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n° 79 September / October 2017

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"Learning from blood cells" by Maddalena Carrai

Contents

Printed by
Grafiche Ambert, Verolengo (TO)

Cover by
Maddalena Carrai

Illustrations by
Elisa Macellari, Nicolò Assirelli, Vito Manolo Roma

Published by
European School of Oncology

Direttore responsabile
Alberto Costa

Registrazione Tribunale di Roma
Decreto n. 436 del 8.11.2004

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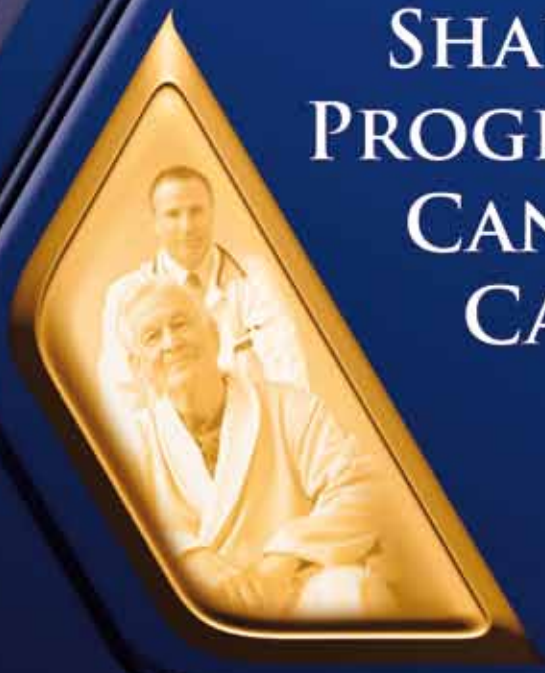
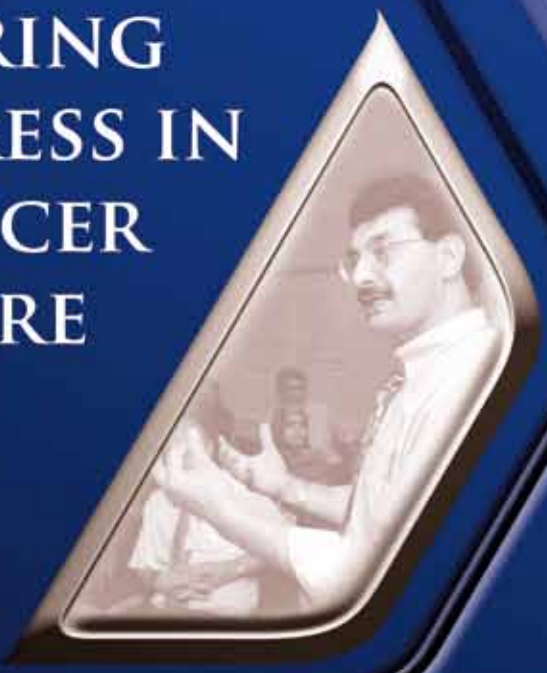
Cancer World is published five times a year by the European School of Oncology. It is distributed at major conferences, and mailed to subscribers and European opinion leaders.

European School of Oncology

Learning to care

Sharing Progress in Cancer Care





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Learning from haematology

Franco Cavalli, Guest Editor

Many of our most profound insights into the nature of cancer and its treatment have originated in the field of haematology. It was the high levels of bone marrow toxicity among soldiers who had been exposed to mustard gas in in World War II that first alerted researchers to the potential of chemotherapy.

The unexpected findings of benefit from systemic cancer treatment was first shown in the treatment of childhood leukaemia and Hodgkin's disease, as the latter was called when its cancerous origin was not yet understood.

For a long time afterwards, the screening of drugs for potential anti-cancer action favoured agents that suppressed bone marrow activity.

While these aspects of our early history may be familiar to most oncologists, the same cannot be said for many profound insights into new paradigms of precision medicine that are emanating from the field of haematology today, which is why *Cancer World* has chosen this topic for its Cover Story.

Over the past 15 years, a number of solid tumours – malignant melanoma, renal cell cancer, some sarcomas, a few subtypes of non-small-cell lung cancer – supplanted blood cancers as the setting for exploring and understanding the use of new precision therapies. Today, however, blood cancers are again becoming the favoured model for learning basic lessons about cancer biology and ways to intervene.

The potential of PD-1/PD-L1 checkpoint inhibitors was first demonstrated in patients with Hodgkin lymphoma who had already gone through many lines of treatment, and the prospect of a 100% cure rate is now in sight. In multiple myeloma and chronic lymphocytic leukaemia, two diseases where 20 years ago we had little to offer patients, our biologic understanding has recently grown exponentially, with an explosion of new treatment possibilities. The concept of a chemo-free systemic therapy – now on the horizon for melanoma and renal cancers – was developed first in follicular lymphoma, on the back of the very-long-term remissions achieved in patients treated with the monoclonal antibody rituximab.

Haematologic tumours are also the model to test the paradigm of long-term, potentially lifelong, systemic therapies, which may yet become 'the rule' for treating advanced solid tumours – with all the associated issues of cost and adherence. Chronic myelogenous leukeamia is the paradigm example, where the possibility of lifelong treatment with imatinib means the great majority of patients no longer need allogeneic transplantation.

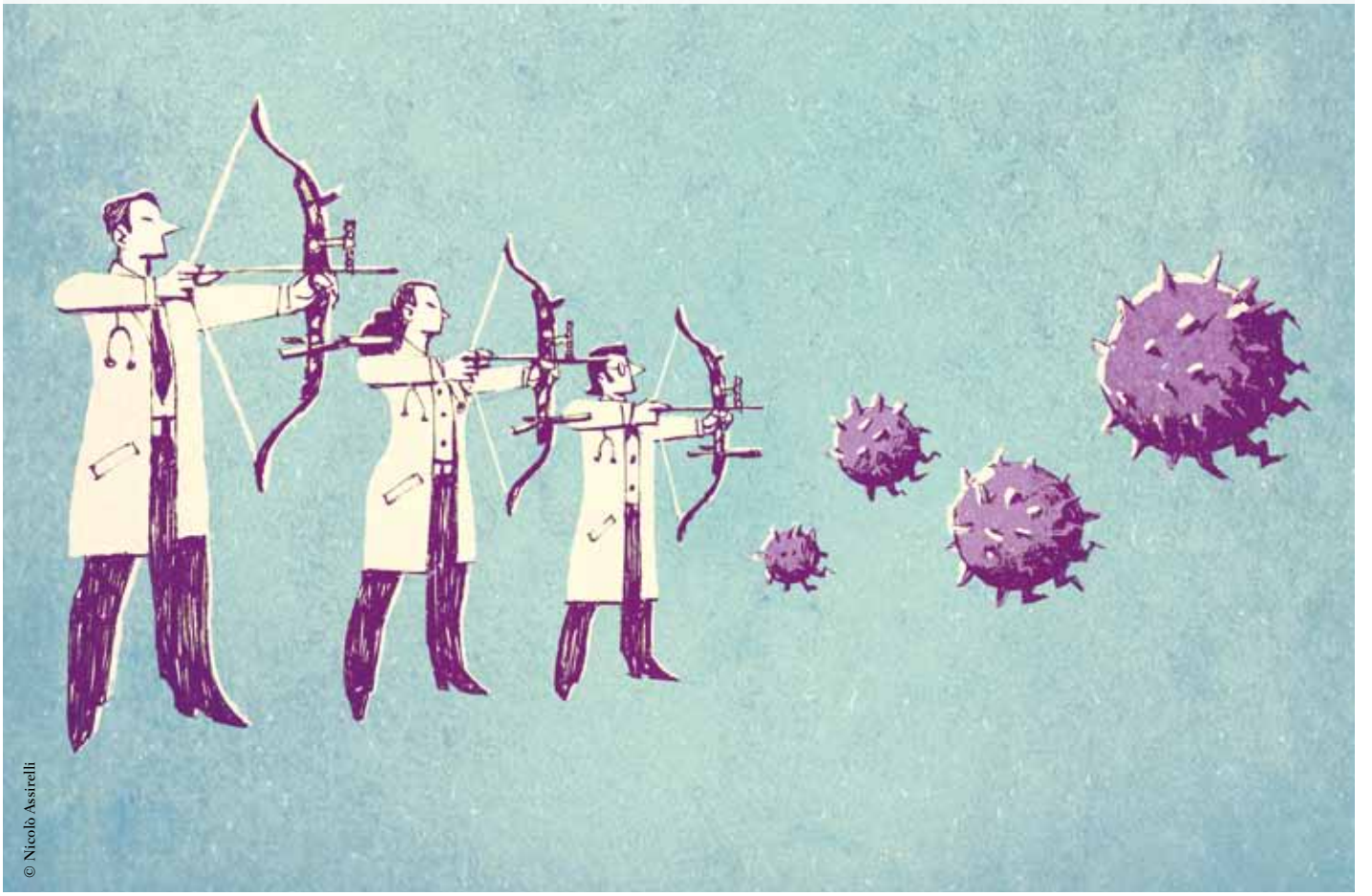
One of the challenges the oncology community now faces is how to spread the new insights coming out of haematological cancers to the far larger field of solid tumours. Unlike the early days of chemotherapy, when fear of using these 'very toxic drugs' meant that medical oncologists were left to take the lead in caring for lymphoma and leukaemia patients, today medical oncologists increasingly deal only with solid tumours. As someone who benefited from training in both blood and solid tumours, I feel this sharp divide risks denying new generations of oncologists a basic grounding in tumour biology and biology in general. Haemato-oncology should be an integral part of any training in medical oncology – as indeed has always been the case for ESO's own flagship Clinical Oncology Masterclass.

