy provision across Europe. The report cites shortages of equipment, variations in training, insufficient integration of radiotherapy into treatment plans, lack of investment in research, lack of general understanding of radiotherapy, and misconceptions about safety as contributing to radiotherapy's poor image and underuse.

Gasparotto believes these initiatives have started to make a difference. "The campaign and meetings at the European parliament allowed ESTRO as a society to be

With Yolande Lievens, ESTRO Past-President and Chair of the HERO project

more visible and to start entering into discussions and debates with decision makers we would not have had a few years back."

The European Commission has put cancer high on its health agenda and is receptive to new ideas for promoting treatment. At national level there has been more readiness to include radiotherapy societies in partnerships and networks. "It is a positive circle. You start a campaign and thanks to the campaign you get attention and start building bridges and those bridges might lead to another wave of campaigning."

A voice in the wider cancer community

The links are also stronger with other European-level cancer societies. Yolande Lievens, President of ESTRO, chairs the Value Based Healthcare project established by the European CanCer Organisation (ECCO) to examine ways of measuring the value of different types of cancer treatments to determine the real benefit to patients. Radiation oncologist Cai Grau, who chairs the HERO project, is also a member of the value-based healthcare expert core group.

In March 2019, ESTRO launched its new strategy for 2030: 'Radiation Oncology. Optimal Health for All, Together,' which puts still greater emphasis on partnerships and on looking outwards. It calls for the creation of more multidisciplinary practice guidelines in which the oncology societies would work together to promote evidence-based combination treatment, with an enhanced role for radiation therapy. It proposes greater collaboration with GPs, carers and patient support groups.

ESTRO is also playing a wider global role, and in 2018 established an 'ESTRO meets Asia' congress, now held annually in Singapore, to share experiences and plan future collaboration. It also partners with the International Atomic Energy Authority, which works to make the case for radiation oncology in parts of the world, in Africa for example, where around half the countries have no radiotherapy services.

Marrying sociology and oncology

When Gasparotto joined ESTRO in January 2009 to manage courses at the ESTRO School, it was the match of skills that attracted her, rather than the oncology. "I've always liked to understand connections and relationships between people and between groups, she says. "What inspires me most today is the sociology of organisations – to see the dynamics between people and the values and behaviours within organisations."

In fact she had reservations about working alongside clinicians. Her father was a radiographer and her mother a hospital secretary (both now retired). Her uncle is a doctor

and hospital manager and her aunt is a nurse. As if this was not enough her sister is a biologist.

"I was panicking a bit because I did not know anything about oncology and because everyone in my family works in a hospital. I was kind of proud that I was the only one who escaped from a healthcare environment … but then you see that things happen for a reason."

She concludes that her choices were probably not by chance. "Very often you are in the right place at the right time. There is a *fil rouge* that connects all my steps."

Born and brought up in north-east Italy, Chiara Gasparotto did her first and second degrees at the University of Udine in Gorizia, close to the border with Slovenia. Her Masters is in European public relations, concerned with European public affairs and international relations.

Between her two degrees she took part in the Erasmus exchange programme, studying social science at Göttingen University in Germany, after which she went to live and work in Brussels, partly because she wanted to travel and partly "because of love".

She took an internship with a consultancy dealing with financial services, where she found herself in charge of organising events, and then worked with a consultancy concerned with EU financing for university education and research.

That experience prepared her for her first job with ESTRO, as their School contact point for professional development courses. In that role she developed a strong insight into the needs of young specialists and into the workings of a European medical society. She also got to understand the value of the 'volunteers' – the specialist radiation oncologists, physicists and radiation therapists who build the organisation, run its influential committees and share their expertise. "The volunteers are extremely motivated and it is motivating to work with them. You feel this energy and commitment they put into the society and that is amazing. I had this when I was working with the School and I still have it today."

The next decade

With so much going on, it is perhaps not surprising that ESTRO is one of the fastest growing professional medical societies in Europe. A 30% increase over the past five years has seen membership grow to more than 7,800 radiation oncology professionals, just over half of whom are radiation oncologists, about a quarter are medical physicists and 10% are radiation therapists and dosimetrists, who deliver the treatment, or radiobiologists, who study how radiation affects the biology of cells.

Gasparotto talks of the need to "time-proof" the future of the organisation by anticipating the need for changing services. "The vision looks at how to empower the radiotherapy community. You listen to the communities, you understand what they need, and then you respond to those needs."

"If you look at the goal of ESTRO and all the other medical associations, it is to ensure that patients do have the best care, and patient treatment by definition is multidisciplinary. So making sure that we are going to work together and collaborate is somehow in the DNA of what cancer care is today. The feeling that I get is that we have much more dialogue with patient societies, organ specific societies and other medical societies."

"You feel this energy and commitment the volunteers put into the society, and that is amazing"

She says that ESTRO has greater potential to make use of the data that emerges from their research projects, both internationally and by supporting national level societies which are gatekeepers for information about radiation therapy in their countries.

Gasparotto is also focused on the challenges of complexity and effective governance that accompany growth and greater visibility. "We need to make sure we have the governance appropriate to get to our goals in 2030," she says. "My personal and professional endeavour is to learn to face this complexity. Personally I am a fan of simplicity, but if problems are complex you cannot expect always to find a simple solution. I would like to learn how to do that a bit more."

She is as enthusiastic about her job today as when she joined ESTRO. "The radiotherapy community is growing stronger and more confident over the years, with a clear standpoint that the role they play in oncology care is central. The professionals ESTRO represents – clinicians, physicists, radiation therapists and radiobiologists – are the main reason why we work for ESTRO. They are brilliant, very bright (they understand this complicated technology) and at the same time humble and down to earth, and very sociable too. They love to party! I think the radiation oncology community is a very joyful one."

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Tackling resistance to anti-EGFR therapies

challenges, options and strategies

EGFR inhibitors work well in certain patients, but resistance often develops after around one year. **Cristina Ferrario** reports on the new technologies and innovative approaches being used to tackle innate and acquired resistance to these drugs and improve their therapeutic impact.

Since their first approval and use, more than 15 years ago, inhibitors of the epidermal growth factor receptor (EGFR) have revolutionised clinical practice and the prognosis for cancer patients, especially in colorectal and lung cancer. The treatment paradigm of these two malignancies shifted rapidly from traditional chemotherapy to targeted therapy. In patients with metastatic colorectal cancer with wild-type RAS and no EGFR mutations, EGFR inhibitors, in combination with chemotherapy, are now considered the standard of care. In patients with non-small-cell lung cancers (NSCLCs) EGFR inhibitors are considered standard of care in those harbouring specific EGFR activating mutations (*ESMO Open* 2016,1:e000088; *Transl Cancer Res* 2019, 8 (Suppl 1):S23-S47).

"EGFR tyrosine kinase inhibitors are miracle drugs: patients with lung cancer simply go back to life after being treated," says Yosef Yarden, an international expert on epidermal growth factor receptor, based at the Department

Practice Point

What's behind resistance?

There are many causes of innate or acquired resistance to anti-EGFR therapies in metastatic colorectal cancers (mCRC) and non-small-cell lung cancers (NSCLC). Some of the key mechanisms identified so far include:

mCRC	• RAS mutations (50–55%) • BRAF V600E (maybe also non-V600E BRAF) mutations • PIK3CA mutations (still debated) • PTEN loss of function • HER2 amplification or mutations • MET amplification • Activation of bypass signalling pathways: secondary RAS mutations; promoter DNA methylation; HER2 amplifications; MEK overexpression, activation of PIK3CA/AKT/mTOR • Microenvironment interactions
NSCLC	• EGFR exon 20 insertions. • Mutations in EGFR: T790M (less common: D761Y, L747S, T854A, C797S) • EGFR amplification (10%) • Mechanisms of acquired resistance: HER2 amplification, MET amplification, other mutations, non-genetic changes, changes in tumour phenotype (from NSCLC to SCLC; epithelial-mesenchymal transition) • ALK mutations • Immune escape via increased PD-L1 expression

Source: D Westover et al (2018) Mechanisms of acquired resistance to first- and second-generation EGFR tyrosine kinase inhibitors. *Ann Oncol* 29 (Suppl 1):i10-i19; CM Parseghian et al (2019) Mechanisms of Innate and Acquired Resistance to Anti-EGFR Therapy: A Review of Current Knowledge with a Focus on Rechallenge Therapies. *Clin Cancer Res.* 2019, 25:6899–908.

of Biological Regulation at the Weizmann Institute of Science, in Israel. "But this is just a temporary miracle," he adds, highlighting one of the major challenges with anti-EGFR therapy – resistance – which usually develops about one year after starting the treatment (*Front Med* 2017, 3:76; *Cancer Lett* 2019, 459:240-7; *Int J Mol Sci* 2019, 20(1):146).

Fortunato Ciardiello, a medical oncology professor at the University of Campania 'Luigi Vanvitelli' in Naples, who has a special interest in mechanisms of acquired resistance to the therapeutic effects of anti-EGFR drugs, identifies resistance as "the biggest clinical issue we must deal with before and while treating patients with these drugs".

The epidermal growth factor

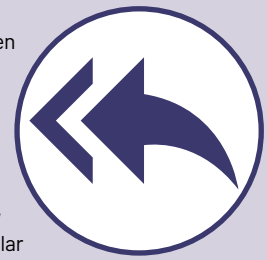
In 1986, the Nobel Prize in Physiology or Medicine was awarded to Italian biologist Rita Levi-Montalcini and the American biochemist Stanley Cohen for their discoveries of growth factors. Cohen's main focus had been on the epidermal growth factor which, together with its receptor, had started to play a pivotal role in basic and clinical research from around the mid 1950s, prompting researchers to gain a deep knowledge of physiological and pathological roles of these molecules, as well as their structural and molecular characteristics. The transmembrane protein EGFR is involved in tumour growth, survival and immune-escape, and it is now considered one of the most potent genes commonly altered in cancers.

Moving from bench to bedside, many cancer therapeutics targeting EGFR tyrosine kinase activity went into development (*Front Oncol* 2019, 9:800; *ESMO Open* 2016, 1:e000088; *Transl Cancer Res* 2019, 8 (Suppl 1):S23–S47). Two classes of drugs developed specifically to target EGFR are currently approved: monoclonal antibodies (mAbs) for use in metastatic colorectal cancer, and tyrosine kinase inhibitors (TKIs) for use in NSCLC.

As first postulated by John Mendelsohn and Gordon Sato in 1980, mAbs against EGFR (currently cetuximab and panitumumab) prevent ligand binding to the receptor, inhibiting activation of the specific tyrosine kinase cascade of events, thereby blocking cancer cell proliferation. TKIs, by contrast, are small molecules that compete with ATP in binding to the intracellular TK domain of EGFR. Three generations of anti-EGFR TKIs are now available. The first generation (erlotinib and gefitinib) are active in patients with diseases harbouring sensitising mutations in the EGFR TK domain. The second generation drugs (afatinib and dacomitinib) were developed to overcome resistance to first-generation TKIs due to the acquisition of T790M mutation in the TK domain of EGFR. The simultaneous inhibition of the mutated and wild-type form of the receptor leads to dose-limiting toxicities for the second generation of TKIs, which led to the development of a third generation TKI (osimertinib), with increased specificity for T790M mutation and a low inhibitory effect on wild-type EGFR (*Ann Oncol* 2018, 29 (Suppl 1):i10-i19; *Front Med* 2017, 3:76; *Cancer Lett* 2019, 459:240–7).

Let's try again! – re-challenging a once-resistant tumour

Traditionally, developing resistance to an anti-cancer drug meant being taken off that treatment for ever. But with an increasing number of treatment options available, using a variety of mechanisms of action, new strategies are emerging that may allow a tumour to regain some level of sensitivity to a drug it had become resistant to. This opens up the possibility of giving a 'second chance' to a treatment that had previously stopped working – a strategy known as the re-challenge. As Fortunato Ciardiello, Professor of Medical Oncology at the University of Campania 'Luigi Vanvitelli' in Naples, explains, "There is a strong rationale behind the re-challenge of an anti-EGFR therapy," and molecular aspects play the major role in the choice. He is following with interest phase III randomised trials looking at this strategy in the context of monoclonal antibodies (mAbs) in patients with metastatic colorectal cancer. "Patients develop resistance to the first treatment with cetuximab or panitumumab, and the process is often mediated by new RAS mutations," he explains. When resistance emerges, anti-EGFR therapy is discontinued and replaced with new regimens, for instance, chemotherapy and anti-angiogenic drugs in metastatic colorectal cancer. "At this point, something may happen at the molecular level that can give us the possibility to reconsider a treatment with mAbs against EGFR." Under chemotherapy regimens without EGFR targeting, the presence of RAS mutations no longer represents a selective advantage: mutated clones are affected by the new therapy and can disappear from the tumour in 3–5 months, as shown by liquid biopsy. "And this is when the re-challenge can be considered," says Ciardiello. For the time being, the strategy remains experimental, pending the findings of the phase III trials.



Who responds, who is resistant?

Several clinical studies have shown that EGFR-targeted therapies are highly effective in sensitive cancers, improving progression-free survival, objective response rates and quality of life, while decreasing toxicity compared to previous standards of care (*Int J Mol Sci* 2017, 18(11):2420; *Transl Cancer Res* 2019, 8 (Suppl 1):S23–S47). Sadly, only a limited proportion of colorectal and NSCLC cancers have that sensitivity, says Ciardiello, which means that in both cancer types, anti-EGFR drugs are indicated for only a selected population of patients. He emphasises the need to take issues of innate resistance and activating (or 'sensitising') mutations into account when choosing the best therapeutic approach.

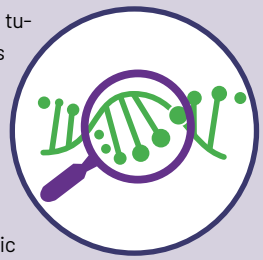
What this means, says Ciardiello, is that in patients with colorectal cancer, anti-EGFR mAbs can be used only for cancers with wild-type RAS (both KRAS and NRAS), which account for about two in five cases of metastatic disease, and they are more effective where the primary tumour was located on the left side. In patients with NSCLC, the proportion of patients who can benefit from anti-EGFR TKIs is even lower. Sensitising mutations in the EGFR TK domain of the receptor are needed for these drugs to be effective. The most common, accounting for 90% of EGFR mutations in the clinic, are deletions in exon 19 and L858R mutation in exon 21 (*Int J Mol Sci* 2017, 18(11):2420; *Ann Oncol* 2018, 29 (Suppl 1):i10–i19). "In so-called Western countries, sensitising mutations are detected in 12–15% of the cases, while in Eastern Asia they are more common, usually in a 30–35% range, reaching 50% in specific populations," says Yarden. "Moreover, we know that EGFR sensitising mutations are mostly found in non-smokers, and are more common in women – most of them in their childbearing age – than in men." Why this happens is not yet clear, he adds.

Mechanisms of acquired resistance

Almost all patients treated with an anti-EGFR drug, whether mAb or TKI, develop resistance even after an impressive initial response. In recent years, many mechanisms of acquired resistance to EGFR inhibitors have been elucidated, showing a very dynamic molecular and cellular landscape, and a great number of different processes involved. Resistance mechanisms can be clustered into at least three major groups: gene mutations, activation of alternative pathways, and phenotypic transformation (*Int J Mol Sci* 2017, 18(11):2420; *Clin Cancer Res* 2019, 25:6899–908). For example, the emergence of the missense T790M mutation within exon 20 of EGFR is the predominant mechanism of resistance to first- and second-generation TKIs, occurring in 50–70% of patients progressing after treatment (*Front Med* 2017, 3:76; *Cancer Lett* 2019, 459:240–7).

"Unfortunately, resistance also

Monitoring molecular mutations



Tailoring treatments to the evolving molecular profile of each tumour requires effective tools to analyse and monitor changes that can inform therapeutic choices. As lung cancer specialist Johan Vansteenkiste commented in an editorial in *Annals of Oncology*, "Molecular profiling of NSCLC is now critical not only at the time of diagnosis, but even so at each step of tumour progression due to molecular alterations in the tumour," (*Ann Oncol* 2018, 29 (Suppl 1):i1–i2). The same is true for metastatic colorectal cancer, where molecular characterisation is mandatory before starting the treatment with anti-EGFR monoclonal antibodies, and is of pivotal importance when considering a second- or third-line therapy (*Clin Cancer Res* 2019, 25:6899–908).
A tissue biopsy can be used to identify the presence of the molecular requirements for a specific anti-EGFR treatment, such as sensitising mutations in NSCLC, but it cannot be repeated very often in the clinical setting. "We need a non-invasive procedure that can be performed quite often without bothering or damaging the patient," says Fortunato Ciardiello, Professor of Medical Oncology at the University of Campania 'Luigi Vanvitelli' in Naples. He believes that liquid biopsy and the analysis of circulating tumour DNA (ctDNA) acquired from a simple blood draw could be the answer. "It gives us a real-time molecular picture of the tumour and it is as specific and sensitive as tissue biopsy," he says. As he points out, ctDNA analysis could also be important in overcoming the problems associated with intra-tumoural heterogeneity. "The ctDNA represents a 'summary' of cancer DNA: the analysis of these small fragments allows us to gain information about the whole tumour in one run," he says. High-throughput techniques such as next generation sequencing – which can be used to analyse liquid biopsies as well as tissue – could be important to get a complete picture of the molecular profile of the disease.
Yosef Yarden, from the Department of Biological Regulation at Israel's Weizmann Institute of Science, agrees with Ciardiello that all patients should have their tumour sequenced to detect mutations . "This will help define a personalised treatment and collect molecular data to better understand and maybe overcome resistance mechanisms."

occurs after the use of third-generation TKIs like osimertinib, due to several mechanisms like the emergence of a tertiary mutation, namely C797S," claims Yarden. Activation of alternative pathways, including upregulation of other members of the EGFR family (HER2 or HER3) or a mutation in BRAF, can also be involved in acquired resistance, as well as the transformation from NSCLC to SCLC (small cell lung cancer) or epithelial–mesenchymal transition of cancer cells (*Int J Mol Sci* 2017, 18(11):2420; *Ann Oncol* 2018, 29 (Suppl 1):i10-i19; *Clin Cancer Res* 2019, 25:6899–908). "This is very complex," says Ciardiello. "But the good news is that many of the players involved in acquired resistance can be studied as potential targets for new therapies to prevent, delay or overcome resistance."

Strategies to overcome resistance

Progress has been made in identifying cellular and molecular mechanisms responsible for resistance to anti-EGFR drugs. The question remains of how to counteract them. When resistance occurs, patients are often treated with chemotherapy, alone or in combination with other drugs (e.g. anti-angiogenics). This could work in some cases, but as Yi-Chen Zhang and colleagues commented in a recent paper, "novel agents with higher potency, broader selectivity and better intracranial activity are urgently needed," (*Cancer Lett* 2019, 459:240–7). New drugs targeted on EGFR TK activity are in development. Given what we know about resistance mechanisms, however, it would make sense to look a bit further, says Yarden. "We could think, for example, to use different approaches targeting both the kinase activity of EGFR and alternative pathways." His laboratory is experimenting on mice carrying human tumours (xenografts), using a double anti-EGFR strategy (mAb+TKI) together with a blockade of human epidermal growth factor receptor 2 (HER2), which is activated after EGFR inhibition.

"This combination showed a very strong synergistic effect, and all the tumours disappeared during the treatment," says Yarden, but he adds that, as with other therapies, "this triple regimen failed to cure patients: the tumour always comes back if we stop administering the drugs."

Good results from combination regimens have also been seen in metastatic colorectal cancer, according to Ciardiello, who mentions concomitant inhibition of wild-type EGFR and mutant BRAF in this setting.

And with the growing number of anti-EGFR drugs coming on the market, particularly TKIs, there is an urgent need to find out more about the most effective sequence of administration (*Int J Mol Sci* 2019, 20(1):146).

ECCO
EUROPEAN CANCER ORGANISATION
corner

Dr Matti Aapro
ECCO President 2020–2021

Big things are made out of small pieces:

The value of convening networks in cancer policy

So the Year 2020 has arrived. Many predictions were made about the lives we would be living by now. Machines were usually a feature. Flying cars, spaceships taking us to Mars and robots doing our tedious chores.

While technology revolutionises our lives with increasing frequency, there is still some way to go before the more imaginative predictions of our future are reached. Not all the components are in place yet. Also, sometimes what appears as 'progress' can create brand new problems to solve, as occasional over-reliance on technology can demonstrate.

It reminds all of us in cancer care that the biggest successes are often achieved not through a single giant leap of technology, but from accumulation of many smaller improvements over time.

This comes to mind as I start my Presidency of ECCO. I do so at the birth of both a new EU Cancer Mission for research, and an EU Beating Cancer Plan designed to coordinate 27 countries towards shared goals. I hope both will not only be significant in themselves, but set a longer term trend for continual high-level inter-governmental cooperation on cancer.

I also start with a freshly minted ECCO Four Year Strategy, developed after ten months of consultation with our members. What came out strongly from that process is not only the need to bring together actors in cancer care to give one voice on certain key policy issues, but also the value in convening interested parties around complex topics where joint work can help overcome persistent obstacles to progress.

So we now are launching eight 'Focused Topic Networks' of ECCO members and our Patient Advisory Committee members, but crucially, also invited stakeholders, EU players and our 'Community 365' of funding partners. This expansion of the ECCO family to help problem-solve on a bigger scale is very welcome. I pay particular tribute for that development to my predecessor as ECCO President, Professor Philip Poortmans. He was instrumental in identifying this need, and in gaining full support from the members for the new strategy. His devotion to seeing this task through was singular, and I am in his debt.

The first Network to be launched was 'HPV Action Europe', dedicated to achieving the elimination of all HPV caused cancers in Europe as a public health problem. This is a case study of where a range of small steps – on vaccination uptake, on screening, treatment and research – when put together, could achieve an enormous whole, well within our own lifetimes. Many different professions and interest groups have their role to play, and that means bringing people together around a unified purpose.

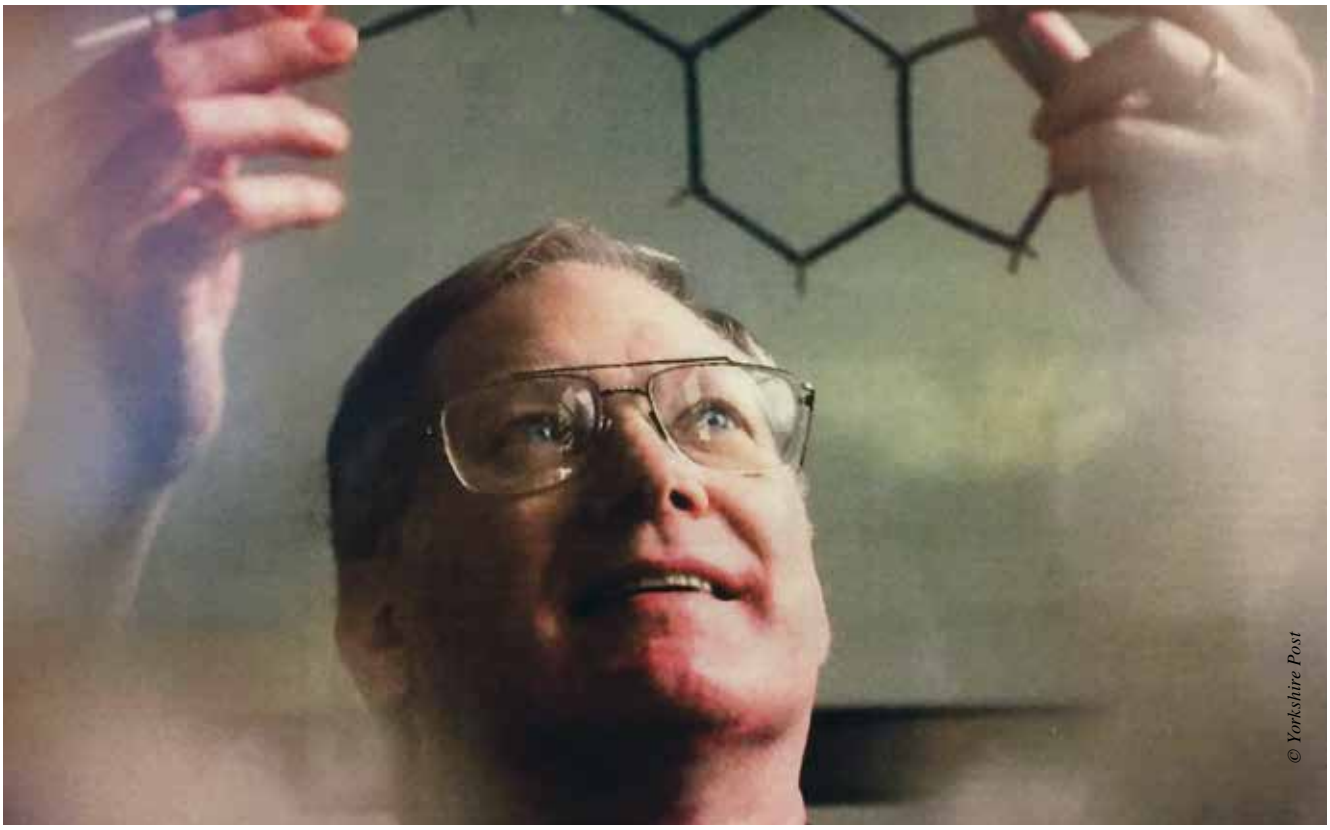
The next two networks to launch will be Treatment Optimisation and expansion of our Quality Cancer Care initiative, with others thereafter.

This means that, as the EU Cancer Mission and Plan are rolled out, we will have communities of action ready to input, and ready to implement; ready to inform about the hundreds of small steps already taken, and ready to advise on what is required to reach the next level.

So for my own prediction of the future: Like the Swiss watches my city Geneva is so famous for, the machines of the past, present and future are united by being made of many different components, big and small, working in concert, to perform their function. Creating effective collaboration for advancement in cancer care is no different. Big and small parts work best together.

This is a reality I hope to oversee, as ECCO puts in place new Networks for improvement and commits itself to supporting the machinery of EU cancer cooperation to achieve a better future.

Dr Matti Aapro is President of the European CanCer Organisation (ECCO) and Dean of the Multidisciplinary Oncology Institute, Genolier, Switzerland.



How to make precision drugs that work better

Six lessons from the development of the first targeted anti-cancer therapy

Why are today's precision drugs falling so short of the impact achieved by tamoxifen, the first ever targeted cancer therapy? **Craig Jordan** puts it down to the lack of detailed pharmacological work, and offers six lessons from his own experience developing not just tamoxifen, but also raloxifene and other SERMs.

Tamoxifen famously started life as a failed contraceptive, developed by ICI (now Astra Zeneca), but with the fatal flaw that it increased ovulation rather than suppressing it.

It's a story sometimes told to show how discoveries can come from unexpected quarters and that scientific progress has a habit of proceeding in zigzags.

Craig Jordan is the pharmacologist who took that failed drug and developed a treatment strategy for tamoxifen, and then did the groundwork for four additional selective oestrogen receptor modulators (SERMs) – saving millions of women's lives. He teaches us that such zigzaggedy progress and unexpected discoveries don't just happen. They require bloody minded, dedicated and creative scientists who refuse to give up on failures, and fight for the resources and people to do the science to turn things that might not look very promising into something that could offer real value.

By 'failures', Jordan includes the vast majority of targeted medicines currently marketed with scant evidence of real benefit. "If you go to the paper that looks at the approvals of all of these targeted therapies, they have if you are lucky 5 or 10% responses. There is no survival data, but they are on the market," (*JAMA Onc* 2018, 4:1093–98; *JAMA Onc* 2018, 4:1789–90).

Companies are able to sell them, says Jordan, on the basis that there's nothing else, so why not use it? "My view is: why does nobody take the time and invest the money to find out which drugs will be used and useful?"

He believes that many failing targeted drugs would turn out to be of great value if more time and resources were invested in doing the pharmacology and translational research to build a detailed picture about exactly what they are doing and how they could be improved. That takes persistence (verging on obsession in his case) and a focus on finding solutions for patients rather than marketable applications for drugs.

> ***"You're not going to cure cancer by sequencing everything"***

He worries that the major lesson to be learned from the tamoxifen/SERMs story won't be learnt, partly because tamoxifen is seen by the younger generation of researchers as "a bit like aspirin" – part of the fabric of cancer therapy that has always been there. Moreover, while tamoxifen may be formally recognised as the first targeted anti-cancer therapy, it is Herceptin (trastuzumab) and Glivec (imatinib) that researchers generally use as a reference point, as they were the first to use new molecular biology techniques to identify targets and create molecules to block them.

For Jordan, this explosion of molecular biology is part of the problem. "Everybody could just go into the lab and take tumours and sequence them and compare them with the normal human genome. All we've really done is developed a map of the world. All of these maps. But nobody has a got a clue about: What is going on in Africa? Why is Detroit different from Los Angeles? What's going on in Europe, and what are the interactions that create a European Union? Nobody has any idea because the task is so vast. You're not going to cure cancer by sequencing everything."

He says there has been a drift away from the fundamental questions: How does this drug work? How can we make it better? How do we study side effects? Could there be good side effects as well as bad? For Jordan, now professor of Breast Medical Oncology and Molecular and Cellular Oncology at MD Anderson Cancer Center, in Texas, the main drive was how to get a treatment available for women to keep them alive – and that focus seems to have got downgraded.

His one big exception to this critique relates to work on improving immunotherapies, including at MD Anderson, which is also home to Jim Allison, who received a Nobel Prize for his role in discovery of cancer therapy by inhibition of negative immune regulation. "There is a whole team of people looking at the good, bad and ugly of immunotherapy, and fixing it to be more targeted," says Jordan. "Where do the side effects come from? Can we improve this? They are looking at everything that they can to be able to find out advances useful for patients. So this is a big version of the Craig Jordan model, if you like."

Doing the pharmacology: lessons from tamoxifen

When Jordan started working with tamoxifen – then known as ICI 46 474 – in the 1970s, cancer researchers were betting heavily on the potential of combination chemotherapies to deliver a cure.

At the Wisconsin Comprehensive Cancer Center, where Jordan arrived in 1980 to establish his laboratory to explore 'the good, the bad, and the ugly' aspects of tamoxifen. During the decade that followed, he discovered selective oestrogen receptor modulators (SERMs)

They had had a dramatic effect on curing childhood leukaemia and great progress was being made in Hodgkin's Disease. "Most of the clinical community were convinced you could find the right lexicon of drugs to give to any patient with any cancer and you could cure it."

Breast cancer was a case in point, he says. "Heroic efforts were being made to try to treat women with massive doses of chemotherapy and bone marrow transplants, and none of this worked." Tamoxifen, meanwhile, an anti-oestrogenic compound that had just failed as a contraceptive, "was just lying there".

Jordan has described how, fresh from completing his PhD at the University of Leeds on the pharmacology of anti-oestrogens, he got the facilities (at the Worcester Foundation for Experimental Biology in the US) and the backing (from ICI in the UK) to explore the potential of tamoxifen in breast cancer – a story told in 'Tamoxifen the first targeted long term adjuvant therapy for breast cancer' (*Endocr-Relat Cancer* 2014, 21:R235–246) and 'The SERM Saga, Something from Nothing' (*Ann Surg Oncol* 2019, 26:1981–90).

However, it is what happened next, and over the following decades, that is probably more important for drawing lessons that can be applied to developing better cancer drugs today.

Lesson 1: How can this drug save lives? – a conversation with nature

The potential for treating breast cancer by cutting its access to oestrogen had been partly understood since the 1890s when George Beatson had shown that excising a woman's ovaries could delay the progress of some breast cancers. However, ICI's chief interest in developing ICI 46 474 was as a contraceptive, so until Jordan got the go-ahead to work on the drug in the early 1970s, not a single anti-tumour experiment had been done with it in the laboratory.

Arthur Walpole, who had been in charge of developing the agent as a contraceptive, but had a deep interest in cancer research, played a key role in convincing ICI not to ditch their drug at this point, but to advance it for approval as an orphan drug for use in advanced breast cancer. With his PhD background in anti-oestrogens, Jordan was tasked with doing the pharmacology to understand about its mechanism of action and clinical opportunities.

Tamoxifen's impact in the metastatic setting, used across all tumours regardless of their hormonal status, was not spectacular. With a response rate of around 30% and a duration of response of around one to two years, it was no better than the hormonal therapies – high-dose oestrogen or androgen – that were already in use. The side effect profile was admittedly better, but the costs were higher, and ICI were not convinced there was money to be made with it.

But everything Jordan was learning about the drug was telling him that its true potential lay with a different strategy. His experiments with carcinogen-induced rat mammary cancers showed rapid tumour induction in controls, while those treated with tamoxifen remained completely tumour free: "Two depot injections of tamoxifen, which each had a biological action for many months, completely wiped out the development of tumours."

He also showed that administering the tamoxifen sooner after inducing tumours with carcinogen was more effective than later, and that shorter duration delayed tumour development, but continuous administration had a long-term preventive effect (figure opposite).

The pharmacology, which Jordan describes as "a conversation with nature", was telling him that the strength of tamoxifen lay in its potential as a preventive, or at least in very early disease. There were good reasons not to go down this route, however. Firstly, prevention would mean giving the

drug to healthy women who may never go on to develop the disease, so the side effects and risk would have to be negligible. Secondly, it is always more difficult to demonstrate efficacy in prevention than treatment, as prevention measures non-events. And anyway there was a high degree of scepticism within the research community about the efficacy of the drug, says Jordan.

The question was never: What is the easiest endpoint to prove? or What is the quickest route to market?

"They were saying 'With chemotherapy women get sick, we see their blood cells go down, we know it's killing cancer cells because it's killing their healthy cells as well. This has virtually no side effects and you are saying use this because you think it will be able to kill cancer cells. You have no real evidence it will be able to do that.'"

For Jordan, however, the key question was never: What is the easiest endpoint to prove? Or what is the quickest route to a marketable drug? but rather: "What will keep women alive?"

Lesson 2: Face down the sceptics – nature does not lie

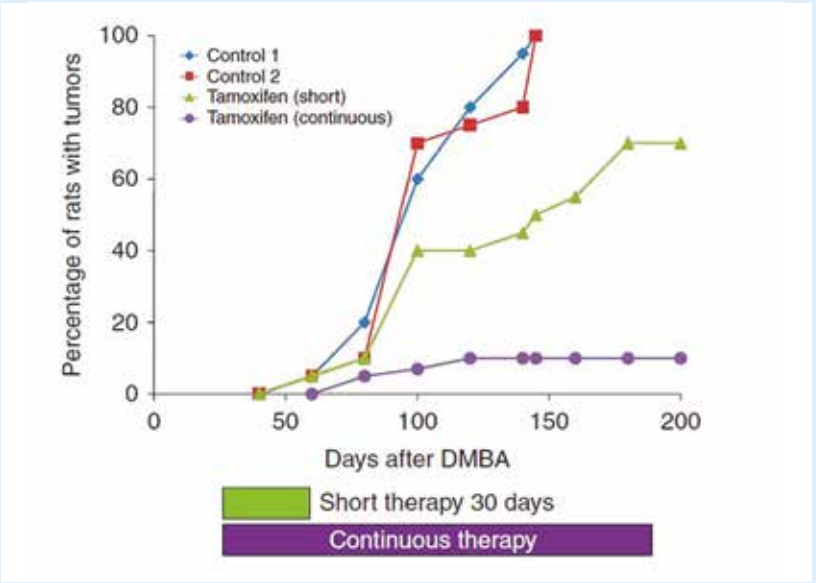
By the mid-1970s, and with Jordan now back in the UK, the concept of hitting cancer early was beginning to gain traction on both sides of the Atlantic, particularly in the form of adjuvant treatment following surgery for early breast cancer. "My philosophy was that it is no good trying to cure people at the end of life. You've got to hit it strategically somewhere along the way that will become vulnerable. That is after a woman had had a mastectomy and there are micrometastases around her body but we can't see them."

In September 1977, at a packed Breast Cancer Symposium at King's College Cambridge, Jordan presented his data showing that, in rats, a continuous dose of tamoxifen could offer long-term protection against breast cancer. It was here that he first argued the case for the potential of long-term use of tamoxifen in an adjuvant setting. The suggestion did not go down well.