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

Haematato-oncology

Where precision medicine is finding its target

With the prospect of a chemo-free cure for some blood cancers, and with new targets and new drugs emerging at an unprecedented pace, **Simon Crompton** asks: Is haematology where the promise of precision medicine will finally be realised?



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We have come a long way since pioneering French microscopist Alfred Donné provided the first cellular description of a blood cancer in 1844. "More than half of the cells were mucous globules [white cells]," he wrote, which "dominates so much that one wonders, knowing nothing about the clinical course, whether this blood does not contain pus."

In the past 60 years, haematological cancers have provided the testing ground for systemic therapies, the first cure by chemotherapy, the first proof of principle of targeted medicines.

In the 1960s, the first chemotherapy cancer cure came with MOPP (nitrogen mustard, oncovin, procarbazine, prednisone) for Hodgkin lymphoma. In the late 1990s, rituximab for non-Hodgkin lymphoma was the first monoclonal antibody to be approved by the US regulators. And imatinib, the first anticancer tyrosine kinase inhibitor, was approved for chronic myeloid leukaemia in 2001 – and has since dramatically improved the outlook for the disease in the solid gastrointestinal tumour GIST.

"Over the past 65 years, survival rates for many blood cancer patients have doubled, tripled and even quadrupled," says Louis DeGennaro, CEO of the Leukemia and Lymphoma Society. "Almost 40% of the new cancer drugs developed since 2000 were first approved for blood cancer patients, and are now helping patients with other cancers and chronic diseases."

The figures tell the story of how innovation in blood cancer continues. The FDA has designated 12 novel blood cancer therapies as "breakthrough medicines" – requiring expedited development because of their promise in treating a life-threatening disease. Around 250 of more than 800 cancer medicines in development are in leukaemia, lymphoma and multiple myeloma. And genetics studies have recently revealed there are at least 35 types of leukaemia and 50 types of lymphoma – each with distinctive characteristics to target.

"There are multiple advances happening at the same time, reflecting an explosion of knowledge in haematological cancers," comments Anas Younes, medical oncologist and head of the Lymphoma Service at Memorial Sloan Kettering Cancer Center in New York. "It sounds like a cliché but it's true." Along with others working in haematological cancers, Younes believes there is now the genuine prospect that, as precision medicines become more widely embedded into clinical practice, the days of toxic chemotherapy may be numbered. At least in blood cancers.

Given the continuing frustration over the unfulfilled promise of precision medicine in solid tumours, the question then arises: Would the rest of the cancer world do well to pay more attention to the new paradigms that are proving their value in many blood cancers?

Franco Cavalli, Scientific Director of the Institute of Oncology of Southern Switzerland, believes they would. He argues that the difficulties for precision medicine stem mainly from the heterogeneity of the tumours – a challenge which he says was first encountered in blood cancers. "Now, the experience in blood cancers of efforts to overcome such difficulties – for example, devising groups of patients who are as homogeneous as possible – may serve as a guide for many solid tumours as well."

In his editorial in this issue, he points to the increasing separation of haematological and solid tumours in the training of medical oncologists, and argues that specialists in solid tumours could glean valuable insights into the basics of tumour biology by paying more attention to developments in haematological oncology.

Hodgkin lymphoma and the quest to end toxic treatment

The benefits of moving from chemotherapy-based regimens to ones based on precision medicine are amply demonstrated in Hodgkin lymphoma. Although aggressive chemotherapy and radiotherapy regimens made Hodgkin lymphoma one of the first curable cancers in the 1960s and 70s, the cost was high.

Studies indicated that the risk of developing neoplasms after treatment was 18 times higher than in the general population, and people who survived Hodgkin (which most commonly affects young adults) were at increased risk of coronary artery disease, valve disease, congestive heart failure, pericardial disease, stroke, arrhythmia and sudden cardiac death.

The advent of the monoclonal antibody drug brentuximab vedotin five years ago brought a radical change, bringing induced remission in 75% of patients with relapsed or refractory Hodgkin. Today, according to Andreas Engert, professor of internal medicine, haematology and oncology at the University Hospital of Cologne, new data will show that the drug works well as a first- and second-line treatment in combination with chemotherapy.

"But in the end, brentuximab vedotin is still a kind of targeted chemotherapy, and patients who have received a lot of chemo are more likely not to respond to brentuximab. That could be a problem for heavily pretreated patients."

New immunotherapy approaches provide the promise to solve the problem. The first immune checkpoint inhibitor in lymphoma, nivolumab, was approved by the FDA for relapsed or refractory classical Hodgkin lymphoma in May 2016. It is the first monoclonal antibody targeting the programmed death-1 (PD-1) immune checkpoint

pathway. The effect is to enhance T-cell anti-cancer activity and induce tumour cell disintegration.

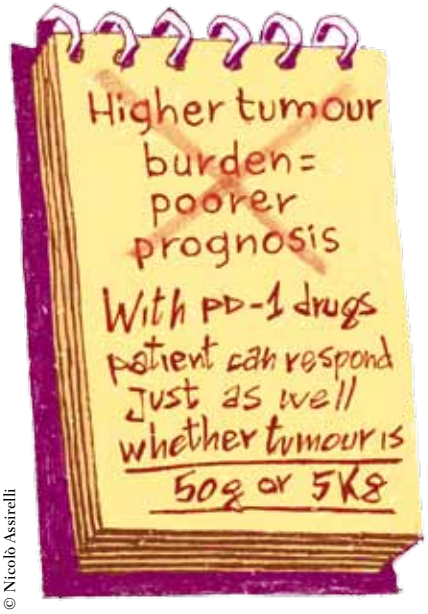
Early phase trials indicated a good safety profile, and 66% of patients achieved an objective response after nine months (assessed using immune-related response criteria – IrRC). New trials presented this year at ASCO indicated an objective response rate of 65% after 19 months in patients who had previously had autologous stem cell transplants (ASCT) but not been treated with brentuximab vedotin. There was a complete response in 29% of patients. Engert's centre in Cologne became involved in the trials at an early stage – having "banged on the door" of Bristol-Myers Squibb to expand the trial from the United States to Europe.

"We are using these antibodies right now in the relapsed and refractory setting," he says. "We saw many patients who we originally thought might be too frail, who responded remarkably well."

The drug, he says, has completely changed expectations about response and cure. "It doesn't matter if the patient has a 50 g tumour or a 5 kg tumour – the patient can respond just as well with PD-1 drugs. That's remarkable, and it completely interferes with our knowledge about who's going to respond and their chances of cure."

The latest nivolumab trial results, announced at ASCO in June and then presented by Engert at the European Hematology Association Congress in Madrid, demonstrated responses in adults with relapsed or progressed Hodgkin lymphoma after ASCT, irrespective of whether they had also been treated with brentuximab vedotin (BV). In the group that had BV therapy after ASCT, the objective response rate was 68% after 23 months, with complete response in 13% of patients.