They were horrified, says Jordan, and protested that he wasn't a doctor, didn't understand anything about drug resistance, and presented a danger. "It was completely counterintuitive in cancer, having a therapy you give for ever. Everyone said it can't happen."

Everything that clinicians had learnt about the limitations of systemic therapies – including tamoxifen, which in advanced cancers stopped working after a year or two – pointed to the intractable problem of acquired resistance, says Jordan. The dominant feeling in the audience – with a few important exceptions – was that a strategy that risked

Nature says... continuous tamoxifen is the way to go



This data was first presented at the King's College Cambridge Breast Cancer Symposium, September 1977. Jordan's argument that tamoxifen was best used as a continuous administration in a preventive setting found a very mixed reception in a clinical audience, who insisted that the strategy would inevitably lead to resistance. Subsequent trials showed Jordan was right.

Source: VC Jordan (2014) *Endocrine-Related Cancer* 21:R235–R246, republished with permission

With Bernie Fisher, one of the pioneers of breast conserving surgery with adjuvant therapy. Jordan and Fisher were the two inaugural winners of the Brinker International Breast Cancer Award (1992) for basic and clinical research respectively.

developing resistance in an adjuvant setting meant having one less option to use if the woman then went on to develop advanced disease.

But Jordan's pharmacology was telling him long-term adjuvant treatment was the way to go. Undeterred, he took his data to the US, where he presented his case to Paul Carbone, who was setting up the Wisconsin Comprehensive Cancer Center, one of six original comprehensive cancer centres designated by the National Cancer Institute.

Here he met a very different response. Carbone invited him to join them, and head the breast cancer programme.

Lesson 3: Find the right research environment

The labs at Wisconsin became the cradle where the concept of selective oestrogen receptor modulators was developed, where raloxifene, the second SERM after tamoxifen was developed, and where early work led to three further SERMs, each addressing multiple key women's health issues.

The impact of tamoxifen in advanced breast cancers gave no clue about its amazing value in an adjuvant setting

Here, for the first time Jordan was based at an institute that treated patients, where clinicians and pharmacologists learned together via feedback loops between lab and clinic – long before the term 'translational research' was coined. The very significant public funding made available as part of the 'War on Cancer' gave researchers the freedom to pursue scientific strategies led by seeking solutions for patients, without constant pressure to demonstrate marketable applications for a drug, take out patents, or spin off biotech companies.

So began the interaction with clinical trials organisations such as the National Surgical Adjuvant Breast and Bowel Project (NSABP) led by Bernie Fisher, a key instigator of the trials of adjuvant chemotherapy, but also with triallists in the UK, such as Michael Baum – who was the first to trial adjuvant tamoxifen for two years rather than one (the strategically named NATO trial) – and Helen Stewart, who ran the Scottish Adjuvant Tamoxifen trial that looked at the benefit of administering the drug for five years immediately after mastectomy compared with waiting until recurrence.

The results of the Scottish trial showed "significantly prolonged disease-free survival" in the adjuvant arm for patient population.

It was not until more than 10 years later, however, with publication of the 1998 Oxford Overview Analysis – a meta-analysis of data from multiple trials done on adjuvant breast cancer therapy at that time – that the true size of that benefit became clear. In premenopausal women whose tumours were oestrogen receptor positive, adjuvant tamoxifen given for one year produced no reduction in recurrence or death rates. Two years' administration produced a small benefit on both measures. Five years gave an astonishing 50% reduction in recurrence and a 30% reduction in death rates.

If there's one lesson that Jordan wants to get across, it is this. The impact of tamoxifen used in advanced breast cancers gave no clue about its amazing potential given long-term in an adjuvant setting. "Nobody could have predicted that at all."

Winning the argument on the issue of resistance was an important key to that success – we now know that tamoxifen can continue to be administered for 10 years or more. Demonstrating that tamoxifen was a precision treatment that should only be used – and its value measured – in women with hormone-dependent breast cancer, was also key.

Lesson 4: Mechanism of action – how tamoxifen became the first precision cancer therapy

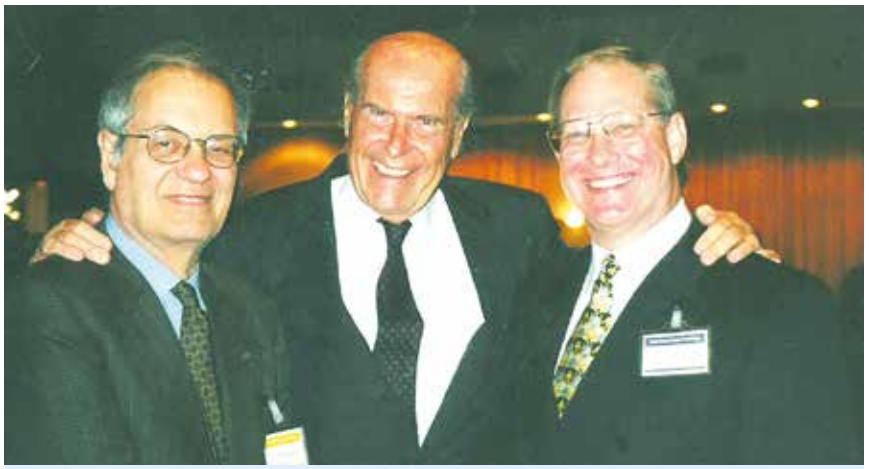
Jordan understood from the start that the oestrogen receptor was likely to play a key role in tamoxifen's mechanism of action. In 1973

Elwood Jensen, who had identified the receptor some 17 years earlier, offered him the chance to visit Chicago to learn assay techniques. By 1975 Jordan's labs were able to show that tamoxifen blocks estradiol binding to human tumour oestrogen receptors.

The pharmacology told him that, unlike cytotoxics, which target every replicating cell, tamoxifen would work only in certain breast cancers – those with high levels of oestrogen receptors. This was one of the first indications that that biological drivers behind breast cancer might not all be the same. But it took another 10 years before the concept of testing and selective administration was widely accepted, says Jordan.

One reason for the delayed recognition was that the pharmacological findings had not been confirmed in the original Scottish trial, or the NATO trial, probably due to a lack of preparation of the tissue before it got to the lab, which destroyed the oestrogen receptor.

By the early 1990s, though, testing breast tumours for their hormonal status became routine, signalling the arrival of the concept of precision cancer medicine.



A snapshot of breast cancer history. The three men pictured here were key players in transforming the prognosis and management of early breast cancer in the final quarter of the twentieth century. Umberto Veronesi (centre) had pioneered the breast-conserving quadrantectomy and the sentinel node procedure in the 1970s and 80s. Gianni Bonadonna (left) led the first clinical trials of adjuvant breast chemotherapy together with Veronesi. The picture was taken at the European Institute of Oncology (EIO) in Milan, where Jordan was presented with the 2001 EIO annual Breast Cancer Award. Jordan went on to win numerous further awards and accolades for his work, including the 2011 St Gallen Breast Cancer Award, presented by Hans-Jörg Senn, who had founded the St Gallen International Breast Cancer Conference to enable experts to review the emerging evidence on management of early breast cancer and formulate consensus recommendations. In 2016, Jordan, Senn, Veronesi and zur Hausen (who discovered the link between the human papilloma virus and cervical cancer) were named by the German Society for Gynaecology and Obstetrics as the 'Big Four of the Millennium' in recognition of their role creating the standard of care for women's health in the 21st Century.

Lesson 5: Search for 'the good, the bad and the ugly'

Tamoxifen was now a block buster drug delivering unparalleled benefit to hundreds of thousands of women across the world. At this point, Jordan decided to do something that drug sponsors never do: he and his lab went back to the molecule to find out everything they could.

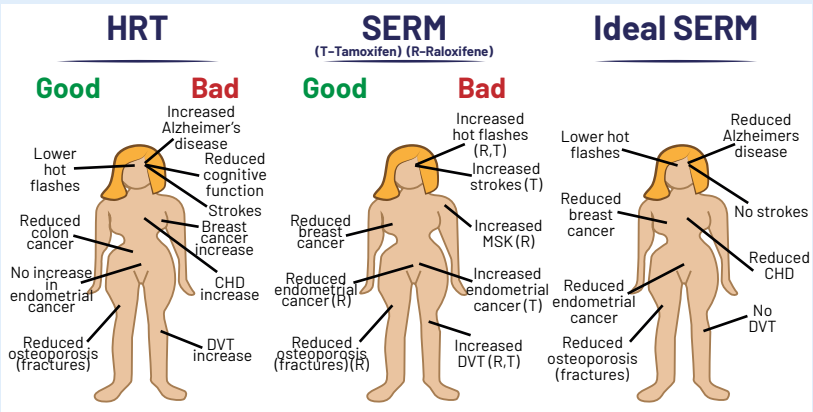
"I was trained as a pharmacologist to look for the good, the bad and the ugly. You've got to be able to spot what is going to go wrong, so people do not die. We took it apart like nobody else had taken it apart. Nobody else was interested. The drug was on the market. Who cared?"

He had won the argument about long-term administration of a cancer drug. He would now take responsibility for exploring every aspect of its impact, to look for potential side effects and drivers of resistance.

That is how Jordan – having devoted his career to a drug he believed in and steered to success – ended up as the person who sounded the alert over the raised risk of endometrial cancer associated with taking tamoxifen.

Jordan's lab had noticed that the drug had a uterine 'tickle', inducing small changes, principally a thickening of the uterine wall. To find out more, his lab conducted experiments with immune-deficient mice, implanting human cancer cell lines, injecting oestrogen to make them grow, and then administering tamoxifen. This time they introduced a breast cancer cell line on one side of the mouse, and an endometrial cancer cell line on

SERMs concept and consequences in cancer



Source: VC Jordan (2004) *Cancer Cell* 5:207–13, © 2004. Reprinted with permission from Elsevier

The big surprise with the 'anti-oestrogen' drug tamoxifen was that it turned out to be anti-oestrogenic in some parts of the body while promoting oestrogen expression in others. The discovery led Jordan to develop the concept of developing selective oestrogen receptor modulators (SERMs) that could deliver combinations of oestrogen agonist and antagonist effects to address multiple oestrogen-related health problems, including coronary heart disease and osteoporosis, two of the biggest killers of women. The figure above was published by Jordan in *Cancer Cell* in 2004, with two SERMs already on the market, to illustrate the idea. At that time raloxifene - the second SERM - was already in widespread use as a treatment for osteoporosis that avoided some of the bad effects of the hormone replacement therapy then in standard use, while actively preventing breast cancer as a 'good side effect'. In 2007 the FDA approved raloxifene as a primary chemoprevention in women at high risk for breast cancer. Three further SERMs have since been approved for various indications.

HRT – hormone replacement therapy, CHD – coronary heart disease, DVT – deep vein thrombosis, MSK – musculoskeletal

the other. "Here was the revelation. The breast cancer was completely blocked by tamoxifen. Gone. But the animal was dragging around a huge endometrial cancer."

Nothing was being flagged up in the clinical setting, however, so Jordan found it hard to get his concerns taken seriously. Taking matters into his own hands, he decided to announce his findings at an international meeting he was due to address. His findings prompted a doctor, who was sitting in the audience, to report some clinical cases of endometrial cancers in women he had treated with tamoxifen.

A correspondence then opened in the pages of *The Lancet* between the doctor, Leonard Hardell, and Jordan. Jordan suggested checking the Scottish trial data for raised incidence of endometrial cancers. "Never seen it!" was the response, says Jordan. But then the Scottish trial, reported in *The Lancet* in 1987, had never actually collected data on the incidence of endometrial cancers. In the end it was a Scandinavian clinical trials group cancer registry that delivered the smoking gun. "They looked at their data gathered on five years of tamoxifen versus two years versus control, and said we were right… They had nine years of data, but they hadn't looked at it."

Yet again, says Jordan, it was the pharmacological work and not the clinical data that brought this essential information to light. Subsequent studies revealed that the raised endometrial risk only affected women post-menopause, as monthly menstruation is a protective factor.

This finding destroyed Jordan's hopes of a chemopreventive role for tamoxifen in postmenopausal women. But it did mean that, by the time chemoprevention trials on tamoxifen derivatives began, researchers were looking at the whole gynaecological picture. This was due to the work of his lab. "I consider it one of the best things I have ever done," he says.

Lesson 6: Can we do better? Raloxifene and more…

Painstaking exploration of 'the good, the bad and the ugly' had revealed not only the heightened risk of endometrial cancers, it also revealed some potentially 'good' and completely counterintuitive effects of tamoxifen.

Tamoxifen was only selectively anti-oestrogenic, and actually acted as an oestrogen agonist in some instances. "It would switch on and switch off sites around the woman's body that nobody had ever seen before," says Jordan. "Anti-oestrogen was thought to be anti-oestrogenic everywhere in the body, so it would cause osteoporosis, it would cause

coronary heart disease… What we found was that tamoxifen tickles the bones to make them stay strong, and it lowered circulating cholesterol."

He developed the idea of looking for derivatives of tamoxifen that might carry no risk of endometrial cancer, but could treat coronary heart disease (a bigger killer than breast cancer among women) and treat osteoporosis (another major killer of older women, due to complications of fractures), while preventing breast cancer at the same time.

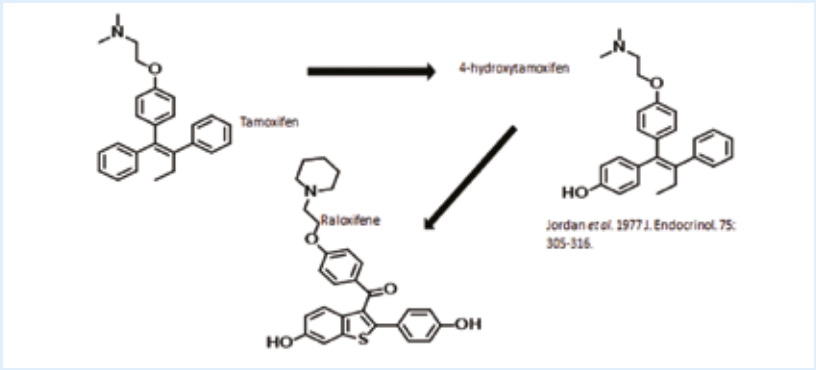
That is how the concept of selective oestrogen receptor modulators, or SERMs, was born in 1989, with the ability to "treat multiple diseases with one pill".

Being the 'go-to' lab for all things related to oestrogen receptors and anti-oestrogen, over the years Jordan had accumulated a number of tamoxifen-like synthetic compounds that he'd been asked to test against tamoxifen. He now turned his attention to pulling together information about this group of drugs.

Persistence and the deep knowledge accumulated over 30 years specialising in this area, paid off in 1997 with approval of raloxifene – the second SERM discovered in Jordan's lab – for treating osteoporosis. The drug carried none of the risk of endometrial cancer associated with tamoxifen but gave protection (though only 75% as effectively as tamoxifen) against breast cancer when taken continuously.

A theroretical study, ten years later, that compared rates of new breast cancers among women treated for osteoporosis with raloxifene compared to the then-standard hormone replacement therapy (HRT), or bisphosphonates, showed how effective this strategy was.

The start of SERM chemistry



The discovery that tamoxifen was hydroxylated to the metabolite 4-hydrotamoxifen was first reported in 1977. That metabolite became the leading compound in medicinal chemistry for the synthesis for raloxifene, which has 100 times the binding affinity of tamoxifen for the oestrogen receptor, and was approved in 1997 as a treatment for osteoporosis that also prevented breast cancer.

Source: VC Jordan et al (1977) *J Endocrinol* 75:305–16

Applying the different rates to the 500,000 women estimated to have been treated with raloxifene across the world, analysis suggested that over a ten-year period, about 27,000 breast cancers were being prevented as a side effect of active treatment for osteoporosis – a marked success for the chemoprevention strategy Jordan had always believed in (*EJC* 2006, 42:2909–13)

In 2007, the FDA extended the indication for raloxifene for primary use in preventing breast cancer for women known to be at particularly high risk.

Three further related SERMs have since come to market: bazedoxifene – approved in Europe and the US as part of a treatment for vasomotor symptoms associated with menopause and the prevention of postmenopausal osteoporosis; ospemifene – approved on both sides of the Atlantic for the treatment of symptoms of vulvar and vaginal atrophy due to menopause; and lasofoxifene. The last of these – "an old drug from the contraceptive days," and "a miracle of medicinal chemistry", according to Jordan – decreases fractures from osteoporosis using 1% of the dose required for equivalent impact with raloxifene, while also reducing breast cancer, stroke and – a first for any SERM – coronary heart disease, though with increased risk for venous thromboembolic events.

Sadly, says Jordan, due to the intricacies of pharma marketing strategies, lasofoxifene has been left sitting on the shelf, approved but not marketed in Europe, and not even approved yet in the US.

Can drug development get back on track?

A 2014 review on Past, Present and Future Challenges in Breast Cancer Treatment, written by a star cast of authors and published to mark the 50th anniversary of ASCO (the American Society of Clinical Oncology), claimed that

In November 2019 Jordan was appointed a Companion of the Most Distinguished Order of St Michael and St George by the Duke of Cambridge at Buckingham Palace, in recognition of his contribution to the field of women's health. This is one of the highest honours given in recognition for service at an international level, and usually reserved for service in the diplomatic sphere. Photo © PA

anti-oestrogen treatments had arguably had "greater global impact that any other treatment intervention in cancer medicine," (*JCO* 2014, 32:1979–86).

The reference included not just tamoxifen and its derivatives, which work through selective modulation of oestrogen receptors, but also aromatase inhibitors, a newer class of drugs introduced in the mid-2000s that work by suppressing oestrogen production.

The value of tamoxifen itself, says Jordan, can be measured by the fact that 25 years on it has not been replaced, and is still used as treatment for advanced disease, as an adjuvant in early disease, as a treatment for ductal carcinoma *in situ*, as chemoprevention in high-risk premenopausal women, and in male breast cancer. "No other therapy has that penetration in cancer across the board."

Contrast this with the drugs that have come on the market in the age of molecular biology and precision cancer medicine. A 2017 study in the *British Medical Journal* reported that, 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 (*BMJ* 2017, 359:j4530).

Jordan argues that one big factor is that governments have ceded the task of drug development to the private sector, "which is expected to raise private capital and get it done". The public money that funded much of his early work at the University of Leeds and at Wisconsin has all but dried up. In the US, he says, only around 1 in 15 young scientists can get a grant today – in his day it was 1 in 4. "[Governments argue] Why should we fund the research? Go out and start your own biotech company and raise private capital and get it done."

Pharmaceutical companies have also stopped doing their own drug development work. "Places like [ICI/Astra Zeneca's] Alderley Park, which developed dozens and dozens of world beating drugs, all that has been closed down." Biotechs, meanwhile, measure their success in terms of coming up with "an idea that looks like it has promise – that big pharma will buy."

But at no point is anyone investing in the pharmacological work to turn that promise into a really effective drug, says Jordan.

Although targeted therapies go to a specific gene target, he says, there are no tests to put the gene target and response to the therapy together. "Nobody is doing that. It is 'suck it and see' with every one of them. We've gone back to the days before the oestrogen receptor and SERMs."

He sees Glivec and Herceptin as rare exceptions "[They are] the benchmarks of the past generation. But now we have 200 different targeted drugs and where do you start?

"Now I think it has all gone so far adrift, into what we can find from the sequencing machine, that we have lost the skills to be able to ask the questions about how is this treatment going to impact on this disease, and what is the good, bad and ugly of my new drug?"

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Women make great surgeons, so why is the profession still dominated by men?

Once seen as an exclusive 'men's club', women have broken into the surgical profession over the past 50 years and proved their value. Yet they remain significantly underrepresented, particularly at the higher echelons, even in countries where family responsibilities are no longer a major barrier to a career. **Simon Crompton** asks why, and what has to change?

Professor Isabel Rubio is a surgeon at the top of her profession. She is Director of Breast Surgery at Clinica Universidad de Navarra, Madrid. She is President-elect of the European Society of Breast Cancer Specialists (EUSOMA) and head of public affairs at the European Society of Surgical Oncology (ESSO).

And yet, when male surgeons introduce her, they use her first name when other men are given their surname and title. When she suggests conference sessions on women in surgery, some male colleagues say they don't see the need. And recently, when a society she was involved in decided to publish a booklet on surgery, it somehow escaped everybody's notice – apart from hers – that every single surgeon pictured was male.

None of this is as bad as the patronising attitudes Rubio encountered on her way up the surgical ladder, when she was often treated as if she were a child – male colleagues regularly suggested she didn't have their stamina and told her to take a break while they ploughed on. Nonetheless, such everyday expressions of sexist attitudes do have an impact.

"Our unconscious attitudes, which have arisen from pre-formed associations, can affect what we say and do without our knowledge – and may even contradict our conscious beliefs," says Rubio. This affects how women progress in surgery. And without enough women at the top, where are the role models for future female surgeons? How will the gender gap in cancer surgery ever be closed?

"There are too few female mentors in surgery and the lack of female role models in surgical leadership contributes to the perpetuation of male stereotypes," says Rubio.

Women in surgery: the numbers

How much have such attitudes affected the number of women entering, and staying in, surgical specialities? Although getting authoritative statistics on the number of women cancer surgeons across Europe is difficult, the disparity between genders is clear. A forthcoming survey from the European Union of Medical Specialists (UEMS) indicates that in most European countries the proportion of women surgeons is 30% to 40%, while in some countries it is as low as 20%.

Given that the number of women surgical trainees in some European countries now equals the number of men, there's hope that greater equality is on the way. However, not all of those will choose to pursue a career in surgery, says breast surgeon Malin Sund, a professor of surgery at Umeå University, Sweden, who organised the UEMS survey. She points to findings showing a relatively high dropout rate in many countries. While the number of trained women surgeons not actively working as surgeons is very low in Nordic countries, the UK and Netherlands, it is higher in Germany and reaches 25% in some southern European countries.

"In these countries there are a lot of female surgeons who have trained and then decide not to work as surgeons – which is of course a terrible loss to the system, and a catastrophe for the women themselves," she says.

The problem is exacerbated by the fact that those women who do stay in the profession appear to face far more obstacles than men in reaching the surgical heights. Equality in positions of seniority is still a long way off.

Changing attitudes

Surgery has traditionally been seen as a profession involving characteristics that are stereotypically ascribed to men: aggression, courage and the ability to make split-second decisions in the face of life-threatening risks.

But in recent decades, increasing numbers of women surgeons have broken into what was once regarded as an exclusive 'men's club', challenging these outdated assumptions. Between 1970 and the mid 1990s the UK saw a tenfold increase in women surgeons.

Thanks in large part to technical progress, the split-second decisions taken in high-risk situations are now seen as far less important than good planning and preparation. Being good at listening and communicating – characteristics more closely associated with women – are now seen as essential clinical skills. At the same time, these stereotypes have themselves been challenged, with the recognition that men can be caring and attentive, while women can be aggressive and courageous – though such behaviour is often still seen as less acceptable in female surgeons than in their male counterparts (*Human Organization* 1997, 56:47–52).

The biggest driver of changing attitudes was probably down to the pioneering women who began to join the profession in ever increasing numbers, and proved their competence in the operating theatre.

That competence was recently confirmed in a Canadian matched cohort study of postoperative outcomes published in the *BMJ*, which provided evidence of what everyone already knows: women make just as good surgeons as men. If not better. It found that patients treated by female surgeons had a small but statistically significant decrease in 30-day mortality and had similar surgical outcomes compared with those treated by male surgeons (*BMJ* 2017, 359:j4366).

"Those women who do stay in the profession appear to face far more obstacles than men in reaching the surgical heights"

So the question remains: why is it that women are still significantly underrepresented in surgery as a whole, and particularly at the higher echelons of the profession?

Is protecting family life the problem?

If surgery still has a gender problem, what lies at the root of it? Could it simply be the old issue of how to combine family demands with the demands of a traditionally high-pressure career? Data from 'implicit bias' testing of surgeons, published in *JAMA Network Open* in 2019, found that male surgeons had a tendency to associate men with career and surgery and women with family and family medicine.

"It's true that balancing family and surgery sometimes is difficult and I think that this is one reason that women refrain from entering surgical specialties," says Rubio. "But I don't think we should be focusing on that. It's far more complex than that."

Malin Sund, who became the first ever female professor of surgery in Sweden in 2013, believes the family issue is definitely significant, but is more important in some countries than others. Sweden is one of the countries where the number of women in surgical training is equal to men.

"In the Nordic countries, with our generous social support and good quality day care, it's fully possible to be a practising surgeon and mother, whereas in many countries that might not be the case," she says. "There are studies showing that academic surgeons tend to have no children or fewer children than other female physicians, but whether you have to make that sacrifice depends on the country you live in.

"Our survey responses from southern European countries tend to focus on the difficulties of organising family life. So it wasn't doing the surgery itself that was the problem, but the expected lifestyle of the surgeon – that the work hours are very hard to combine with a functioning family. In the more northern countries, the problems were less about external day care, and more about the division of labour in the home: a lot seems to depend on who you choose to start a family with."

Is bias and lack of role models the problem?

But there is more going on than lack of financial and social support. Even in Nordic countries there are concerns about equality, not because there aren't enough women in cancer surgery but because there are not enough women at the top of cancer surgery. This isn't just an issue about being able to stay in the profession; it's about being able to be successful in the profession.

Recent research suggests that, although we may like to think that the days of glass ceilings and job discrimination are over, women still face far more obstacles than men in reaching the surgical heights. A UK survey of women surgeons published in the *BMJ* this year found that 59% had reported or witnessed discrimination. Trauma surgery and orthopaedics were identified as having the most sexist cultures by more than half of respondents. More than one in five said they perceived a "glass ceiling" in surgical training (*BMJ Open* 2019, 9:e024349).

In the US, a recent survey of plastic surgeons revealed similar findings. Women were more likely than men to have experienced sexism or bias, and were less likely to feel recognised for ideas, authorship, promotions, or pay rises. Women also felt that their sex was a disadvantage in career advancement (*Plast Reconstr Surg* 2018, 142:252–64).

As Isabel Rubio points out, role models are important here. Her own mentor, Suzanne Klimberg, was an important influence during her US Fellowship – and afterwards. "I saw how she worked and

how she had the same difficulties as me, but she still succeeded. Seeing a woman who can achieve anything – give talks at big congresses, be president of societies, be chief of breast surgery – helped me a lot. It helped me realise that I didn't have to enter into the male thing of demonstrating that you can operate for 12 hours at a stretch, for example. We can do it our own way and be just as good."

Malin Sund agrees that role models help young female surgeons see a way of navigating the system. Until they become more common and visible, there may be problems making any ambition seem realistic. But she points to another problem continually pulling that kind of aspiration back.

Is it about 'old-boys' networks' and just being different?

The UEMS survey showed that women feel excluded from the male-dominated networks where promotions are unofficially discussed and decided. "This is interesting from a Scandinavian or Swedish perspective, because I don't think women don't get up the hierarchy because men aren't being nice. It's just that the networks that develop before training and during training become somehow self-promoting of men," says Sund.

Facing such issues is key if women are to be properly represented in the highest echelons of cancer surgery, according to cancer surgeon Peter Naredi, Professor of Surgery at the University of Gothenburg and Sahlgrenska University Hospital, Sweden.

He points out that, while socio-economic factors may still explain the gender imbalance in those seeking a career in surgery in many areas of Europe, this is no longer a major factor in countries like Sweden – and yet the gender ratio remains stubbornly weighted towards men. "In Sweden both the man and the woman have to take maternity or paternity leave and you don't lose too much on your pension if you are home with kids for two years. Yet even if parents share the social responsibilities, it is still hardly changing the ratio of female to male surgeons." Part of the problem, says Naredi, is lack of opportunity for younger entrants. "We are so many older surgeons taking up the space."

So in northern and western Europe, it's partly a matter of waiting for "old dinosaurs like myself" to move on, he says, leaving space for women coming up through the ranks. But Naredi worries that there is still a considerable and subtle barrier preventing this – the unconscious discriminatory force which he recognises he himself, as a male, is part of.

"When I'm looking for a successor as head of my breast surgical unit, or of a research group that I'm running, there's an official system in place that's very objective. But in practice, what you tend to do is choose someone who's very much like you. As the present – male – head, you might think of that male surgeon, 20 years younger than you, who you've been working with for 15 years. And then you find arguments why this person has more merits than the female surgeon who has also been working with you for 15 years."

And so, the male dominance of senior positions continues. "This is the hidden network," says Naredi. Truly promoting equality in surgery, he says, means choosing people according to formal competence, not whether they 'fit in'.

> ***"Networks that develop before and during training become somehow self-promoting of men"***

"We need the most competent person, the person who can diversify the cancer care, can look at how we serve our society best. There are some countries in Europe, and in the United States, where this has become standard practice, while in other countries we are 10 to 20 years away from that and we continue to choose persons according to the hidden network."

From the exception to the rule

No matter how much has been achieved in some countries, the current experiences of women surgeons tell their own story.

Isabel Rubio thinks of all those board meetings of surgical societies where she wishes there would be many more women – not simply because she feels outnumbered, but because women and men often approach things differently.

"It's not a fight, because we need men to work all this out too and to understand that there is a problem with gender bias. To solve it, there's a need for everyone to realise that some things need to change."

Sakari Karjalainen, President of the Association of European Cancer Leagues (ECL), Secretary General of the Cancer Society of Finland, Finnish Cancer Registry, and the Cancer Foundation of Finland

Celebrating 40 years of reducing the impact of cancer on people's lives

The Association of European Cancer Leagues (ECL), a network of national and regional cancer leagues all over Europe, is celebrating 40 years of actions to reduce the impact of cancer. It was founded in Rome by 14 prominent leagues and 21 well-known cancer experts in 1980, to fight against a disease that was considered a death sentence at the time. Cancer knows no borders and is relentless. And so has been our collective determination to fight it.

In the 1980s, cancer mortality was projected to rise beyond the year 2000. Today, not only have mortality rates in Europe declined, but we have sufficient knowledge to prevent half of all cancers. Our members have helped translate scientific findings into concrete actions. What seemed impossible is now a reality.

ECL members are the main public resource for cancer control information and services. Sharing the ambition of eliminating cancer, nothing less is good enough for us or for the citizens, patients and survivors we serve. The ECL network has empowered cancer leagues to accelerate cancer research and actions to support patients and their loved ones.

In 40 years of existence, ECL has grown in achievements and leadership. ECL's eminent status in cancer control in Europe today is due to successful collaboration, including with the World Health Organization, the International Agency for Research on Cancer, the European Commission, the European Parliament and others.

Co-funding from the European Union has enabled ECL to intensify our work, especially in influencing policy, raising awareness of prevention through the European Code Against Cancer, encouraging Youth Ambassadors to improve dissemination among young people, and enhancing networking opportunities for leagues to share best practice and collaborate more efficiently, especially to reduce health inequalities.

The Future

In the next 40 years, we seek to put ourselves out of business. Our vision is nothing less than a future without cancer. To some this will sound utopian. How can we aim for a cancer-free Europe when experts are predicting that more people will be diagnosed with cancer because we are living longer, and cancer is an age-related set of diseases?

While we do not have all the answers, the following considerations will be key:

- Prevention is the best cure.
- A more robust approach to research on innovative cancer prevention and treatment solutions is needed.
- Cancer is a health inequality issue that cannot be resolved by the health sector alone.
- A substantial amount of data and expertise is available across the continent; we must collaborate to make the most of these tools.

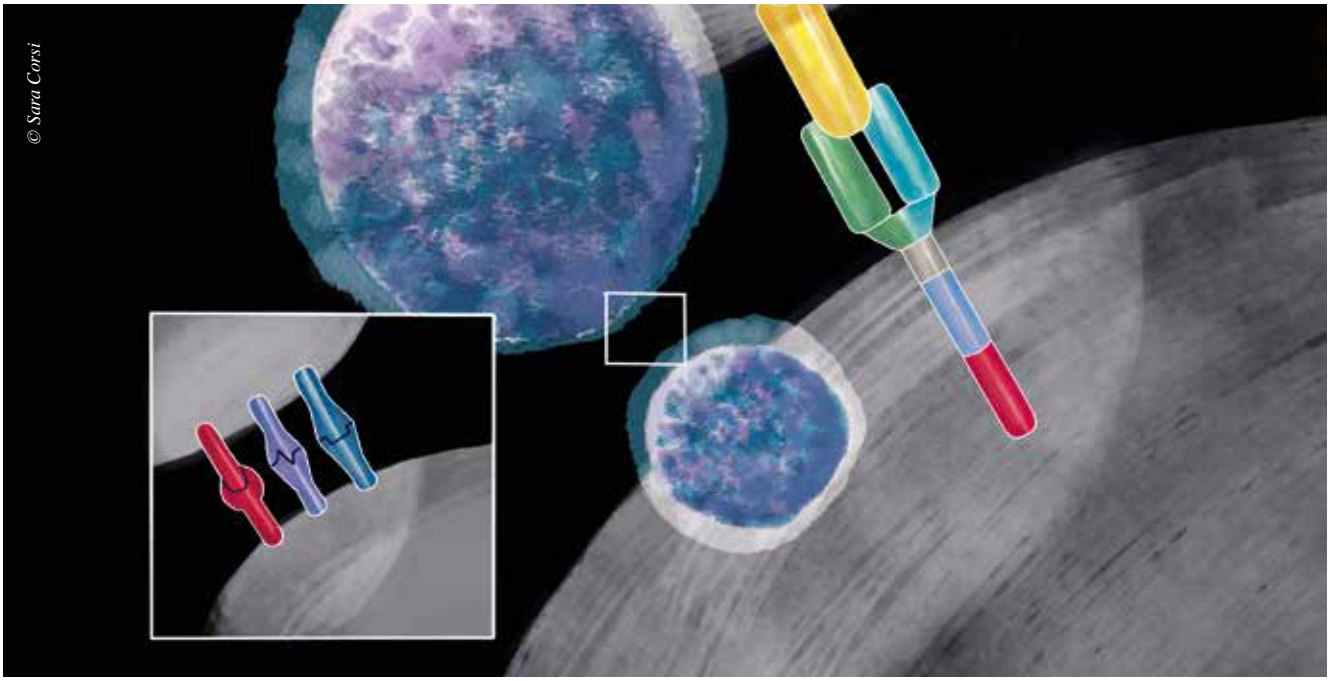
Our major projects for this anniversary year are to:

- encourage countries to step up tobacco control efforts such as outlined in the new tobacco control country ranking report (www.tobaccocontrolscale.org)
- ensure that EU policies and the regulatory environment support collaboration across the cancer community and strengthen the role of representative organisations, such as the ECL
- shape the #EUCancerPlan and Agenda 2030 and Sustainable Development Goal 3.4.

Call to Action

On this 40th anniversary, ECL calls on everyone to join the dedicated efforts of cancer leagues. As the European Commissioner Kyriakides said at a conference on Better Access to Cancer Treatment, in December 2019, "We don't have to look too far for inspiration. The European Cancer Leagues are doing incredible work." Our impact on cancer control and our good reputation are based on the strong influence of cancer leagues all over Europe.

Together, we can make beating cancer a Mission Possible.



The unique toxicities of CAR T cell therapy

Toxicities related to CAR T cell therapy are very different from the toxic side effects associated with classical chemotherapy or targeted therapy. Oncologists need to know what to look out for, how to assess them and how best to manage them. **Elena Riboldi** reports on what is known and what needs further research.

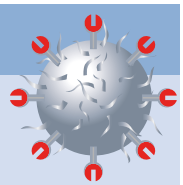
The advent of chimeric antigen receptor T cell (CAR T cell) therapy generated great excitement in the field of onco-haematology. Clinical trials have shown remarkable results in patients with relapsed/refractory B cell malignancies, and two CAR T cell products have been approved in the US and in Europe. Efforts are now underway to extend this approach to other haematological malignancies and even to solid tumours.

Yet the clinical trials that have shown the huge potential of CAR T cells, at the same time revealed their unique toxicities. Cytokine release syndrome (CRS) and immune effector cell associated neurologic syndrome (ICANS) are two key toxicities associated with CAR T cell therapy, though other adverse events also occur and need to be taken into consideration in clinical practice.