"The new data look great," says Engert. "In particular, it is quite astonishing to see that those patients who just achieved a partial response or stable disease still did remarkably well overall. This is a clear indicator that PD-1 inhibition offers a really new and different mechanism of action.



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"It's very surprising and rewarding to see these major achievements. Now there's a good chance of curing patients in both the early and advanced stages of the disease. That's particularly good news for young patients with Hodgkins.

"The development of these new antibodies is exciting because it will reduce long-term side effects in young people. We're conducting studies in early stage patients and I'm convinced it will take just a few more years before we can say with conviction that we can cure Hodgkin patients without chemotherapy or radiotherapy. I think that's what we always wanted to achieve."

However, there is a problem in bringing these advances to fruition. Drug companies, says Engert, are reluctant to invest in Hodgkin trials because they are overwhelmed by opportunities in solid tumours. "It's a question of where you put your money, and where the highest value is. So far we have done well with brentuximab and the PD-1s. Some companies are uncertain if they want to invest in first-line Hodgkin treatments with much bigger trials, but I think data is going to look so good that they will have to."

Targeting the micro-environment: learning from CLL

The story of chronic lymphocytic leukaemia (CLL) provides another example of how precision medicine paradigms are playing out in blood cancers.

Twenty years ago, little was known about CLL, which accounts for around a third of all leukaemias worldwide. We knew that it affected the B-cell lymphocytes. We knew there were two types, determined by the presence of mutations in the immunoglobulin genes – one aggressive and requiring treatment, one more indolent. We knew that the leukaemia carried a few recurrent cytogenetic abnormalities, but how they contributed to the disease was unclear. We knew that the treatment invariably revolved around chemotherapy – sometimes combined with a monoclonal antibody (chemo-immunotherapy). And we knew that it was incurable.

"When we had only chemo-immunotherapy, there was a proportion of patients that was chemo-refractory – and this proportion was larger the more the disease was treated," says Davide Rossi, leader of the experimental haematology group at the Institute of Oncology Research, Switzerland. "We were unable to provide effective treatment for these patients."

Chemo-immunotherapy failed in 20–25% of patients. For these patients with ultra-high risk CLL, survival after failure was less than three years, and the only effective salvage option was

an allogeneic stem cell transplant. The rigours of this approach, however, meant it was only available to a minority of patients who were fit or young enough.

Then, three years ago, everything changed, with the introduction of two new types of compound – one that inhibits the signalling between the cancer and its micro-environment, and one that blocks the signalling that prevents

cell death. The drugs are: B-cell receptor (BCR) inhibitors, such as ibrutinib and idelalisib, and B-cell lymphoma 2 (BCL-2) inhibitors, such as venetoclax.

Durable responses are now common in many patients with previously relapsed CLL. "In clinical practice, we now have potent drugs that almost, although not completely, overcome chemo-refractoriness in CLL," says Rossi. "In ultra-high risk patients, ibrutinib, idelalisib and venetoclax all provide an unprecedented high response rate in the range of 70–80%, which are durable."

This, he said, points the way towards the end of what he calls "bombastic" therapy – the old paradigm of bombarding the patient with treatments. Clinical research is now investigating the possibility of combining BCR and BCL-2 inhibitor drugs with each other, and also with other monoclonal antibodies, "to try to provide deep responses and hopefully the cure for CLL".

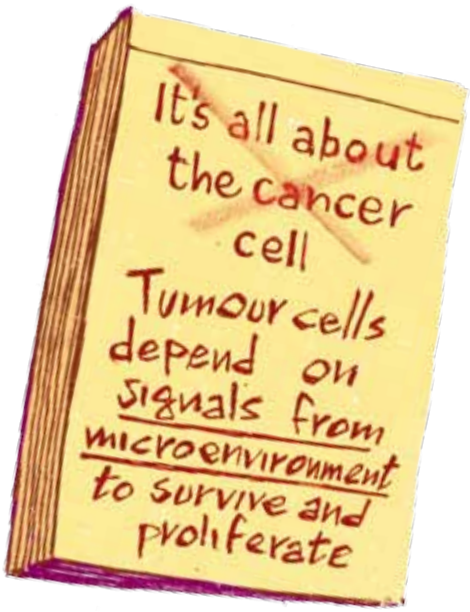
The significance of the CLL revolution goes beyond a single disease. Rossi says it is exciting because it demonstrates the absolute dependence of many cancers on their microenvironment – and ways to exploit that weakness.

"There's a long story of basic and translational research in CLL that, in the end, established the addiction of this tumour to signals coming from the microenvironment, to gain survival and proliferation signals," says Rossi. "Many cancers are addicted in the same way. The key point is understanding which of the cellular programmes and pathways are central, and are to be targeted. In CLL, we gain this understanding from fundamental science."

"I want to underscore that CLL is a paradigm, because as well as BCR inhibitors, which interfere with the mechanisms coming from the microenvironment, we have the BCL-2 inhibitors, which block the anti-apoptotic cellular programmes, which tumours activate through genetic lesions. So we are addressing both the microenvironment and the genetics of the tumour as drivers of cancer."

Nearing a chemo-free cure

The move towards precision medicine in CLL could herald the end of chemotherapy for many patients, says Rossi. A BCR inhibitor has already been approved as a first-line monotherapy for CLL patients in the United States and Europe. And there are hopes that, within three years, the results of trials combining different BCR and BCL-2 inhibitors may indicate that combinations bring



longer remissions, and reduce the need for long-term treatment.

The prospect of chemo-free treatment spreads far beyond CLL. A multiple myeloma diagnosis used to mean a life expectancy of three to five years, with standard treatment consisting of chemotherapy and stem cell transplant. Today, average survival has nearly trebled thanks to new proteasome inhibitors, immune-modulating therapies like thalidomide – and then combinations of these drugs with steroids, in doublet and then triplet therapies.

A randomised trial presented at the American Society of Hematology last year suggested that triplets should now be the standard of care for patients newly diagnosed with multiple myeloma.

"Today, we have learned to talk in terms of tablet triplets," says Rossi. "In the future, I can see the possibility of a chemo-free, novel agent based treatment paradigm for every CLL patient."

Philippe Moreau from the University Hospital of Nantes, France, believes that for the first time there is the possibility of curing the 50–70% of multiple myeloma patients who are classified as

"standard risk", using all the effective drugs and stem cell treatments. "The goal is to achieve very fast and very deep responses and to reach minimal residual disease negativity," he says.

The challenge of exponential knowledge growth

But the explosion of knowledge in blood cancers also presents massive challenges. Researchers and clinicians have at their fingertips exponentially increasing data about their genetics, subtypes and precise biological relationship to their microenvironment. Dozens of novel therapies are being developed, each of which may have a more potent effect if used in combination with any of dozens more.

Yet there are only limited clinicians, researchers and facilities to be able to act on the information. So where do priorities lie?

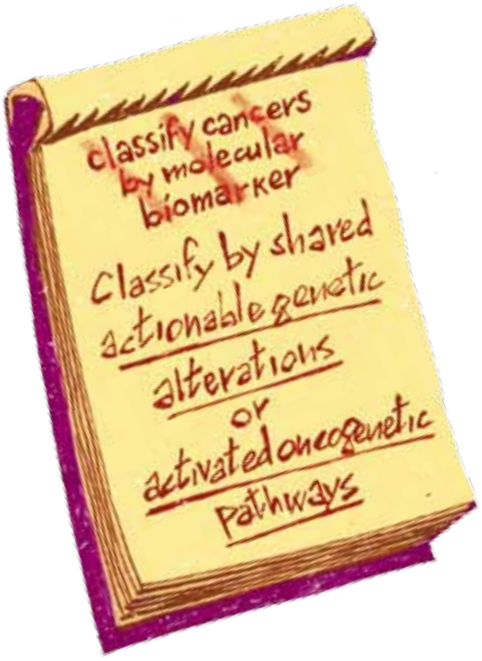
Franco Cavalli believes that increasing knowledge about different molecular types of blood cancer requires a rethink about how resources are allocated.