The morbidity associated with the side effects is not irrelevant. Though generally reversible, on rare occasions it has led to death. Oncologists need to know how to diagnose and manage toxicities related to CAR T cell therapy.

According to published studies, after CD19-targeted CAR T cell ther-

CAR T cells at a glance



Cytotoxic T cells (CD8) are lymphocytes that can be armed to recognise and destroy cancer cells via the antigens they display on their surfaces. This can be prepared by harvesting a patient's own T cells from their blood, with a process called apheresis, isolating the cells, and then introducing a chimeric antigen into them, which is done by inserting a gene, mostly using a viral vector, as if 'infecting' the cell with the antigen receptor gene.

The chimeric antigen receptor (CAR) is a fusion protein. The extracellular portion of the receptor is an antibody-derived targeting domain. It is constituted by the single-chain variable fragment (scFv) of an antibody directed against an antigen expressed by cancer cells.

The chimeric construct then enables the cell to express and localise the chimeric antigen receptor to the surface of the T cell, from which location it will be able to recognise a specific marker (known as an antigen) on a cell's surface. Many different antigens exist on cells, but to date most CARs have been designed to recognise a marker called CD19, which is found on the surface of all B cells (the white blood cells responsible for producing antibodies), including the malignant B cells that cause certain leukaemias and lymphomas. The modified T cells are then cultured and returned to the patient in a single infusion. This is usually preceded by a course of chemotherapy, designed to deplete the patient's own immune cells, which helps the CAR T cells to multiply in the patient's body. The CAR T cells then fuse to cancer cells thanks to the CD19 marker, which initiates several signalling pathways, leading to elimination of the targeted cancer cell as well as triggering the 'expansion' (multiplication) of the CAR T cells.

apy, CRS was experienced in different grades by 37%–93% of patients with lymphoma and 77%–93% of patients with leukaemia. Rates of any grade ICANS were, respectively, 27%–67% and 40%–62%. In the early clinical trials, approximately half of the patients needed intensive care management.

The task of developing optimal strategies for managing these toxicities has been hindered by the considerable variation in the way they have been assessed and graded across clinical trials and across institutions. In an attempt to address this problem, in 2019 the American Society for Transplantation and Cellular Therapy (ASTCT) published recommendations for "an objective, easy-to-apply and accurate classification of CAR T cell-related toxicities," based on a consensus reached by almost 50 experts in the field (*Biol Blood Marrow Transplant* 2019, 25:625–38).

Sattva Neelapu, from the Department of Lymphoma/Myeloma, at MD Anderson Cancer Center in Texas, is the senior author of the ASTCT consensus recommendations. He emphasises that CRS and ICANS can be fatal if not recognised. Therefore, patients who undergo CAR T cell therapy need to be managed by specialised teams including physicians with expertise in these toxicities, intensive care specialists and neurologists. Things may be more complicated when the therapy is administered in the outpatient setting. In those cases, patients should be hospitalised as soon as they develop a symptom or sign of toxicity, and caregivers must be taught to recognise symptoms of ICANS.

Be aware, spot the signs

Cytokine release syndrome

Neelapu outlines some of the signs and symptoms to look out for. "The first clinical manifestation of CAR T cell toxicity is cytokine release syndrome. It usually starts with fever, that can even exceed 40°C," he says. "Other symptoms are malaise, headache, myalgias, and tachycardia. Possible manifestations include organ dysfunctions, cytopenias, and coagulopathy. In severe cases, patients can develop life-threatening capillary leakage with hypoxia and hypotension." Rarely, haemophagocytic lymphohistiocytosis – a condition in which the body makes too many activated immune cells – can arise. CRS usually occurs in the first week after CAR T cell infusion, although delayed CRS is possible. Time to resolution is generally seven to eight days, but some patients may need more than 30 days to recover.

Immune effector cell associated neurologic syndrome

Immune effector cell associated neurotoxicity syndrome (ICANS) may occur as a CAR T cell related encephalopathy syndrome.

The clinical manifestations of ICANS are very wide ranging, as toxicity does not affect a specific region of the central nervous system. They include encephalopathy (confusion or delirium), expressive aphasia or language disturbance, motor weakness, myoclonus or tremor, headache, seizures, and a depressed level of consciousness. In rare cases patients can rapidly develop diffuse cerebral oedema. Expressive aphasia seems to be a typical symptom. ICANS onset can range from a few hours to three to four weeks after

CAR T cell infusion. It can occur almost simultaneously with CRS or even after CRS has resolved. ICANS is usually self-limiting, and most symptoms reverse in three to four weeks, with persistent abnormalities being uncommon.

Predictors of severe toxic effects

Both treatment-specific and patient-specific factors have a role in determining the gravity of CAR T cell related toxicities, says Neelapu. "The severity of CRS has been correlated with the peak of *in vivo* CAR T cell proliferation and disease burden. A faster T cell expansion can be promoted by higher cell dose, heavily pretreated bone marrow disease, and also by some kinds of preconditioning, such as fludarabine-containing regimens." The risk of severe CRS is also increased in patients with comorbidities and in those who develop the syndrome within three days of infusion.

Severe ICANS develops almost only in patients who have experienced CRS, adds Neelapu, with severity being influenced by disease type, disease burden, patient's age, and treatment history.

Differences in the design of the chimeric antigen receptor may account for variations in toxicity between different CAR T cell products. Second-generation CARs contain an intracellular domain, called co-stimulatory domain, derived from either CD28 or 4-1BB (CD137), to enhance CAR T cell survival and proliferation. CD28-based CAR T cells expand rapidly, while 4-1-BB-based CAR T cells expand more slowly. CRS has an earlier onset with CD28-based CAR T cells, and higher rates of severe neurotoxicity have been observed with CD28-based CAR T cell products. However, an association between the severity of these toxicities and a particular co-stimulatory domain has not been conclusively demonstrated.

The search for biomarkers to predict which patients are likely to develop severe CAR T cell related toxicities, before they become critically ill, is an active field of research.

Grading toxicities

For CRS, the ASTCT consensus grading is based on three elements: fever, hypotension, and hypoxia (*Biol Blood Marrow Transplant* 2019, 25:625–38). Severity can range from grade 1 to 4, with the grade being determined by the most severe event.

The consensus panel that agreed on the recommendations took the decision to focus on criteria that could be measured in the clinic rather than the laboratory, for pragmatic reasons. "Significant alterations in many laboratory parameters clearly occur with CRS," they wrote. "Cytokine aberrations have been well described, but such data are not routinely available in most academic centres in a time frame that is useful for assigning grade and planning management of a patient experiencing CRS." They nonetheless encourage clinical teams to monitor cytokines, C-reactive protein, ferritin levels, and other parameters, "so that additional data may be generated for future study".

For ICANS, the ASCTC consensus grading is based on five elements: the 10-point ICE (immune effector cell-associated encephalopathy) score, depressed level of consciousness, seizure, motor findings, and elevated intracranial pressure/cerebral oedema. Severity can range from grade 1 to grade 4, with the grade determined by the most severe event.

The ICE score is a tool that measures alterations in speech, orientation, handwriting, and concentration. For children aged 12 or younger, the ICE score is replaced by the Cor-

Pathogenesis of CAR T cell therapy toxicities

The mechanism underlying cytokine release syndrome (CRS) is essentially a 'cytokine storm', which produces and sustains a systemic inflammatory response, says Sattva Neelapu, from the Department of Lymphoma/Myeloma, at MD Anderson Cancer Center in Texas. Activated T cells and bystander immune cells, such as monocytes/macrophages and dendritic cells, release several cytokines, including interleukin-6 (IL-6), interferon-γ (IFNγ), granulocyte-macrophage colony-stimulating factor (GM-CSF), and numerous chemokines that recruit more immune cells. The pathogenesis of immune effector cell-associated neurologic syndrome (ICANS), by contrast, is largely unknown, he says. "It is linked with a strong production of cytokines, but none of the cytokines seems specific. Severe ICANS is associated with increased blood-cerebrospinal fluid [CSF] barrier permeability. Elevated levels of cytokines in the CSF may result from both influx and local production." The accumulation of glutamate and quinolinic acid (two excitatory N-methyl-D-aspartate receptor agonists) in the CSF may explain some of the symptoms, adds Neelapu. The finding that patients with severe CRS and ICANS have high blood levels of angiopoietin-2 also suggests an involvement of endothelial cell activation.

Making CAR T cell therapies safer

Scientists are working to generate more potent immune effector cells. However, the increase in persistence that would raise CAR T cell anti-tumour efficacy carries the risk of more severe toxicity. From that perspective, a 'safety switch' would be highly desirable.

Franco Locatelli's group at the Bambino Gesù paediatric hospital in Rome has developed a 4-1-BB-based CD19-specific CAR construct that incorporates an inducible caspase 9 (iC9) safety switch. The gene of human caspase 9 has been engineered with a drug-binding domain. By administering a nontoxic compound, the iC9 dimerises and activates the cascade domain. In the event of uncontrolled toxicity, CAR T cells can thus be killed by apoptosis within a few hours. Other, more radical, innovative changes include changing cell type. "We are working on trials using CAR-Natural Killer (NK) cells, because this strategy could offer several advantages in comparison to CAR-T cells," says Locatelli. He sees a number of advantages to this approach. "First, possibly – although it has to be validated in the clinical setting – the NK cell-related toxicity could be lower than that of CAR T cells, because the cytokine production of NK cells has a less toxic, more favourable profile." Second, the cells could be immediately available, he says, "We can figure out how to prepare banks of CAR-NK cells." A great advantage is that they can be obtained without the blood apheresis process needed for patients' T cells enrichment. Third, he concludes, the cancer cell killing effect of the NK cells is greater than that of the T cells, as NK cells are the most potent cytotoxic lymphoid cells in the body.

nell Assessment of Pediatric Delirium. "The updated encephalopathy screening tool includes elements for assessing the receptive aphasia seen in these patients," write the authors of the consensus recommendations, but they add that, while the ICE screening tool is helpful for assessing patients for encephalopathy, the grading of ICANS requires not only assessment of the ICE score but also evaluation of other neurologic domains, as other manifestations can occur with or without encephalopathy.

Managing toxicities

The standard of care for CRS is tocilizumab, an anti-IL-6 receptor antagonist. If the patient does not respond to tocilizumab, corticosteroids can be effective in reversing CRS. Some data suggest that the anti-IL-6 monoclonal antibody siltuximab or the IL-1 antagonist anakinra may have clinical efficacy. In CRS, patients can require vasopressors to correct hypotension and oxygen supply or intubation for hypoxia.

Tocilizumab is not generally recommended for isolated ICANS. In fact, some studies showed a slight increase in severe ICANS rates in patients treated with this antibody. Corticosteroids are widely used to treat ICANS, but type and dose can differ significantly between institutions. Intubation is critical in patients with ICANS who have severely impaired consciousness. Speaking at the 2019 Congress of the European Hematology Association, Stanley Riddell, Scientific Director of the Immunotherapy Integrated Research Center at the Fred Hutchinson Cancer Research Center in Seattle, highlighted the importance of timing and dose in managing CRS."There are now algorithms to treat CRS with blocking antibodies to cytokines and with steroids, but the timing when you administer those medications can be really critical in determining the patient's outcome. Being aware of the complications and intervening at the right time and with the appropriate dose of those medications is important," he said.

Riddell emphasised the urgent need to understand more about the pathogenesis of CRS, to work out and test better ways to manage it. While it is clear that CRS is initiated by the T cells recognising the cancer cells and producing cytokines, he said, "After that there is a cascade of events that is very complicated, involving different cell types." He pointed to the unexpected finding of several recent studies which showed that, in preclinical models, a major mediator of CRS is adrenaline or its catecholamines. "In the clinic, when patients get CRS, we give them catecholamines to treat their blood pressure, so we are maybe throwing fuel on the fire in some circumstances."

Riddell anticipates "some major advances" in strategies to avert CRS over the coming year or two. "We need to do the scientific research to understand the pathogenesis and then we need to do the clinical work to test interventions in a logical way on controlled clinical trials, so that we understand which ones are working and which ones do not work," he said. Right now, it is a manageable problem, he added, "And I am pretty confident that it will be getting increasingly manageable in the future."

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- certifying quality
- enhancing Outcome Research based on real-life data from OECI Member Centres
- meeting our patients' expectations
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In collaboration with:

HUS Helsinki University Hospital

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Oncology Days

OECI42

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June 10th

Patient Day

Building on the successful experiences of Patient Involvement in OECI cancer centres/institutes

Session 1: When patients improve Care and Research
Session 2: Measuring impact of Patient Involvement
Session 3: Breaking down Barriers to Patient Involvement
Session 4: Engaging patients and family in digital solutions

Health-Economics Session

Pricing, Coverage and Access to Innovative Cancer Drugs

Topics:

- Access to innovative cancer drugs in Europe
- The drug pipeline and financial sustainability of cancer care provision
- Coverage decisions: RCTs as basis for cost effectiveness, real world data and registries

Pathology Session

Molecular diagnosis reproducibility: a European mission

Topics:

- The "HERCULES project on ovary HGSC" - a proposal for rapid biomarker validation
- Standardisation of generic Pre-analytical procedures for in-vitro diagnostics and the European Committee for Standardisation "CEN"
- Integrated and standardised NGS workflows for Personalised therapy
- BBMRI-ERIC: biobanking as a support for clinical cancer research
- Digital Pathology and Artificial Intelligence

June 11th

Scientific Conference

Quality improvement and Evaluation Paradigms in Cancer

Session 1: Developments in the OECI Quality Programme
Session 2: Multidisciplinarity in Cancer Centres and Networks
Session 3: Quality throughout the patient journey
Session 4: Quality in the context of the EU Cancer Mission

Dr Fraud's jungle, where science is the prey

With the advent of Open Access – a new publishing model that asks researchers to pay to make their research publicly accessible – unscrupulous predators were granted easy access to a house full of naïve scientists and doctors, and today thrive at their expense, and at the expense of science, including cancer research. **Fabio Turone** reports.

"The email appeared legitimate. It spelled my name correctly, referenced some of my previous work, and used correct grammar. The journal wasn't on *Beall's List of Predatory Journals and Publishers*. I thought I had done my due diligence. I submitted my manuscript. Shortly after, I celebrated the first round of favorable reviews. Things were going great – or so I thought." More and more scientists – like Alan Chambers who recently wrote his dramatic story in *Science* magazine ('How I became easy prey to a predatory publisher')

– are experiencing the hard way a nasty side-effect of the revolution that shook the world of scientific publishing and conferences, to increase access to published research.

Black sheep in disguise

Several animal metaphors – from black sheep to sharks – have started to pop up because new, unusual and dangerous 'beasts' started making their appearance on the desks and in the mailboxes of scientists of all disciplines: publishers who lure academics and researchers into publishing in journals with impressive names, and into presenting their research at conferences abroad. More and more often, academics and researchers are ceremoniously invited to sit on editorial boards and even chair them, regardless of their qualifications and scientific production.

One might assume that fraudsters are easy to distinguish from honest enterprises but research shows that the opposite is true

Those invitations are sent by the new actors in the publishing arena: A journal editor called them 'black sheep' back in 2008 (http://gunther-eysenbach.blogspot.com), but the expression that stuck with the international scientific community to describe unscrupulous publishers and conference organisers was 'predators'.

It was Jeffrey Beall – then librarian-researcher at the University of Denver, in Colorado – who coined the expression 'predatory journals and publishers', back in 2010. Willing to warn scientists about the risks, in 2008 he had started to publish a blacklist, which was freely available online.

At first, one might assume that fraudsters are easy to distinguish from honest enterprises but research shows that the opposite is true: in developed countries such as Germany, the UK and Italy, as many as 5% of academics like Chambers continue to fall prey to these shady operations.

A fast-growing and changing scenario

According to the most recent report by the International Association of Scientific, Technical and Medical Publishers (bit.ly/2018-STM-Report), "there were about 33,100 active scholarly peer-reviewed English-language journals in mid-2018 (plus a further 9,400 non-English-language journals), collectively publishing over 3 million articles a year". These numbers keep growing, at an accelerating pace: "The number of articles published each year and the number of journals have both grown steadily for over two centuries, by about 3% and 3.5% per year respectively," the report continues. "However, growth has accelerated to 4% per year for articles and over 5% for journals in recent years."

The number of 'predatory' journals – which generally go hand in hand with conferences based on the same lack of scientific scrutiny – has also grown very rapidly: according to estimates, there were 8,000 predatory journals in 2014. This drains some $75 mn from legitimate operations, essentially through the publication fees that legitimate journals use to replace lost income from subscriptions.

As of August 2018, the most recent figure from Cabell's – a publisher that started offering a blacklist at a hefty price – was of 9,179 journals verified as predatory. This list began after legal threats and all kinds of pressures convinced Jeffrey Beall to remove his own list.

In this scenario, researchers looking for an outlet to present their research to the world in a legitimate way,have a really hard time.

The hunter, the hunted and the exploiter

According to a recent analysis of the scientific production of all Italian academics who applied for the National Scientific Qualification to get access to career improvement (*Res Pol* 2019, 48:462–77), more than 2,200 authors – about 5% of the total – published at least one article in a predatory journal on Beall's list, and about 30% of those did so more than once.

After identifying the articles published in those questionable journals, the researchers invited the authors to answer a few questions, anonymously: "Some of them said that they were duped, but some admitted to having been lured by the idea of easily publishing an article, because in the short term that would increase their chances of getting the qualification," co-author Mauro Sylos-Labini, a political economics researcher at Pisa University, told *Cancer World*. "They told us that they regretted having done so, in retrospect."

The explanation for the apparent non-sense is in the fact that almost one in four of the journals classified in the study as predatory based on the Beall's list were also present on Scopus, one of the leading international databases of journals, and used by many research institutions – including the

Italian agency for the evaluation of research – as a proxy for quality.

The trouble is that nobody has yet found a clear way to determine whether those journals were wrongly included in the Beall's blacklist or in Scopus' whitelist: "We can say that in most cases – I would say 98% of them – it is easy to say if a journal or a publisher is predatory, but there are borderline cases for which it can be very difficult," Beall told *Cancer World*. "Bad science and questionable publication practices existed long before Open Access, but the advent of Open Access and the Internet offered them more opportunities for thriving."