"What were once a handful of haematological cancers are in fact hundreds of different ones when you look at their molecular biology. So this re-classifying has implications for specialist pathology and for specialisation.

"Classifying individual cancers has become very difficult, so worldwide the big problem is how to have a correct diagnosis. And haemato-oncologists may also now have to subspecialise. There are already specialists in leukaemia, lymphoma and myeloma. This is making everything more expensive and more difficult in terms of practical organisation."

According to Anas Younes, who conducts translational research into novel treatment strategies for Hodgkin and non-Hodgkin lymphoma at his own laboratory at Memorial Sloan Kettering, the key to moving forward constructively is to rationalise. For example, all the new molecular information characterising different types of cancers needs to be reviewed – and the cancers need to be re-categorised into types that are clinically useful, not simply observable.

"The trend is divide and conquer," he said, "slicing each large cancer type into small pieces." But classifying them according to morphology, clinical



behaviour and genetic composition is not in itself useful. "We need to slice them based on a genetic landscape that is actionable – not just saying a particular biomarker expresses so and so. Unless it's actionable it's not going to help me design a clinical trial.

"So at Memorial, we're going backwards to try and re-group lymphomas into common baskets that share actionable genetic alterations or activated oncogenetic pathways – then try to build clinical trials based on that. So there's a huge effort going on trying to authoritatively gene sequence all the different types of lymphoma.

"Every patient who walks through our doors is asked to fill out a consent form, and we will sequence their tumours for free, to collect this information. Then we can decide which genetic alterations are common across different subtypes, and then design clinical trials based on that."

There is no doubt that dividing diseases like CLL into subtypes according to biomarkers is very useful, says Davide Rossi. For example, in CLL the mutational status of the immunoglobulin gene provides prognostic information as well as informing therapy. And the status of the p53 gene can stratify patients according to which will respond best to chemo-immunotherapy.

"But perhaps in the future it may not be the same," says Rossi. "Now the field is quite confused because we don't have a lot of clinical studies to support our treatment decisions, so we have to support them by biomarkers. But in the future, who knows? Will we still need biomarkers, if treatments become chemotherapy free? It's a field in continuous evolution."

The challenge of prioritisation

For Anas Younes, the single most important challenge as knowledge explodes in blood cancers – and increasingly in all cancers – is how to prioritise the research agenda.

"We now have more than 600 agents available in pre-clinical testing or testing for cancer, he says, "and we never had this before. So how do you choose? Every time you commit yourself to one trial you're locking in your patients, your progress, your resources for at least three years. You can't test all of them at the same time."

The problem escalates, because combinations need to be tested. Very few cancers have one unique Achilles heel – most use multiple oncogenetic

pathways to thrive. So finding drug combinations to inhibit several pathways simultaneously is essential. Younes points out that a vital next step is to test immune checkpoint inhibitors in combination with other immune therapeutic agents, small molecule drugs or even traditional chemotherapy. But trialling just ten drugs in all their doublet combinations could take 90 years. "So how do you prioritise those combinations?"

The answer, said Younes, is to use preclinical studies to try to establish the most promising drugs and combinations – evaluating safety and then comparing them head to head. These preclinical studies need to be run completely independently of drug companies.

"You need to step backwards and be an independent judge, because each sponsor comes to you with their own ideas, but it might not be the best idea. So it's very important for academic centres to do these combinations in an unbiased way – test *in vitro*, and then in mice. Then, even if two combinations seem to meet in efficacy, you can see which has the best safety profile and make a judgement as to the best available based on your own data."

"It's not perfect. But that's what larger cancer centres are doing these days – they're no longer being passive recipients from sponsors who ask you to do things."

Setting an agenda

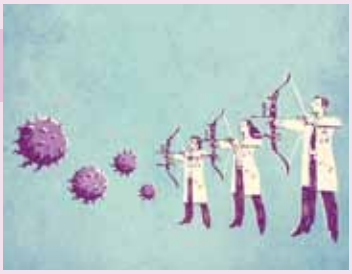
No one, says Younes, could claim that developments in blood cancer are ahead of those in solid tumours. "There are areas where blood cancer is leading the way and other areas where we're learning from solid tumours. The reason is that a lot of knowledge is being shared, and this is because there are shared genetic alterations among some solid tumours and some blood cancers that can be targeted.

One area he mentions where blood cancers are "way ahead" is in developing chimeric antigen receptor (CAR) T-cell therapies – a novel type of immunotherapy which early trials have shown to be effective in patients with refractory lymphoma and leukaemia (see box).

But as he adds, "Just for practical reasons, some solid tumours that have a high frequency and a higher unmet medical need – like lung, colon, breast and prostate cancer – tend to have more funding and concentrated clinical research effort, so they often take an early lead."

The fact is that the most common cancers will always attract the big research investment. But given their annexed existence from the mainstream of funding, discussion and research focus, haematological cancers are still charting a remarkable course in unlocking the potential of precision medicine. The way in which clinicians, researchers and funders build on the explosion of knowledge in the next ten years will demand the attention of the rest of the cancer world.

Learning from blood cancers: CAR T-cell therapy



Chimeric antigen receptor T-cell therapy is an experimental form of immunotherapy that revolves around genetically engineering T-cells to recognise and then attack cancer cells.

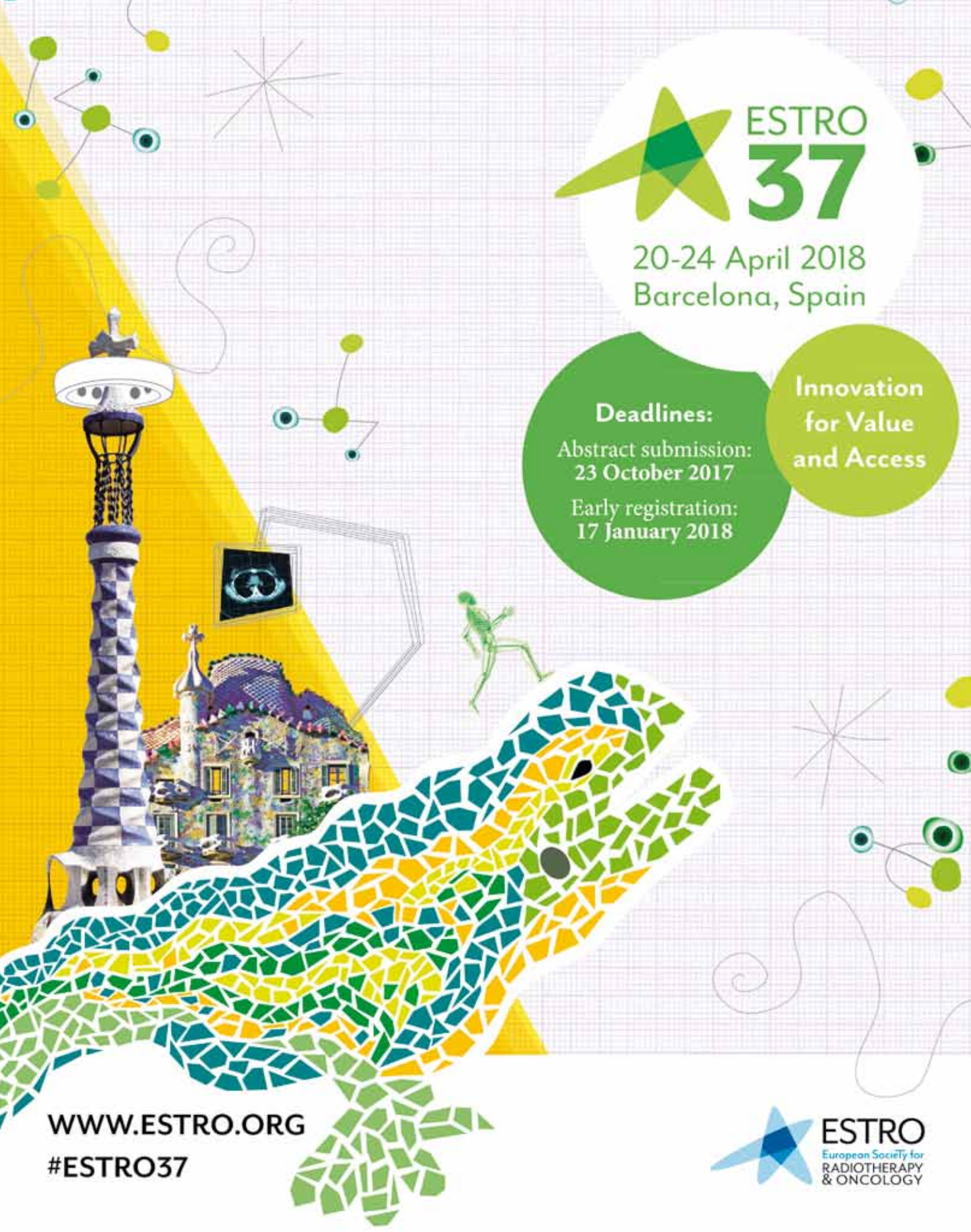
Groundbreaking studies have shown durable complete remissions in patients with therapy-refractory lymphoma and leukaemia. The results prompted the US regulators to grant CAR T-cell therapy breakthrough status for B-cell malignancies like acute lymphoblastic leukaemia and chronic lymphocytic leukaemia, as well as B-cell lymphoma and non-Hodgkin lymphoma.