Last April, one of Beall's sworn enemies, Indian publisher and conference organiser OMICS, was finally sued by the US Federal Trade Commission and sentenced to pay over $50 mn for "unfair and deceptive practices". Needless to say, the company is still in business.

My name is Fraud, Dr Anna Fraud

After *Science* magazine published, in 2013, the first shocking investigation by John Bohannon, which showed that many Open Access journals claiming to use peer-review were more than willing to publish a fake scientific article full of obvious mistakes, just to cash a fee (Who's Afraid of Peer Review? *Science* 04 Oct 2013), other sting operations demonstrated that the situation is not improving, and might be worsening.

In today's world, to become editor in chief of a scholarly journal or scientific director of a scientific conference, all one needs is an online presence and some pocket money. Of course, the chutzpah helps.

The case of fictitious scientist Anna O. Szust (Oszust is the Polish word for fraud, fraudster) is a good example. A group of scientists created a plausible, but totally fake, online resumé, and applied on her behalf to the editorial boards of 360 journals: "The profile was dismally inadequate for a role as editor. Szust's 'work' had never been indexed in the Web of Science or Scopus databases, nor did she have a single citation in any literature database. Her CV listed no articles in academic journals or any experience as a reviewer, much less an editor. The books and chapters on her CV did not exist and could not be found through any search engine. Even the publishing houses were fake," they wrote (*Nature* 2017, 543:481–83).

"The aim of our study was to help academics to understand how bogus versus legitimate journals operate, not to trick journals into accepting our editor. For this reason, Szust was not a persistent applicant," they continued. "In many cases, we received a positive response within days of application, and often within hours. Four titles immediately appointed Szust editor-in-chief."

"If you look at the scientific literature on predatory publishers, you find a significant lack of consistency"

Apart from egregious cases like this one, there are more and more operations – often based in the developing world – that are not up to the highest standards, but are doing their best to learn: "It's not binary, but rather a complex scenario," summarises Beall, who has retired after being cleared of the allegations of research misconduct by his University, sparked by a complaint by OMICS.

Oncotarget: friend or foe?

Then there are highly unusual cases, such as the Open Access journal *Oncotarget*, owned by US-based publisher Impact Journals: "One day an outstanding researcher of my Institute who had published in *Oncotarget* called me in shock because he had just realised that one of his research articles had abruptly lost much of its value," recalls Vanna Pistotti, former librarian of the Mario Negri Institute of Pharmacological Research in Milan, now moved to a position as researcher in oncology. "*Oncotarget* was in the middle of a storm, and we were unable to understand the reason for that."

The journal, described as "the most proliferative journal of oncology and cancer research of the past decade" (*Scientometrics* 2018, 117:2195–205), was dropped from Medline – the database of the US National Library of Medicine – and later delisted from the Journal Citation Reports published by Clarivate Analytics that assigns the highly valued 'impact factor' to listed journals.

Weirdly enough, a few months earlier Clarivate Analytics had listed the journal among the 'Rising Star from Essential Science Indicators', basically recommending scientists to submit their research there.

The lack of scientific consensus on predators

"If you look at the scientific literature on predatory publishers, you find a significant lack of consistency," Kelly

Warning signs of a predatory conference

Scientific conferences are today's golden goose for predatory publishers. As with journals, there is no simple way of distinguishing them from legitimate ones. If you have received an invitation, ask yourself the following questions (adapted from Academic Positions, bit.ly/predator-warning):

- *Is the conference in* **your field***?*
- *Does the conference appear to be* **a first***? Look for information about the previous meetings.*
- *Who is organising the conference? Is it a for-profit enterprise? If so,* **does it have a connection to a legitimate research organisation/society/institute***?*
- **What sort of fees** *are associated with attending the conference? Beware if organisers try to bundle registration fees with accommodation, meals, and travel.*
- *Does the conference claim that abstracts and papers will be* **peer-reviewed***?*
- *Does the conference advertise a* **fast review time or high acceptance rate***?*
- *Does the conference guarantee your work will be published in the conference proceedings? Have you ever read any papers from these* **conference proceedings** *before?*
- *Does the theme seem overly broad or that the organisers are trying to combine* **multiple fields** *into one event?*
- *Did the* **email invitation** *come from a free email provider such as Gmail?*
- *Is the* **conference organiser** *responsible for other conferences this year on the same topic?*

If the answer is "yes" for one or more of these questions, caution is advised. Ask around, and use Google.

Cobey, a social psychologist and publication officer from the Centre for Journalology, at Ottawa Hospital Research Institute, told *Cancer World*. Cobey conducted a systematic review of the literature, identifying many more opinions than empirical research (*F1000Research* 2018, 7:1001). The analysis included 38 empirical studies, that overall proposed 109 different criteria: "One of the great challenges is finding and validating criteria, and agreeing on the relevance of each of them," she explains.

Every approach seems to have its limitations: "For sure, the idea of making profit from this, like Cabell does, is bizarre," says Cobey, who still has not found a way to access that list for lack of sufficient funding.

Cabell's blacklist doesn't seem to offer more than freely available services do. A recent study by a group of researchers of the Swiss Science Foundation (*mBio* 2019, 10:e00411-19), compared two blacklists: Cabell's and the updated Beall's list, and two whitelists; the Directory of Open Access Journals (DOAJ) and the Committee on Publication Ethics (COPE). They concluded that "the lists tend to emphasize easily verifiable criteria, which are easier for journals to meet, whereas dimensions that are more difficult to assess, such as peer review, are less well covered." Furthermore, disagreements suggest that some journals are misclassified and others operate "in a gray zone between fraud and legitimacy".

It takes two to tango

Researchers publishing or presenting in the wrong place are mostly the victims. Alan Chambers, for example, and the many who chose *Oncotarget* before it was brought down from the stars to the stables. Still, they may soon be invited to justify their behaviour. "Publishing on a predatory journal or likewise presenting an abstract at a questionable conference is not considered misconduct, but still it damages research integrity," explains Cinzia Caporale, a bioethicist and expert in research integrity at the Italian National Research Council in Rome. Caporale's group has worked on a list of recommendations, to be published soon. "We came up with a main list of eight items, with five additional items worth checking. We know that none of the criteria is decisive, but the overall picture is certainly useful," she says.

This careful screening requires a remarkable investment: "In a way, the introduction of Open Access removed the subscription cost, but imposed an additional, hidden cost, which is still hard to quantify," concludes Beall.

AI will help Cinderella to see herself in the mirror

Almost three in ten patients who undergo breast reconstruction after cancer surgery are unhappy with the results. This may be due to objective failures, but often dissatisfaction comes from unrealistic expectations. **Daniela Ovadia** talked to **Maria-João Cardoso** about a tool in development that will use artificial intelligence to help women predict how they will feel about their body after surgery.

Many women who undergo breast reconstruction after mastectomy end up disappointed. It is estimated that as many as 30% of women have to live with aesthetic results they are not happy with. On the other hand, some of those who opt against reconstruction may have chosen otherwise had they had a good idea in advance about how it would turn out.

Maria João Cardoso is head breast surgeon at the Champalimaud Cancer Centre in Lisbon. She founded the patient support centre Mama Help and co-leads a research group on improving outcomes in breast surgery at the Institute for

Systems and Computer Engineering, Technology and Science in Porto. Using their combined expertise in breast surgery and computing, the group are addressing a new challenge. They are trying to find a way to help patients with breast cancer to foresee the realistic results of breast surgery – any procedure, from conservative to radical, with and without reconstruction – before going ahead with the operation.

"Breast cancer overall survival has increased impressively in the last 20 years. Although improved survival is crucial, quality of life should parallel this endpoint," says Cardoso.

Quality of life is heavily dependent on the side effects of treatment. In breast cancer, besides the side effects of systemic treatments, there is also the visible and lasting impact of surgery and radiotherapy. "Breast-conserving treatment or mastectomy with immediate breast reconstruction are the most common surgical options. Moreover, with more sophisticated treatments, better aesthetic outcomes are anticipated. Some of the possible causes of patients' disappointment could be prevented if the outcomes could be measured consistently and possible causes of poor satisfaction identified," says Cardoso. She wants to develop an evidence-based tool to visualise the range of aesthetic results that are likely following breast reconstruction, in order to allow the women to predict how they could feel with their new body image.

What surveys can and cannot tell us

Recent studies done in North America show that women who opt for breast reconstruction after a mastectomy have a high rate of complications: one in three develops a postoperative complication over the following two years, and one in five requires more surgery; in 5% of cases, reconstruction fails (*JAMA Surg* 2018, 153: 901–8; *ibid* pp 891–9). The published findings also showed that women who undergo autologous breast reconstruction are generally more happy with the results in the long term than women who choose reconstruction with breast implants. In order to evaluate satisfaction, the researchers surveyed women on their quality of life 90 days before their mastectomy, and at 1, 2, 3 and 4 years after reconstruction. They asked the women about their perception of their breasts, and their emotional, social, sexual and physical wellbeing. Specific questions addressed how their breasts appeared, how satisfied they were with that appearance, how bras fit, and how their breasts felt to the touch. Emotional and social wellbeing were investigated, asking questions about their body image, their confidence in social settings and their sexual wellbeing. Questions about physical wellbeing, pain and physical difficulty while performing daily activities were also included in the survey.

The surveys revealed that satisfaction is not always related to an objective failure. In a study published two years earlier, Cecilia Dahlbäck from the Department of Plastic and Reconstructive Surgery at Skåne University Hospital in Malmö, Sweden, tried to identify risk factors for poor satisfaction with conventional breast-conserving surgery (*World J Surg Oncol* 2016, 14:303). "The majority of the women, 84%, were satisfied with the overall aesthetic result. But if we look in detail at the results, we see that the rate of satisfaction regarding symmetry between the breasts was 68% and for skin sensitivity in the operated breast it was 67%," says Dahlbäck.

Factors contributing to a poor subjective level of satisfaction with overall aesthetic outcome included excision of more than 20% of the preoperative breast volume and axillary clearance. A high BMI (≥30 kg/m^2) was associated with complaints related to symmetry. Re-excision and postoperative infection were associated with lower rates of satisfaction regarding both overall aesthetic outcome and symmetry.

According to the researchers, the choice of the surgical technique should take into account both objective data and the patient's preferences.

The questionnaires used to measure satisfaction in many of these studies were developed in plastic surgery and not specifically for cancer patients (*Plast Reconstr Surg* 2009, 124:345–53). "The most common evaluation methods on the impact of treatments are patient reported outcomes," says Cardoso. "They consist almost exclusively of questionnaires, usually with low reproducibility due to the subjectivity inherent to patient's self-evaluation. That's why we are trying to find a more objective way to determine the risk factors of poor patient satisfaction in breast reconstruction after cancer therapies."

A gold standard for evaluating outcomes

It is often very difficult for professionals to fully understand and explain why an excellent result, based on the technical analysis of

Reconstruction techniques included in the study

The CINDERELLA project is developing a tool to help candidates for the following common breast surgery procedures predict how they will look and feel about their body:

- ~ Conservative surgery – unilateral
- ~ Conservative surgery with bilateral reduction
- ~ Conservative surgery with LD or LICAP/TDAP flaps
- ~ Mastectomy with unilateral reconstruction with implant
- ~ Mastectomy with unilateral reconstruction with autologous flap
- ~ Mastectomy with bilateral reconstruction with implants
- ~ Mastectomy with bilateral reconstruction with autologous flaps
- ~ Mastectomy with unilateral reconstruction with implant and contralateral symmetrisation with implant (augmentation).
- ~ Mastectomy with unilateral reconstruction with autologous flap and contralateral symmetrisation with reduction
- ~ Mastectomy with unilateral reconstruction with autologous flap and contralateral symmetrisation with implant (augmentation)

LD – latissimus dorsi, LICAP – lateral intercostal artery perforator, TDAP – thoracodorsal artery perforator

the starting situation, might still be far from ideal, and more or less satisfactory in the patient's eyes. This is because there is no standard model for comparison, and other personal factors, such as age, marital and socioeconomic status, and psychological factors, can contribute to the final appreciation.

Objective methods, using artificial intelligence (AI), have been tried to circumvent the lack of reproducibility of patient reported outcomes. However, there is a poor agreement between questionnaires and AI.

The project Cardoso and colleagues are working on aims to create a gold standard method for the aesthetic evaluation by giving patients a better insight into the outcomes, allowing them to judge more objectively, also using inputs from both objective and subjective factors. Named CINDERELLA (**Co**mpar**in**g patient's **de**cision on aesthetic outcome with the BCCT. co**re** objective evaluation after contro**ll**ed te**a**ching in patients proposed for breast cancer locoregional treatment), the hope is that the project will "lead to a better choice of locoregional treatments and better quality of life," says Cardoso.

The CINDERELLA project

Apart from self-reporting, surgical outcomes can be evaluated by an expert assessment. This is ideally done by someone who is not involved in the treatment, to avoid bias, and the evaluation should be preferably be done by more than one person. This type of expert assessment is often done using digital photographs, but it is very costly and time-consuming. If you have a large number of patients, it's very difficult to ask the experts to look at all the pictures. Then there is the so-called objective assessment, which is usually done through measurements looking at the patient's images on a screen. "We measure the distance between the nipples, the distance to the arm and the edge, we compare symmetry, etc." explains Cardoso. "Our research team already developed a software called BCCT [Breast Cancer Conservation Treatment], used by almost 300 centres all over the world, that does it automatically using the pre- and post-surgical photos of thousands of patients, which will allow the analysis and comparison of a large number of pictures in many different centres and countries."

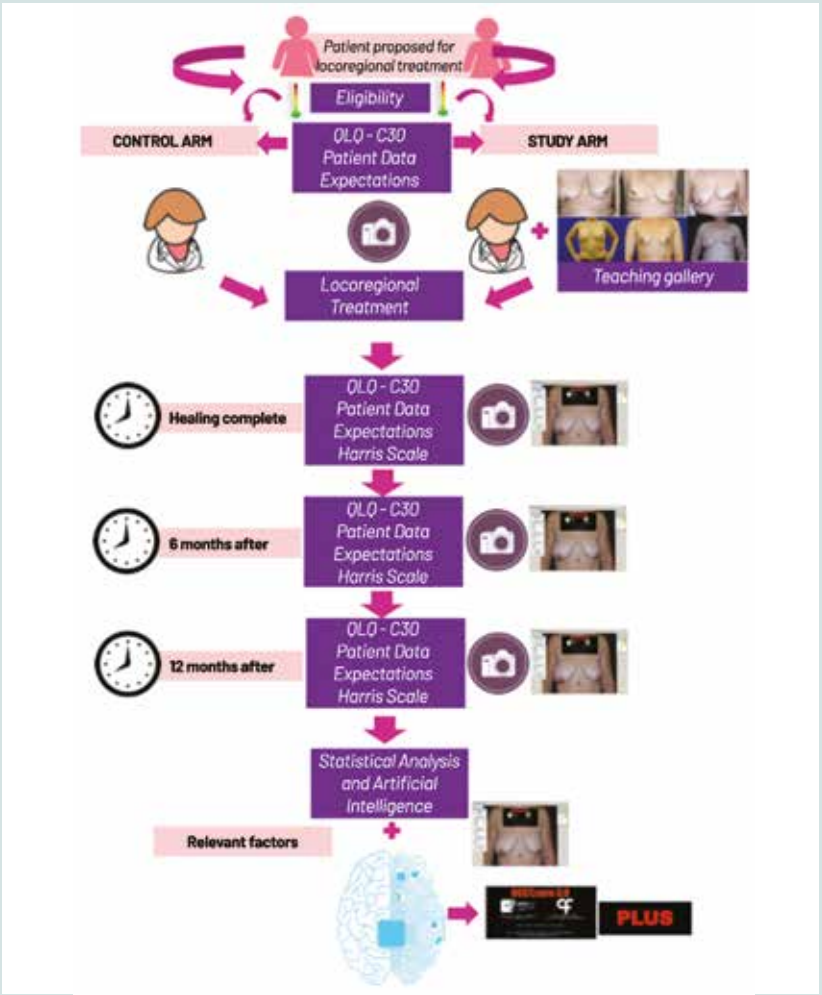
Within the CINDERELLA study, she explains, candidates for breast surgery who are included in the intervention arm will receive educational training with an expert using a teaching software, while the control group will receive the general information currently provided to all their patients. "We will also be able to evaluate the importance of cultural environment on patients' satisfaction, as we already know that Eastern and Western countries have a different cultural approach toward body image, but we will also be able to identify objective risk factors for dissatisfaction, including the surgeon performance."

Beyond photoshop

Digital photo retouching techniques have been used in plastic surgery for many years to anticipate aesthetic results, but Cardoso's project aims to go well beyond that.

The realistic outcomes that the surgeons can automatically simulate today are based on the photos of the patient and on the expected changes that the surgical tech-

The study design



Patients proposed for locoregional treatment will be randomised to the control or study arm. Pictures pre- and post-surgery will be taken in both arms. The control arm will receive general information about the surgical outcomes, while the study arm will receive training with an expert using a teaching gallery of pictures. Patients in both groups will be evaluated using the QLQ-C30 quality of life questionnaire, and expectations will be collected using the Harris Self-Concept scale after complete healing of the scar, and at month 6 and 12. Later on, statistical analysis coupled with the use of artificial intelligence to evaluate the outcomes (through the existing BCCT program) will be applied to the database to identify predictors of poor satisfaction. The software will be updated (BCCT Plus) to include the patients' opinions.

nique will introduce. AI allows the system to become smarter and more efficient, by adding more cases and more photos. Any possible confounding or influential factor will be recorded, including age, body mass index, bra size and cup, education degree, profession and hobbies. Marital status, pregnancies and offspring, together with breastfeeding habits and menopausal status, can also influence the results of reconstructive surgery, so they will be included in the analysis. The database will consider also possible complication such as smoking, diabetes and radiotherapy (total dosing and fraction number).

Taking personalised surgery one step further

The trial has been approved in Portugal and has already completed the feasibility phase. A first group of 340 patients and 340 controls will be recruited in the next phase. An expert evaluation of each outcome will be compared with the results from the AI analysis to focus on the determinants of poor outcomes or poor satisfaction, including the kind of training the patient received before the surgery and how it shaped her expectations.

"We hope to modify and upgrade our software to include the patients' perspective as it comes out from the statistical analysis of the questionnaires and surveys. It will be called 'BCCT Plus', and will be available open access to all the surgical centres dealing with breast cancer surgery," says Cardoso. "We don't have sponsors and support from companies, as it is an open-access project, even if we have a large number of pictures in our database and enough nurses volunteering to be trained to be educators and to use our teaching tool. But we already have our proof of concept: machine learning can help us get the best possible result out of each surgical procedure – fostering the idea of personalised surgery – and develop a tool that people will be able to use all over the world, in a multidisciplinary team including oncologists, nurses and surgeons and patients, each of them with their own expectations."

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CERTIFICATE OF COMPETENCE IN LYMPHOMA

FIFTH COHORT 2021-22

The European School of Oncology in co-operation with Ulm University offers a structured Certificate of Competence in Lymphoma Programme, an academically recognised curriculum of studies, which was developed with the contribution of internationally recognised physicians and scientists in the field of haemato-oncology.

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S. Stilgenbauer, DE

PROGRAMME

The Programme, which is offered on a part-time basis using blended-learning modules and seminars, is divided in **three attendance seminars** (in Germany and Switzerland) and **four e-learning modules**.
Over the duration of **14 months** the Programme provides a total of 405 hours of comprehensive learning, accordingly reported with a workload of 14 European Credit Transfer and Accumulation System Points (ECTS) by Ulm University.

ELIGIBILITY

The Programme is designed for **oncologists** and **haematologists** (medical oncology, haematology, internal medicine, radiation oncology, pathology), but it is equally accessible to **graduates in natural sciences** who are engaged in the field of oncology, especially in the field of lymphoma.

ADMISSION AND DEADLINES

Admission to the Certificate of Competence in Lymphoma Programme is by competitive application only and the selection is based on the eligibility criteria and the selection procedure.
Attendance is limited to **20 participants** per cohort.
Applications for the fifth edition will open in May 2020 and submission is required by the deadline of **14 September 2020**.

CERTIFICATE

Upon successful completion of the Programme, participants will obtain an **academic certificate** issued by the European School of Oncology and Ulm University assigning **14 ECTS** and a diploma supplement by Ulm University.

CERTIFICATE OF COMPETENCE IN BREAST CANCER

FOURTH COHORT 2021-22

The European School of Oncology in co-operation with Ulm University offers a structured Certificate of Competence in Breast Cancer Programme, an academically recognised curriculum of studies, which was developed with the contribution of internationally recognised physicians and scientists in the field of breast cancer.

CHAIRS

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H. Rugo, US

PROGRAMME

The Programme, which is offered on a part-time basis using blended-learning modules and seminars, is divided in **three attendance seminars** (in Austria, Portugal and Germany) and **five e-learning modules**.
Over the duration of **13 months** the Programme provides a total of 381 hours of comprehensive learning, accordingly reported with a workload of 13 European Credit Transfer and Accumulation System Points (ECTS) by Ulm University.

ELIGIBILITY

The Programme is designed for **physicians with experience in the field of breast cancer** (medical oncology, radiation oncology, gynaecology, senology, pathology), but it is equally accessible to graduates in **natural sciences** who are engaged in the field of breast cancer.

ADMISSION AND DEADLINES

Admission to the Certificate of Competence in Breast Cancer Programme is by competitive application only and the selection is based on eligibility criteria and the selection procedure.
Attendance is limited to **20 participants** per cohort. Applications for the fourth edition will open in May 2020. and submission is required by the deadline of **14 September 2020**.

CERTIFICATE

Upon successful completion of the Programme, participants will obtain an **academic certificate** issued by the European School of Oncology and Ulm University assigning **13 ECTS** and a diploma supplement by Ulm University.

Biosimilars – Policy failings that deny savings to some of Europe's poorest countries

Competitor drugs entering the market are opening opportunities to make important savings on an increasing number of biological anticancer agents. But, as **Rachel Brazil** reports, many countries, including those with the most stretched health budgets, could do a lot more to reap the potential rewards.

The promise of cheaper biological drugs is now coming to fruition in oncology. Biosimilars for supportive therapies used in oncology have been available in Europe for over a decade. Over recent years, biosimilars of key monoclonal antibody (mAb) anticancer treatments have also become available, including for trastuzumab, used to treat HER2+ breast cancer (reference drug, Herceptin), bevacizumab, used to treat colon and lung cancer, as well as glioblastoma and renal-cell carcinoma (reference drug, Avastin), and rituximab, used to treat some B-cell lymphomas (reference drug, Rituxan).

At least a further eight oncology biologics will come off patent in the next four years, bringing cheaper prices, with the hope of investing the savings in treating more patients, and increasing access to other therapies (http://bit.ly/CW88-biosimilars).

So far biosimilar take-up has not been uniform across Europe. Some countries are already reaping the benefits, whilst others – including many countries with the most stretched health budgets – are yet to do so.

Switching has led to big savings

In September 2019 the UK's National Health Service (NHS) announced it had saved £294 m (€340 m) from its drug budget in 2019 and a total of £707 m (€820 m) over the two-year period 2018–2019. The biggest saving (£110 m/€127 m) came from switching to biosimilars of Humira (adalimumab) – a medicine used to treat inflammatory conditions.

In another recent analysis, looking at the economic impact of switching to trastuzumab and rituximab biosimilars, an Italian team evaluated five phase II trials including 2,362 patients being treated for advanced breast cancer or follicular lymphoma. They found the economic advantage of biosimilars amounted to €274 per month for rituximab and €3,283–€6,310 per month for trastuzumab, up to the time of treatment failure, which represented a 40% saving on the cost of the originator drugs (*Anticancer Res* 2019, 39:3971–73).

A recently published analysis suggested that Europe as a whole could save between €0.91 bn and €2.27 bn over the next five years by switching to trastuzumab biosimilars (*BioDrugs* 2019, 33:423–36). A separate budget impact analysis, focused just on Croatia, showed that switching to a trastuzumab biosimilar could save between €0.26 m and €0.69 m – representing a saving of between 15% and 35%. Reinvesting this amount, the study found, would make it possible to give the treatment to an additional 14–47 patients per year (*Appl Health Econ Health Policy* 2017, 15:277–86).

Switching has increased access in some cases

Decreasing prices has in some cases brought increased access, says Adrian van den Hoven, Director General of Medicines for Europe, the organisation representing Europe's generic and biosimilar medicines industries. "Use of filgrastim, the growth factor that stimulates white blood cell production, was heavily restricted in Europe until the arrival of a biosimilar. You really had to be diagnosed with severe neutropenia before you could get access to this product."

Today in the UK, he says, with access to biosimilars costing around 30–40% less, "they [have] allowed doctors to prescribe this for preventive use." In some countries, such as the southern healthcare region in Sweden, use of filgrastim has increased five-fold (*Future Oncol* 2019, 15:1525–33).

Increased use of almost 435% in Hungary and 515% in Slovakia was also reported by industry sources at the 2019 Biosimilars Commercialisation Summit (bit.ly/Biosimilars-Summit).

In some countries savings are also being invested in providing access to novel, more expensive treatments, which may partly explain why oncologists, in the experience of van den Hoven, have been generally more open to switching than were clinicians working in the more chronic diseases, such as rheumatoid arthritis, where biosimilars were introduced earlier. "The acceptance and the willingness of clinician to use biosimilars has been much faster in the area of oncology, for first-line and second-line treatments" he says.

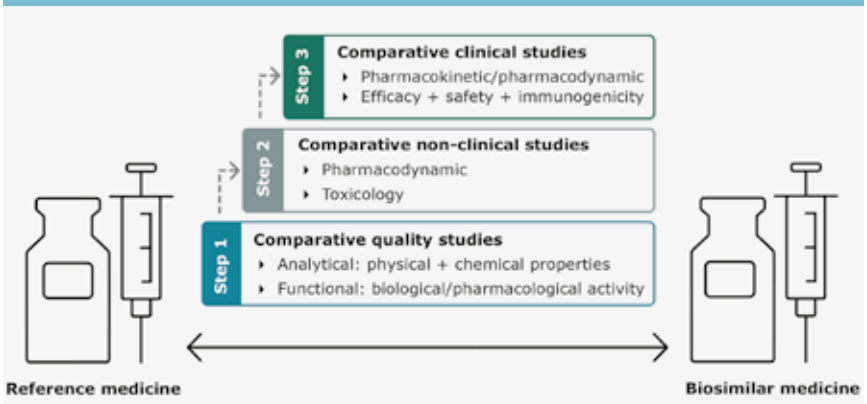
Big differences in take up

That rapid take up applies to some countries much more than others, however, according to Paul Cornes, an oncologist from Bristol, in the UK, and part of the Comparative Outcomes Group – a research cooperative interested in healthcare value. And it is some – but by no means all – of the richer countries that seem to be leading the way. "The biggest uptake [and] the greatest economic benefits appear to be in the UK and the Nordic countries, and increasingly Germany."

"Where we have the biggest problems is actually in the poorest countries of Europe"

A recent study on the take-up rate of rituximab biosimilars for treating patients with non-Hodgkin lymphoma, for instance, showed big differences across the so-called EU5 countries (France, Germany, Italy, Spain, UK). Approved in

Biosimilars – stepped pathway to regulatory approval



Biosimilars have highly similar physical, chemical and biological properties to their reference medicines – any differences are not clinically meaningful in terms of safety or efficacy. They are approved according to the EMA's pioneering regulatory pathway, introduced in 2004. Approval means demonstrating biosimilarity – similarity in function and effect – by showing comprehensive comparability data, including from clinical studies, to show that the biosimilar moves in a similar way within the body (similar pharmacokinetics) and has a similar effect and mechanism of action (similar pharmacodynamics).

Source: ***Biosimilars in the EU*** *Prepared jointly by the European Medicines Agency and the European Commission,* bit.ly/Biosimilars-EU, *accessed 28/01/2020*

Europe in early 2017, prescription rates averaged across the five countries increased from 7% to 35% between July 2017 and September 2018. But there were important differences between countries. For patients treated with a rituximab-including regimen, prescribing of any EMA-approved rituximab biosimilar in the third quarter of 2018 was 72% in Germany and 63% in UK, while France, Italy and Spain reported 47%, 32% and 30% respectively (*JCO* 2019, 37:15 suppl, e19054).

In Scandinavia, where biosimilars are strongly promoted by health authorities, the fast uptake contrasts with countries like Italy, where health authorities have had a more conservative approach. Cornes believes it's the result of entrenched differences in attitudes to healthcare and the extent to which it is seen as a communal responsibility that must be nurtured. "[In the UK] there's a kind of awareness that you have to save where you can," says Cornes. "They do revere their health services and they joke that the NHS is a religion."

"Where we have the biggest problems is actually in the poorest countries of Europe – Romania [and] Bulgaria," says van den Hoven. "They have been very slow to get their machinery in order to incentivise the use of biosimilars, and so they don't benefit from the competition. Those are probably the countries that need this the most. A lot of patients don't have access to those biologics today."

He mentions the example of the hospital tender for trastuzumab in Romania, where he says, "the incumbent [i.e. Roche, which produces Herceptin] was able to get a tender issued one month before the biosimilars entered the market. So obviously, it was the only supplier and so it won a tender before the biosimilars could even compete… until the next round of tenders."

Medicines for Europe has set up a task force to help these countries improve their uptake.

Clinicians need confidence in biosimilars

Part of the issue is clinicians' attitudes to biosimilars, and their willingness to prescribe them. A 2017 survey on knowledge and use of biosimilars, conducted by ESMO (the European Society for Medical Oncology) amongst 393 oncologists, showed that only 49% of them used biosimilars in clinical practice (*ESMO Open* 2019, 4:e000460). "It's difficult to say why only half are using them, given what we know… I hope the rate is higher now," says Giuliani, one of the co-authors.

Uncertainty about the safety of switching was certainly a factor contributing to initial reluctance with some oncologists. But, as Cornes says, "These are not under-tested drugs. The European regulators spend a year reviewing 60–100 tests of comparability, and we hear that they're reviewing 10,000 pages of data, and the volume of data and the time they take to review it is exactly the same as a brand new drug."

The different drug registration pathway for biosimilars could be one reason for hesitation among some clinicians. "We are used to phase I, II and III clinical trials – we need to move our 'angle of observation'," says Giuliani. The ESMO survey showed that clinicians were still paying a lot of attention to clin-

ical data rather than the evidence demonstrating biosimilarity to the reference drug.

Hillel Cohen, executive director of scientific affairs at Sandoz in Princeton, New Jersey, agrees that lack of familiarity with the biosimilar regulatory pathway is an issue with some practitioners, "especially the reliance on analytics, and not large-scale, clinical safety and efficacy studies that physicians have been trained to look at." He believes, however, that this is changing over time. "We've seen that as clinicians are getting more experienced using biosimilars, and it's certainly true in Europe, these concerns seem to diminish."

Early in their history, the potential safety and efficacy impact of switching a patient from a reference product to a biosimilar was heavily debated, but as the drugs have been used by more patients and for longer, confidence has grown thanks to convincing evidence from large numbers of studies.

In 2018 Cohen and co-authors published a review of more than 90 studies looking at this evidence. "These enrolled over 14,000 patients, seven different molecules, including oncology products, in 16 different disease locations," says Cohen. "It provided reassurance to healthcare professionals and the public that the risk of immunogenicity-related safety concerns or diminished efficacy is unchanged after switching… no review today has revealed any reason to be concerned after switching from a reference product to a biosimilar."

Extensive education campaigns carried out by many organisations have helped convince the clinical community. "Peer-to-peer initiatives in education are very influential," says Cohen. Cornes agrees that education initiatives carried out in preparation for the release of oncology biosimilars have had a big impact, and he credits the European regulators with playing a crucial role in supporting and explaining their process.

"The different drug registration pathway for biosimilars could be one reason for hesitation"

The approach taken by patient advocacy groups has generally stressed the importance of ensuring patients are fully informed about any changes in their prescriptions from reference drug to biosimilar, or between biosimilars, and that they are able to discuss changes with their clinicians and know what to ask (see for instance the biosimilars toolkit of the International Alliance of Patients Organizations (iapo.org.uk/biosimilars-toolkit).

Clinicians need an incentive to switch

Take-up of biosimilars is not down to education alone, however. "[Physicians] have to have an incentive to do so," argues Cornes. Different countries have used a variety of carrot and/or stick approaches, he says.

Denmark used an aggressive approach to push physicians to prescribe the first biosimilar, infliximab, used since 2014 to treat a number of autoimmune diseases. "They basically said: you will use the biosimilar unless the doctor can produce clinically supportable evidence as to why that's the wrong action." While that approach had the intended effect, says Cornes – "In a matter of a few months, Denmark switched more than 80% of their patients," – it also caused "some friction between managers and healthcare professionals," according to ESMO's Giuliani.

Sweden, meanwhile, adopted a slightly more consensual approach, which also worked. Clinicians faced no initial obligation, and early uptake was slower. But by 2016, when confidence had been built, patients were informed of a switch by letter, and within four months 90% of them were using a biosimilar (*ESMO Open* 2018, 3:e000420).

In the UK incentives have been offered whereby the prescribing authorities benefit from the savings made from switching to biosimilars, using a 'gain share' model. A well-publicised example relates to University Hospital Southampton and their local Clinical Commissioning Group. When they switched to infliximab biosimilars, the cost savings were divided between the hospital and commissioning group, which then invested the money back into clinical services, creating a win–win situation.

To achieve this switch, says Cornes, they invested in specialist drug optimisation pharmacists. "An investment in a year's salary for a pharmacist was paid back in about a month with the money generated by saving. And [it] indicated that people with knowledge of [biosimilar] drugs, who had the time and ability to talk to patients, could give them the confidence to swap."

The NHS now aims to have 90% of new patients being on the best-

value biological medicine within three months of product launch, and 80% of existing patients within 12 months. The first UK oncology biosimilar, rituximab, launched in April 2017, reached this target within 5 months.

Savings vary according to payer purchasing mechanisms

Another factor that varies between countries is the payer purchasing mechanisms used. A report commissioned by Pfizer from the IQVIA Institute for Human Data Science found evidence that, at a hospital level, the use of single-winner contract tenders led to rapid biosimilar uptake, with biosimilar volume share reaching 80% in less than six months (bit.ly/IQVIA-Biosimilars). However, it also points to evidence that multiple-winner contract tenders may result in lower costs at a regional level (measured by average net molecule costs per defined daily dose), because reductions are obtained on multiple products, often including the originator drug (*ibid*).

Balancing savings with ensuring a sustainable supply

The UK model is praised by van den Hoven for encouraging competition, but avoiding the pitfalls that in some instances have led to drug shortages. "They've organised the tendering for biosimilars to ensure that they have at least three or possibly four different suppliers, including the incumbent maybe in some cases, and that way, they make sure that they always have a guarantee of supply," he says.

Maintaining a healthy biosimilars market may not be down to Europe alone, however. The US regulators, the FDA, approved their first monoclonal antibody biosimilar in 2016, and now there are two or more biosimilars on the market for each of the cancer therapies bevacizumab, trastuzumab and rituximab. But some are questioning how sustainable the US biosimilars market will be, with drug companies creating 'patent thickets' to protect their monopolies through new formulations and delivery methods.

This year Pfizer announced it had abandoned five of its pre-clinical biosimilar programmes. "There's a lot of pessimism,' says Cornes. 'I can see that a lack of traction in the American market, for whatever reason, is going to cause trouble for Europe."

Speaking from the perspective of the European biosimilar medicines industry, van den Hoven warns that, "There is a concern from our side of the industry with the sustainability, longer term, because as the prices are pushed quite low, there's an issue of how sustainable this is… We're concerned that companies will focus more on [high-volume] biologics and less on some of the niche biologics for orphan diseases, because there's no real incentive."

Biosimilars certainly need considerably higher levels of investment than generics – one estimate is that it takes seven to eight years to develop a biosimilar, at a cost of between $100 m and $250 m, making them very vulnerable to low or anti-competitive pricing (*Am Health Drug Benefits* 2013, 6:469–78). Cornes says purchasers have got to consider the issue of sustainability: "Do we just drop the price and take the lowest one, or do we think: what does it take to nurture a market so these companies will be here in 10, 20, or 30 years from now?"