"This is a rapidly growing field," says Anas Younes, head of the lymphoma service at New York's Memorial Sloan Kettering hospital, "but I think CAR T-cell therapy in liquid tumours is way ahead of solid tumours. The platform technology is now beginning to be applied in solid tumours."

There are now more than 100 CAR T-cell clinical trials running. In November 2016, Novartis presented results from a phase II trial with its CAR T-cell therapy CTL019 for B-cell acute lymphoblastic leukaemia. It achieved remission in 82% of patients after three months. This is in a disease with limited treatment options, where currently the chance of survival for children who relapse or fail to attain remission is between 16% and 30%.

The company is preparing to submit applications to the FDA and EMA this year.

Severe side effects, which have included deaths in early trials, are a problem with CAR T-cell therapy. Cost is also an issue. The EMA believes "there are still scientific and regulatory challenges to overcome to bring these innovative products to the market."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Abstract submission:
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A visionary who made a lasting contribution

Patrick Johnston, medical oncologist 1958–2017

The European School of Oncology has lost a supporter, colleague and friend, writes **Mike Clarke**, who co-chaired ESO's Systematic Reviews Masterclass alongside Patrick Johnston.

With the sudden and unexpected death of Patrick Johnston on 4 June 2017, the world of cancer has lost an internationally renowned researcher and practitioner, and Queen's University Belfast in Northern Ireland lost its President and Vice-Chancellor. The loss to his wife Iseult and four sons Seamus, Eoghan, Niall and Ruairi is, of course, so much greater, and we extend our deepest condolences to them.

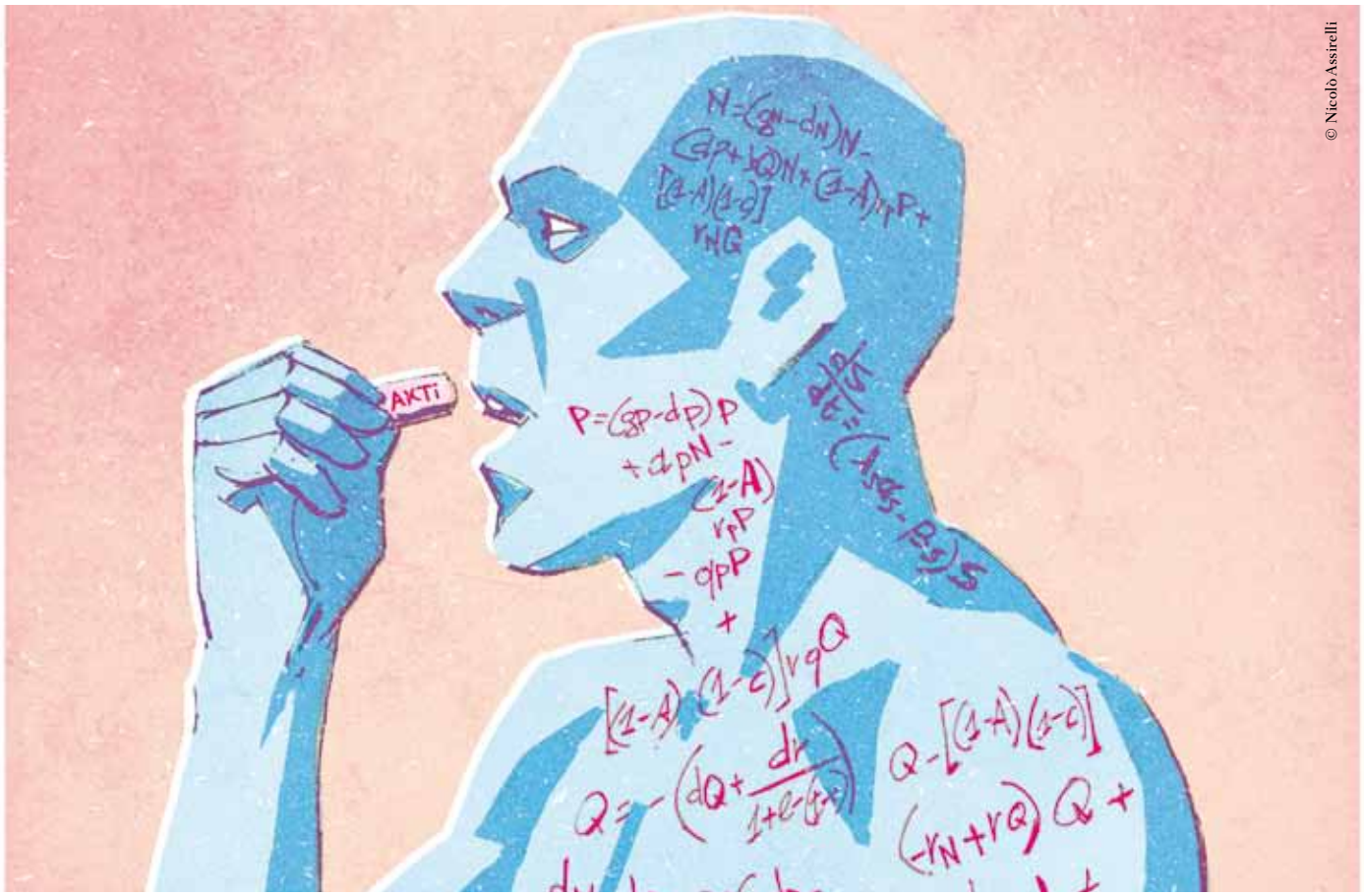
Professor Patrick Johnston, who was instantly recognised by many people in Queen's whenever anyone referred simply to "Paddy", had been working closely with ESO for some time. He co-chaired our 2014 and 2016 Masterclasses on Systematic Reviews, welcoming the participants to Belfast and enthusing them with tales of how his career had seen the growth in the importance of systematic reviews for both practice and research. His death came just as plans were being put in place to stage the third of these popular and successful courses, in Belfast in May 2018.

Paddy was born in Derry, Northern Ireland, on 14 September 1958, and died during a cycling trip in Donegal on 4 June 2017. He studied medicine at University College Dublin, where he graduated in 1982 and obtained an MD in 1988. He took up a Fellowship at the National Cancer Institute in USA, working on molecular pharmacology, drug resistance and drug development, and was awarded the ASCO Young Investigator Award and the Technology Award. Paddy then returned to Northern Ireland and, in 1996, became Professor and Head of the Department of Oncology at Queen's University Belfast and the Belfast City Hospital.

He led efforts to modernise cancer practice and research in Northern Ireland and was fundamental to the opening of the new Centre for Cancer Research and Cell Biology at Queen's in 2007 – the same year that he was appointed Dean of the School of Medicine, Dentistry and Biomedical Sciences. Amongst several awards, Paddy won the international Bob Pinedo Cancer Care Prize in 2013, in recognition of his work to translate discovery science into practice. He co-chaired the European Cancer Concord, leading to the European Cancer Patient's Bill of Rights, which was launched at the European Parliament in 2014.