One area that adds to the cost is the large amount of data required by the regulators, which van den Hoven says could be streamlined. "We've been saying for some time now, we need to look at what is the purpose of all these clinical studies. There have been some small improvements. For example, in Europe, they have reduced the number of animal studies that the industry has to do."

Currently clinical studies also have to be carried out separately for each regulator, rather than being able to use the same data, which all adds to development costs. "We've made incremental progress [in discussions with the EMA], but I think we could do a lot more," he says.

Cohen is still positive about the future for biosimilars. "There's no question that the number of biosimilar oncology drugs will increase, has increased, and is increasing, both in supportive and treatment settings," he says.

Certainly lessons have been learned since the first oncology biosimilars were introduced ten years ago. "The difference is nowadays communication is better and we understand the scepticism and can explain [biosimilar regulation pathways]," says Giuliani.

The question is how to turn those lessons into policies across Europe that can maximise the benefits for all.

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MDT meetings: why patient care suffers if I'm not there

Multidisciplinary team meetings should be where the full details of a patient's cancer diagnosis are discussed by specialists with the cutting-edge knowledge and expertise in treating cancer and the relevant information about the patient – their fitness, medical history, needs and priorities – to reach a consensus recommendation for their treatment and care.

In a disease as complex as cancer it seems the most logical way to ensure uniform standards of high quality care for all patients. Team meetings can also offer opportunities for education, provide a way to increase the number of patients entered into clinical trials, facilitate communication between primary, secondary and tertiary care, and provide team members with opportunities for professional development.

In general, members of MDTs that function effectively can barely imagine working in any other way.

Many MDTs however do not function effectively. In some places, MDT meetings are seen as merely 'rubber stamp' or 'tickbox' operations – something of little intrinsic merit that the system obliges you to go through, where every case is rushed through and the decision reached within the space of a few minutes. In others, discussions are allowed to drag on interminably, for no good reason, with too long being spent on relatively straightforward cases, and many contributions being unduly lengthy or off the point. Sometimes the problem is that one or two voices dominate every discussion, sidelining the contribution of others who have information and expertise that could impact on the recommendation. In some places key team members are often missing from the meeting, because they - or the team organisers or hospital administration –

have not prioritised ensuring they can and do attend. Then there's the whole question of what happens to the discussion and recommendations. How do these feed into the decision making process with the patient, if they do at all?

Sadly, large numbers of cancer practitioners across Europe end up resenting the time they are obliged to spend at MDT meetings, because it seems like an unnecessary and bureaucratic waste of time that yields little of benefit to either patients or doctors.

In an effort to challenge this perception, and explore the realities of team meetings in different places across Europe, *Cancer World's* Janet Fricker asked the core members of a well-functioning prostate cancer multidisciplinary team at Addenbrooke's Hospital in Cambridge, to describe from their own perspective why their team meetings matter to the quality of patient care. Specifically she asked each member of the core team about their role, about what they contribute that their colleagues need to know, about the information they need to receive from their colleagues, and general observations about what makes the meetings work well or how they might be more effective.

We hope to follow this up with a further article where we ask readers to comment on how the functioning of this team compares – the good and the bad – with their own experiences.

Addenbrooke's multidisciplinary team meetings

The Addenbrooke's prostate cancer MDT, one of around 40 different MDTs convened every week at this Cambridge hospital, meets on a Monday afternoon to discuss treatment plans for newly diagnosed prostate cancer patients. Attending the meeting are members of the core team composed of urologists, oncologists, pathologists, radiologists and specialist nurses.

The meeting is divided into two parts. The first part considers patients from regional hospitals, whose healthcare teams dial-in using conferencing facilities. For these patients (usually around 15 are reviewed), local hospitals have already made a diagnosis, but require expert opinions to explore whether patients are suitable for brachytherapy or robotic surgery, which is only provided at Addenbrooke's. In the second part the team considers local patients, who are listed for discussion when their imaging and pathology results are ready. For these patients (usually around 40 are reviewed), the team decide between recommending surveillance or active treatment in the form of surgery and radiotherapy. Altogether the MDT meeting takes around three hours.

Key to the smooth running is the EPIC system where the patient information is entered on to the computer system by the MDT coordinator prior to the meeting. "This allows us to view all the information on one screen and saves having to spend time hunting it down," says Veneeta Thankappannair, the prostate cancer specialist nurse. Other important facilities needed are teleconferencing to communicate with external hospitals, a microscope and projection system for the pathologist to show slides, and screens to display the EPIC patient information and radiology images.

Fundamental to the approach of MDTs is that the MDT makes recommendations, rather than taking decisions, with the final decision about the way forward made by the patient in face-to-face discussions with the urologist or specialist nurse in clinic after the meeting.

Urologist – Vincent Gnanapgragasm

What does your role involve? "In Cambridge the urologist leads the MDT because they are the team member who first sees the patient in clinic and records their medical history and takes the biopsy specimen. Prior to the MDT, the urologist spends about an hour reviewing the notes, biopsy results and imaging, and brings everything

together to suggest a treatment plan for each patient that the MDT can discuss."

What does the team need from you? "The biopsy specimen and the patient's medical history, which is important in balancing whether the patient is likely to die of something else sooner than prostate cancer."

What information do you need from colleagues? "Their advice about the different treatment options and whether they are aware of any suitable trials."

Other thoughts: "In Cambridge we've pioneered the Predict Prostate tool for the MDT to use at the point of prostate cancer diagnosis for patients with non-metastatic disease (*PLOS Med* 2019; 16: e1002758). The tool, developed using data from over 10,000 men diagnosed with non-metastatic prostate cancer between 2000 and 2010 with a median follow-up of 9.8 years, estimates survival with and without treatment. The model helps patients and clinicians to decide between active surveillance and radical treatment. For radical treatment it does not distinguish between surgery and radiotherapy. It is really important in balancing whether the patient is likely to die of something else sooner than prostate cancer. The Predict Prostate tool has been endorsed by the UK National Institute for Clinical Excellence as a decision aid in prostate cancer management."

Clinical oncologist – Yvonne Rimmer

What does your role involve? "In the UK, clinical oncologists combine the role of radiation oncologist and medical oncologist. Our role is to consider the whole patient and their prostate cancer in the context of comorbidities. We provide in-depth knowledge of radiotherapy and systemic anticancer therapies (hormone treatments and chemotherapy) and know about associated toxicities. We can also let them know about relevant trials. As well as treating patients in the curative setting, oncologists are responsible for treating metastatic disease."

What does the team need from you? "They need the clinical oncologist's view about whether the patient is suitable for radiotherapy and systemic treatments."

What information do you need from colleagues? "We need information about the patient's fitness for treatment and existing comorbidities. Essentially, someone who is fit enough for curative radiotherapy needs to be walking into the clinic unaided. I also need to know about urinary frequency and flow, as a large prostate or bladder insufficiency can affect their ability to have radiotherapy, as can some bowel conditions, such as inflammatory bowel disease. It is also valuable to know about social circumstances, as elderly patients with caring responsibilities may not wish to travel daily for radiotherapy."

Other thoughts: "To help make things clearer within the busy and time-constrained MDT discussion, it would be valuable to have patients grouped together, for example to have a section in the meeting for men presenting with raised PSA, another for localised prostate cancer and a third for those presenting with metastatic disease."

Pathologist – Anne Warren

What does your role involve? "Throughout the week, sub-speciality pathologists assess microscopically prostate biopsies that have been processed into paraffin wax blocks and cut into thin sections and stained. For each specimen pot (containing fine 'cores' of tissue representing different parts of the prostate) we screen for cancer foci. If cancer is found, we provide a histology report detailing the number of cores with tumour, the maximum length of the cancer in a single core and architectural appearance (known as grade) of the tumour. For tumour grading we use both the traditional Gleason Grading system and a

new 'Grade group' system (proposed by Jonathan Epstein from John Hopkins University) that help to guide the most appropriate treatment options for patients.

For each patient, the whole biopsy reporting process takes between 30 minutes and two hours, depending on the number of biopsies taken. On the morning of the MDT, the pathologist attending the meeting does a quick review of cases to check that no mistakes have been made. Even if the patient has a negative biopsy (~ 30% of patients) they still need to be discussed in the MDT due to the possibility that the biopsies could have missed the cancer."

What does the team need from you? "Information about whether cancer is present in the prostate biopsies, and if so the number of cores involved, the maximum length of the tumour present in a single core, the tumour grade (Gleason score and Grade group), and whether there's evidence of extra prostatic spread."

What information do you need from colleagues? "The patient's clinical history. Many people think biopsies give black-and-white results (like a blood test), but in reality it's an interpretation of the image you see before you. We can get that interpretation completely wrong if we don't consider it in context of the patient's clinical history. We need to have information such as whether the patient has had prior radiotherapy or chemotherapy, whether they have known metastatic spread of the prostate cancer or even a different type of tumour arising in another organ."

Other thoughts: "Going forward it would be helpful to always undertake the biopsy after the MRI scan, as this would allow you to screen out the patients where there are no visible lesions on imaging and to focus on biopsying patients with visible 'target' lesions.

The difficulty with biopsying everyone is that you identify lesions that aren't clinically significant and don't need to be treated. Doing an MRI scan first would be better for patients and allow us to improve efficiency by rationalising the amount of pathology we need to do."

Specialist nurse – Vineetha Thankappa Nair

What does your role involve? "The nurse provides the first point of contact for prostate cancer patients and their families at Addenbrooke's Hospital, ensuring that the pathway runs smoothly with tests undertaken in a timely fashion, and helps to counsel patients through the decision making process after the urologist has broken the bad news. Specialist nurses provide holistic support and signpost patients to other support services, such as psychological support services."

What does the team need from you? "I act as the patient's advocate and provide information about the patient to other team members and communicate the recommendations with patients.

A nurse will have met the patient prior to the MDT and found out about comorbidities, their social situations, and any treatment preferences."

What information do you need from colleagues? "We need information about diagnosis and treatment recommendations to relay to patients, including how different treatments would impact on comorbidities. It's also helpful to know whether there are research studies that the patient might be suitable for in future, allowing us to flag up the possibility to them at an early stage."

Other thoughts: Patients are normally only considered by the MDT at diagnosis, and referred directly to the oncologist if they have a recurrence. From the nurse's point of view I would find it valuable to run patients with recurrent prostate cancer past the MDT to discuss benefits of different treatment approaches. For example, this could be when progression is identified and men become eligible for hormone therapy, or when men become resistant to hormone therapy and are considered for second line treatment or chemotherapy."

Team Talk

Radiologist – Tristan Barrett

What does your role involve? "Prior to the MDT, a radiologist will have reviewed the MRI and CT scans. MRI is used for local diagnosis to determine where lesions are located in the gland, while CT scans are used for advanced or metastatic disease. While CT is a generalised radiology skill, MRI is much more specialised and needs radiologists who are proficient at interpreting different anatomical areas. For example, I am experienced in prostate, bladder, and kidney MRIs, but am not nearly so expert at analysing liver and gynaecological MRIs."

What does the team need from you? "Information on TNM staging, which describes the size of the tumour, and whether the cancer has spread to the lymph nodes, or different parts of the body. Radiology can also provide a definitive answer to say no disease is present here and further investigations are not required."

What information do you need from colleagues? "We need information from the urologist about the specific focused question they want answered, as this can help reduce the number of images that we need to view. Also, it's useful to know whether the patient has any other relevant clinical history that may make a tumour likely, or indeed information that may make a benign process more probable, such as a treated prostate infection and a subsequent reduction in the PSA levels."

Other thoughts: "The MDT process could be streamlined, removing straightforward cases and allowing longer slots for patients who need more time for discussions. When I worked in the US and Canada they limited MDT discussions to four or five cases that are considered to be management or diagnostic conundrums."

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References:
1. Sparano et al. *N Engl J Med*. 2015.
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4. Paik et al. *J Clin Oncol*. 2006.
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HER2–=human epidermal growth factor receptor 2 negative; HR+=hormone receptor positive; TAILORx=Trial Assigning Individualised Options for Treatment (Rx)

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EXACT SCIENCES

Solange Peters

President of the European Society for Medical Oncology

The second woman ever to hold the ESMO presidency, Solange Peters brings to the role impressive clinical and research experience in lung cancer, one of the most challenging and fast-moving areas of oncology. ***Cancer World*** asked her about how ESMO is adapting to meet the needs of oncologists in today's complex and rapidly changing clinical landscape, and about her vision for ESMO, and its role in the world.

Cancer World: *New treatments are coming to market much faster than the evidence doctors and patients need to make informed choices about how best to use them. What issues does this raise for ESMO's task of developing evidence-based guidelines?*

Solange Peters: Evidence-based guidelines are increasingly important as treatments are becoming more expensive and healthcare resources are more restricted. It is very important to offer evidence-based medicine to the maximum number of patients, so spending money on therapies that are not of benefit has to stop.

In response to current challenges, we are working to improve our guidelines in a number of ways. Firstly, our statement of benefits of each intervention is always qualified to indicate the level of evidence and grade of recommendation. Secondly, as the number of options expand, and as biological subgroups of cancers are identified, guidelines have been getting increasingly lengthy and complex to read and apply. We are therefore looking to adopt a more schematic approach to presenting the evidence, for instance by making greater use of algorithms.

Thirdly, with the clinical landscape changing so fast, we need to ensure our guidelines are always up-to-date. We have now started publishing online so-called 'living guidelines', which incorporate new evidence in real time, as it emerges from the literature.

The fourth thing is the ESMO Magnitude of Clinical Benefit Scale (ESMO-MCBS). With so many treatment options now available for many cancers, you need to make a choice. The ESMO-MCBS qualifies the extent of clinical benefit in terms of various dimensions including overall survival, progression-free survival, toxicity, long-term survival, quality of life and so on, which means you can use it to prioritise the strategies to use in patients.

So in the ESMO Clinical Practice Guidelines you now have the level of evidence, the clinical grade of recommendation and the ESMO-MCBS score.

CW: *The ESMO Guidelines Committee can only work with the evidence that is available. How do we ensure the right studies are done to answer unresolved questions about which treatment strategies work best for which patients?*

SP: There are many outstanding questions: the usual examples are about duration of immunotherapy as well as the optimal frequency of administration and doses of these drugs. These questions that the community is asking will in general only be answered by academic research. ESMO is committed to doing as much as we can to support the academic and collaborative groups doing

research, so whenever a request comes for any operational or policy support we always try to respond.

But there are also ways to incentivise the pharma industry to ask the right questions. The ESMO-MCBS has an important role here. As the scale includes mandatory measures of aspects such as toxicity, quality of life, and long-term benefits, then if industry trials do not evaluate those data, they won't qualify to reach the maximum score. So that could be one incentive for industry to generate the evidence doctors and patients need.

CW: *You are only the second woman president of ESMO, and you've been instrumental in significantly boosting the profile of women in senior ESMO roles. How did you do that, and what advice do you have for others trying to address gender bias in oncology?*

SP: Martine Piccart, ESMO's first woman president, started ESMO's Women for Oncology initiative, I picked that up from her. When I first joined the ESMO Executive Board, it was composed of more than 10 men, and me. I was the only one who really saw this as a problem. The attitude was that, more and more women are entering the profession, so the gender gap will resolve 'spontaneously'. So I asked for funding to do a study to better define the magnitude of the problem. When we looked at the numbers it turned out that less than 30% of ESMO committee members, less than 25% of invited speakers at ESMO meetings, and less than 15% of ESMO Board members were women. Importantly, this picture had not changed at all over the previous 10 years, despite the marked increase in the proportion of women working in the profession over that time.

Once the ESMO Board realised there was a problem, we saw rapid change. Today the Executive Board is composed of 50% men and 50% women, and at the last ESMO Congress (2019), women accounted for 45% of speakers. So the advice I can give to anyone wanting to start challenging gender inequalities is that you first have to prove and describe that the problem exists.

Challenging the gender balance has been important for equality within ESMO, but it also helps challenge some of the bias and barriers that women members say hold them back in their careers, by offering role models, building confidence and changing negative perceptions about women's capabilities in leadership positions.

We are now also encouraging the industry to address the entrenched gender gap when choosing their principal investigators, first authors and members of their advisory boards, as it is almost impossible now to build a career in oncology without some involvement in industry trials.

CW: *ESMO has undergone a significant change in identity in recent years. Is it still a medical oncology society and is it still European?*

SP: In everything we do now, we are not just medical oncology, we are multi-professional. All our guidelines, all our faculties across diseases, encompass all the treating subspecialties, the cancer caregivers.

Our roots are European, our membership is international – 25% of ESMO members are in Asia. Our approach is to deliver education according to our members' needs and consequently this includes organising activities in countries outside Europe. We have the capabilities, we have the energy, we are happy to do that. But we are always very respectful of the local knowledge in cancer, what is in place and what is needed.

One of the aims of my presidency is to move ESMO towards philanthropy, to fund travel costs, for instance, for doctors in under-resourced countries to learn about how a new radiation machine is working, or education about how to optimally manage patients in different settings. I expect we will offer such support primarily to countries in Asia, Africa, South America, but also in Europe when necessary.

I think that when an organisation such as ESMO has become so reliable in developing resources and services for patient care, it must ensure appropriate resources are accessible to its members and patients in countries with more fragile situations. This is one of the most important things for me. We will also provide funding for new types of fellowships, which will be more closely tailored to national needs. If I have to think of any legacy at the end of my presidency I hope it will be this.

Solange Peters is in charge of teaching and patient care in medical oncology and thoracic malignancies at Lausanne University Hospital, Switzerland. Her main field of interest is new biomarker discovery and validation in preclinical and clinical settings. She is also strongly involved in multimodality trial building for locally advanced non-small-cell lung cancer, as well as clinical and translational cancer immunotherapy. She is co-chair of the Swiss Lung Cancer Research group, and has responsibility for trials organisation and scientific coordination, as well as related databases for the European Thoracic Oncology Platform – a foundation promoting exchange and research in the field of thoracic malignancies in Europe, with more than 10 collaborative groups in 10 countries and more than 210 participating sites in 18 countries.

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