Paddy opened the first of the ESO Masterclasses on Systematic Reviews in June 2014, shortly after becoming the 12th President and Vice-Chancellor of Queen's University Belfast. It was a not too unusual summer's day in Belfast, with pouring rain, and after giving his formal welcome, Paddy had to go on to fulfil one of the many aspects of his new role at a University rowing regatta. However, as President and Vice-Chancellor, Paddy did so much more than preside over such events. He was instrumental in creating an ambitious vision for the university into the 2020s, striving to boost its global reputation and stature, and laying the foundations for his successors.

Paddy's legacy will continue to be felt in the growth of Queen's University Belfast, the improved care of people with cancer, and the achievements of the students and colleagues he inspired. Paddy was a man with a vision and with the drive to achieve it. His early death means that he will sadly not be here to see it delivered. As one of Queen's faculty said in the days after Paddy's death: death doesn't care how busy you are or how much you might have left to give. We are here for a brief time but some, like Paddy, make a contribution that will endure.



Virtual trials in virtual patients

Is this how we will accelerate progress in personalised treatments?

If mind-boggling complexity is the barrier to developing personalised cancer care strategies, could mathematical modelling – long used by economists, meteorologists and others – be the answer? **Marc Beishon** talks to leading figures who are exploring this approach.

We're making progress of sorts in personalised medicine, as headline results at ASCO revealed, for example on certain prostate and ovarian cancers. But at the current rate, finding long-term solutions for cancer patients as a whole will take an unthinkable period of time at an unsustainable cost.

A growing number of researchers are now convinced that the radical progress we need will only be possible if we start using computational and systems biology approaches to model patients at an increasingly individual level, to determine what treatments could (and would not) work for any given person.

As Hans Lehrach, head of vertebrate genomics at the Max Planck Institute for Molecular Genetics, Berlin, comments, the biggest selling drugs – not just cancer drugs – benefit at best only a quarter of people who take them, and some as low as about 5%. "Meanwhile adverse drug reactions are responsible for more deaths than colon cancer, and generally we are paying a huge economic price because we can't always predict who will respond to a drug. You can only really find out if a drug works by trying it on a patient – but we don't have to do it for real. We can do it on computers where of course there is no risk to the patient."

Lehrach is one of Europe's leading proponents of the idea of conducting virtual clinical trials with cohorts of virtual patients, using "fantastically detailed" information now emerging on the biology of tumours and the vastly increased power of computers, which are now available at reasonable cost – certainly within the same 'ballpark' as efforts in other fields such as self-driving cars and computer gaming. He argues that, in the foreseeable future, it should be possible to gather such information from individuals with cancer and at least manage their disease to a much better extent than now.

Making better predictions of what will work

Lehrach emphasises, however, that this is about much more than taking a panel of gene variants and applying statistical modelling – it's about deploying the full array of 'omics' information and signalling pathways of cells at a much deeper, 'mechanistic' and individual level. Even then such approaches will be far from perfect and many will still fail – but they will fail in a computer model instead of in live patients.

He believes that oncologists will begin to ask whether it is really appropriate to start with the blunt instrument of chemotherapy, and will instead apply treatments that address actionable targets first, especially for those with advanced disease. The aim, he says, is to model the mechanistic processes much more quickly, to make better predictions of what will work for an individual. "If we can predict therapies that will work for say 40% of patients, we will be way ahead of existing clinical practice," he comments.

"His vision is to model both patient and tumour at an individual level, as a cancer evolves"

Lehrach – who is keen on analogies from other fields – says that aeronautical engineers have many equations to model how new planes will fly, for example. In medicine, other branches are paving the way: the development of drugs and combinations to manage HIV is a good paradigm, he suggests, especially as, like cancer, it is an evolutionary system that develops new resistance mechanisms. His vision is to model both patient and tumour at an individual level, as a cancer evolves, to give oncologists a much better toolkit not just for the main cancers, where there are established treatments, but also for the 25% which are rare or have an unknown primary, some of which do not have a first-line protocol.

Another analogy is long-term weather forecasting. As Lehrach and colleagues note in a paper on virtualising drug development through network and systems biology, while statistical strategies aren't very successful in weather forecasting (and other complex systems), mechanistic models can potentially provide a way to simplify the 'data deluge' (*Drug Discov Today Technol* 2015, 15:33–40). And overcoming tumour heterogeneity, evolution and resistance may mean trying to test many thousands of drugs combinations, including drugs for other conditions that could act against cancer, which would only be feasible in virtual models.

A case in point – he cites a woman in Germany with metastatic melanoma who remained stable for a year by being treated with a drug usually used for rheumatoid arthritis. The drug was predicted by a virtual patient model to be effective based on the molecular features of her tumour. "This is the result of matching the molecular make-up of the tumour with the molecular features of a drug." (Work by a US–UK team linking an arthritis drug with melanoma from a zebra fish model made the cover of *Nature* in 2011 – but it was a long way off human clinical trials.)

Moves to apply cancer drugs on a wider, mechanistic, basis as opposed to solely a tumour-specific basis are already under way. For example, the US regulator, the FDA, has for the first time approved a drug, pembrolizumab (Keytruda) on the basis of a biomarker and not a tumour's primary location. But the modelling approach could also uncover many other drugs and combinations currently in the formulary that could have an oncology application, and trials are looking at matching patients with certain genetic markers to certain drugs (e.g. the US National Cancer Institute's MATCH trial).

Lehrach's vision goes further, positing a virtual patient model that could have a staggering amount of data – not

only all the high throughput 'omics' data – genomic, proteomic, metabolic – but also taking into account a tumour's spatial heterogeneity, as well as single cell analysis, immune status, haplotype sequencing (linked genetic markers present on one chromosome, which tend to be inherited together), and clinical information such as lifestyle and comorbidities. The reaction of patients, such as how the liver metabolises a drug, effects on normal tissue (i.e. side effects) and other interactions, as well as non-mechanistic data, such as that derived from non-drug based therapies, can also be modelled.

Lehrach, who has founded a company (Alacris Theranostics) to develop virtual patient models, believes they can be used both for delivering personalised medicine in the clinic, and for drug development. His company is now leading a Horizon 2020 (European Union) programme called CanPathPro (canpathpro.eu). Described as a combined experimental and systems biology platform, it will allow users to integrate private or public data sets to predict the activation status of individual pathways, "enabling '*in silico*' identification of cancer signalling networks critical for tumour development, as well as the generation of hypotheses about biological systems that can be experimentally validated."

Modelling tumour and patient

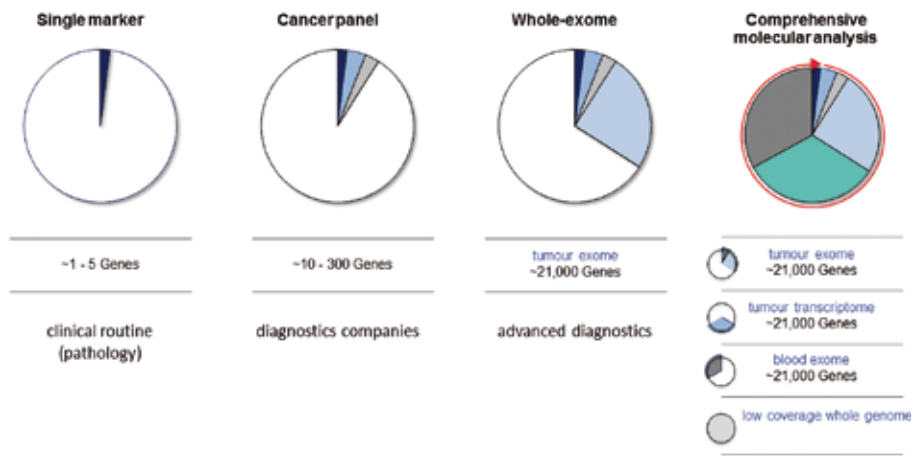
This is a field where the integration with disciplines outside of biology is vital, not least computational experts and mathematicians who work in the '*in silico*' world. A good example is the Integrated Mathematical Oncology Department at the Moffitt Cancer Center, Florida, which has recently shown how a mathematical model can work in improving the translation of preclinical findings to the clinic, coincidentally also with melanoma (*Eur J Cancer* 2016, 67:213–22). They call the idea the 'phase *i*' trial, where *i* means imaginary (or virtual), or indeed '*in silico*'. It is a complex study that aims to create shortcuts between the *in vitro/in vivo* preclinical world and the vastly more heterogeneous reality of patients.

Led by Eunjung Kim, the study is a proof of concept of the idea that a mathematical model based on data from human and animal cell experiments and from existing clinical data is not only able to match what happens in an early stage drug trial but can also pave the way for better early stratification of who is likely to benefit from a therapy, potentially improving the introduction of drugs through the traditional phase I to III process.

The researchers were familiar with a phase I trial of a targeted drug – an AKT inhibitor – that was trialled in combination with various chemotherapies and with another inhibitor in patients with a range of solid tumours, some of whom had advanced melanoma. They note that a number of targeted drugs have been tested in trials either alone or with other agents,

"The phase *i* trial aims to create shortcuts between the preclinical world and the vastly more heterogeneous reality of patients"

From single markers to comprehensive molecular analysis



Schematic comparison of the range of the approaches for molecular characterisation of tumour and patient, which span a continuum from a single marker, through to sequencing a limited number of tumour genes (a gene panel), and analysis of the whole exome, to combined analysis of patient and tumour using both genome and transcriptome information

Source: M Schütte et al. *Public Health Genomics*, published online 9 June, 2017, doi:10.1159/000477157, reprinted with permission from S. Karger AG, Basel

but the majority have not proved to be effective in humans despite showing promise in cell and animal models.

They looked at effects of the drugs only on melanoma, by constructing a mathematical model of the dynamics of melanoma cells when they are exposed to four treatment conditions: AKT alone, AKT and combinations, chemo only and no treatment. They then carried out cell culture experiments to calibrate the model, and validated it further with a series of cell experiments that predicted the effects of 12 different drug combinations and timings.

From this they were able to show what treatments and schedules would give certain patients the best outcomes

Then comes the key part: they generated a cohort of virtual patients according to the clinical trial results. In fact, using a genetic algorithm of tumour volume they produced a virtual patient population of over 3,000, and a sample of 300 of these matched responses seen in the real trial, where just 24 patients had melanoma (out of a total of only 72). From this they were able to show what treatments and schedules would give certain patients the most favourable (and less favourable) outcomes. As the authors note, one of the key limitations of preclinical *in vitro* cell studies is their short duration; one of the benefits of the phase *i* idea is that it can show what the likely longer-term effects on patients will be.

This is the basis of phase *i*, which they also say is not a new idea in essence – there have been simulations in other areas such as in cardiovascular disease, and modelling that has used statistical approaches based on drug metabolism. Their proof of concept study goes a lot further, however, by taking the biological mechanisms seen in cell studies and making a potentially major (and complex) leap into the clinic.

Alexander 'Sandy' Anderson, head of the mathematical oncology department at Moffitt, and a co-author, points out that they had to make a big assumption in the study, namely that there is a key resistance mechanism in play that gives rise to the response differences. "We know patients have a variety of responses owing to resistance, from good to partial to none, and in this case we focused on a mechanism called autophagy, which we assumed is the same we would see in patients, based on a study from the trial. In fact, patients probably have multiple resistance mechanisms, which could be incorporated into a more complex model, but this one alone allows us to make useful predictions."

Put simply, autophagy is a survival-promoting state that can allow tumour cells to survive drugs, but in some circumstances can provoke tumour cell death – a paradoxical finding that has prompted researchers to test drugs that can affect autophagy, including AKT inhibitors.

The Moffitt researchers knew from the real trial that two patients with a certain genetic variation had unexpected long-term responses to the AKT inhibitor combined with chemotherapy, and had reasoned this was due to a differential effect of inducing autophagy. From the cell experiments they could see that the metastatic melanoma cells became autophagic and resistant under the AKT/chemo drug combination, but they also identified two states of autophagy, one of which, when in a persistent state, leads to cell death and more favourable outcomes.

A machine-learning approach

What the model does, Anderson explains, is use an automated, machine-learning approach to find sets of parameters from the experiments that mimic patients' responses, each one being a virtual patient. As the parameter sets can vary greatly, they ended up with more than 3,000, which was sampled and stratified into degree of response. "Then we can go back and see what it is about the underlying mechanisms that make them good or poor responders – in other words, the most important parameters that drive the stratification."

In this case, he says, there are two parameters that appear to stratify well – the proliferation rate of the tumour cells, and the rate at which cells become autophagic. "If we can measure those in a real patient – and it is realistic to measure the autophagic fraction from a biopsy and monitor the cell doubling rate – that will give us a way to select and treat patients who are likely to respond better at the phase II and later stages of a drug trial."

Anderson adds that there is a striking finding: they found almost no overlap of the main parameters in the model between the cell lines and patients. "So if you were to assume the response of the patients would be the same for the same dosing and scheduling as with the cell lines you wouldn't get a good result," he says. The point is that this finding helps to explain why preclinical results are so often not replicated in patients.

What is important about virtual patient modelling is that parameters

can then be varied, including dose amounts, when to apply drugs (in sequence or together), and also applying a treatment 'holiday' – stopping and restarting a drug. In the study, the authors report that using a lower dose of the AKT inhibitor is better in some cohorts, and that "changing the temporal protocol influenced the dynamics of the system significantly." These variations cannot all be trialled in early phase trials or later trial stages, even when fairly large numbers of patients are enrolled.

Indeed, most preclinical data are based on individual drugs. Trials of the sorts of combinations that are becoming so important in oncology are mostly carried out at the phase II/III stages, so these virtual models are likely to become increasingly important, although new preclinical research may be needed, as with the Moffitt work. And such mathematical modelling is not confined to *in vitro* studies, but can also apply to human only ones, as the authors note about a study of radiation dosing schedules for brain tumour patients (*Cell* 2014, 156:603–16).

Parameters can be varied, including dosage, when to apply drugs, and also applying a treatment holiday

Anderson notes that the combination therapy in the AKT trial was not taken forward owing to mixed results, but that if the stratification his team has found is used, it could identify a subset of patients who are very responsive. He also mentions an (unpublished) simulation they did as part of the study, to see whether autophagy inhibitors other than AKT could help poorer responding patients – candidates could include drugs usually used to treat malaria, in an echo of the 'repurposed' arthritis drug mentioned by Lehrach.

Adaptive therapy to address resistance

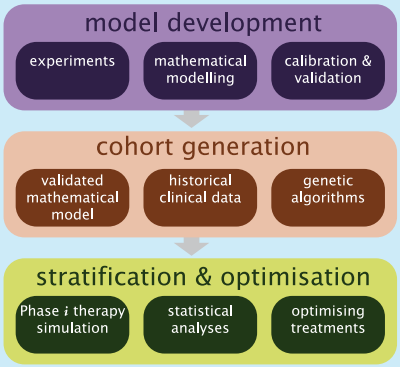
Jacob Scott, a physician–scientist who coined the term 'phase *i*' when he was at Moffitt, says that a critical part of the data discovery process that can feed into modelling is to understand much more about the evolution of tumours and how they develop resistance to drugs. Now working in his own lab, at the Cleveland Clinic, Ohio, this is his current focus. "By figuring out what we call the tumour 'sensitivity network' we can see what will happen after a drug is used – what will change in the tumour, and what secondary therapies will then be most beneficial. This is very different from just determining the current weakness of a cancer."

In a paper recently published in *Scientific Reports* (2017, 7:1232), Scott and colleagues have mapped a way to predict which of the new generation of ALK inhibitors in non-small-cell lung cancer could be the most sensitive agents to use at second line, once the initial drug inevitably fails (the key is avoiding cross-resistance among agents and getting the length of drug cycles right, including using drug holidays).

This growing understanding of the evolutionary nature of cancer may mean oncologists will be in a position to at least manage a chronic disease, if not effect a cure. This has long been mooted, but has so far proved elusive in all but a small proportion of patients with metastatic disease.

Both Scott and Anderson mention work on cancer evolution by Charles Swanton at the Francis Crick Institute in London, which is looking at how dis-

Phase *i* trials



Step 1. A mathematical model is developed based on experimental data. The model is then calibrated and validated by comparing model prediction and experimental results.

Step 2. The validated model and genetic algorithms are used to generate a virtual cohort that statistically matches historical clinical data.

Step 3. Phase *i* therapy, assuming the same schedules in a clinical trial, is simulated using the cohort. The virtual cohort is analysed to predict stratification factors. Optimisation approaches are employed to propose optimal therapy, which may guide better patient selection and treatment strategies in subsequent clinical trials

Source: E Kim et al (2016) *Eur J Cancer* 67:213–222. Reprinted with permission from Elsevier

tinct populations of cancer cells arise within the same tumour – and what we can do about it (see for example *Nat Rev Drug Discov* 2017, doi:10.1038/nrd.2017.78, and Using Darwin's Notebook to Outsmart Resistance, *Cancer World* 77, 3 March 2017).

Anderson agrees that resistance mechanisms are crucial, noting the concept of competitive release, whereby resistant cells are initially outcompeted by sensitive cells because they are less 'fit', but then become competitive and take over when a drug eliminates the sensitive population.

He points to a trial now underway at Moffitt, which seeks to address this mechanism of resistance using what is known as 'adaptive therapy'. This involves using a mathematical model to schedule treatments for prostate cancer by stopping and starting anti-hormone therapy based on PSA levels and tumour burden.

He adds that the principles are similar to the phase *i* strategy, of moving away from a 'dose-dense' approach of applying fixed therapies, to instead finding the best ways of delivering drugs and combinations as a cancer evolves, especially at the metastatic stage. And the virtual patient concept is certainly part of the picture: "We can apply it not only to heterogeneity in a population, but also to uncertainty about a single patient, with a virtual cohort that has all the known aspects of that patient in common and all of the unknown aspects spread throughout the cohort. If we can treat the cohort we have a good chance of treating the patient."

> **"We can see what will change after a drug is used – and what secondary therapies will work best"**

The idea of integrating the power of modelling, biological mechanisms, and evolutionary insight to open up an extensive toolkit for an individual patient – essentially a clinical trial for one person – is now being seriously considered, and would be a huge step on the road to precision medicine. But it needs resourcing – and if Lehrach had his way, we'd see the same sums going into cancer models as are now spent on computer games – society has its priorities seriously wrong, he feels.

For a laugh

"Because when it actually works they just call it medicine."

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Prevention and early detection

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Stephan Tanneberger was Director of the Central Institute of Cancer Research of the Academy of Sciences in the German Democratic Republic 1974–1990. He spent much of his later career with the Bologna-based Associazione Nazionale Tumori, developing their local and international work supporting home-based palliative care services

Oncology is understandably fascinated by ideas around precision treatment. As a medical oncologist who was there when the germs of this approach first appeared 50 years ago, I do of course share the excitement over the news that continues to stream out of molecular tumour biology – but I am also aware of its likely limitations (see, for example, Personalising treatments: lessons from history. *Cancer World* 71, March 2016).

As we gather in our many thousands in Madrid for ESMO-2107, we are right to dream great dreams of progress in our ability to treat cancer. Where we are wrong is in losing sight of the number of lives that can and must be saved by paying more attention to research and implementation of effective policies on prevention and early detection.

Cancer incidence is growing worldwide, and a major public health response is required to turn the rising tide of new cases. Finding resources to do this may be a challenge in developing countries, where infectious diseases continue to pose a major health hazard. But in the developed world, there is no excuse for failing to do more.

The rate of new cancer diagnoses has almost doubled in Germany since the start of the 1970s. This cannot be dismissed as purely a result of an ageing population. Changing lifestyles also play an important role, fuelling year-on-year increases of between 1.5% and 4.5% in new diagnoses of cancers of the breast, lung, and skin (*Bericht zum Krebsgeschehen in Deutschland*. Robert Koch Institut, Berlin, 2016).

Well-known risk factors are at play here, which can and should be reduced, including smoking, obesity, unhealthy diet and alcohol.

Politicians may talk the talk, but how many of them invest serious money and political capital into researching and implementing policies to counter the vested interests that promote unhealthy lifestyles?

In Germany, the tobacco industry spends €200 million a year on advertising, while the products it profits from are by far the largest cause of lung cancer, which drains €2 billion a year from healthcare budgets.

Much more must be done to counter the influences behind the deadly rise in smoking among young women, including confronting the way smoking is portrayed in film, TV and music videos. Convincing Hollywood to be more responsible over its portrayal of smoking led to a sharp drop in the number of cigarettes lit up on screen in the 1980s, but a recent study shows that rate has now bounced back higher than ever.

And with more than 50% of Europe's population now classed as overweight or obese, much more must be done to counter the influence of the fast food industry and promote healthier alternatives from an early age.

As an oncology community, we are good at arguing for the vital need to support cancer research. We are less good at making the case for putting more research and funding into developing and implementing strategies to get the right messages across to the right people at the right time, to help them protect themselves from cancer risk and alert them to possible warning signs and symptoms.

Our voices carry weight and influence, and we must use them to push prevention and early detection higher up the policy agenda. Including these topics at the heart of our own agendas, our publications and our congresses, would be a good start.

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Josep Tabernero

ESMO President Elect

Josep Tabernero is active at many levels. He does hands-on translational research in the lab and clinic, he directs one of Europe's top cancer institutes, and he will shortly be taking over the leadership of the European Society for Medical Oncology. **Alberto Costa** asked him about his strategy for delivering progress for patients.

Alberto Costa: *What are the keys to accelerating progress in treating cancer?*

Josep Tabernero: Thanks to major advances in genomic technologies, including widespread implementation of gene panels to diagnose the molecular causes of solid and haematological cancers, the exciting advent of non-invasive liquid biopsies, and steady progress in precisely targeting drug therapies against individual tumours, we have already come a long way.

But we need to get smarter and move faster. In particular, we need to make progress in reversing cancer drug resistance and counteracting tumour cell spread factors.

Novel therapies – immune-based approaches in particular – are being extended to more tumour types, we are learning more about the cancer genome and epigenome, and we are making progress in fine-tuning anti-cancer medicines according to newly classified subtypes, and identifying new avenues for molecularly targeted therapy against metastatic disease.

But continued progress comes with a hefty price tag. First, the cost of basic and pioneering cancer research: improving outcomes for more of our patients in the current era of precision medicine begins here with our preclinical studies. Second, at clinical level, we need to work collectively towards reducing the high – and controversial – cost of novel cancer therapies by better measuring value and benefit. We must also continue to work in partnership to re-adapt clinical trial design in parallel with predictive science and accelerate the approval processes of the established 'winner' therapeutics, so we can realistically hope to offer these therapies to the patients who are most likely to benefit, wherever they may be.

AC: *How important is the contribution made by academic institutes such as the Vall d'Hebron Institute of Oncology?*

JT: Absolutely vital! Academia not only drives the rapidly evolving emerging landscape of oncology research, refining our understanding of the basic hallmarks of cancer, but it also innovates key efforts in early clinical drug development that can, in partnership with industry, accelerate the development of truly transformative drugs.

In VHIO's case, our purely translational research model benefits immensely from the privileged location situated within the Vall d'Hebron Barcelona Hospital Campus – affording direct access to the entire spectrum of dedicated oncology professionals who care for our patients. This means not only that VHIO's researchers closely interact with physician-scientists at Vall d'Hebron, but also that translational science and clinical research are tightly connected, spurring the bench-bedside-bench cycle of knowledge.

That said, no academic institute, regardless of location, ranking or standing, can realistically hope to drive progress alone. It is thanks to the collective belief in strong partnerships and leading consortia that we avoid costly duplication and speed up results. Academic institutes must combine their strengths with chosen partners, depending on the sphere of research, if they are to reach the end goal faster.

AC: *Could progress in new treatments and therapeutic strategies be accelerated by giving academic research groups more of a say over what questions are asked and how they are answered?*

JT: It's not only a question of more say – it's more about the need for us all to get organised and act in concert to establish the frameworks and tools required to deliver cost-effective precision cancer treatment and care in an equitable and affordable way. In the current climate, with the spiralling costs of novel anti-cancer therapies, healthcare systems are not sustainable. We must now start to make realistic, increasingly evidence-based decisions, with the pricing efficacy of cancer drugs a central consideration. We must work together to objectively gauge the factors that influence drug prices in each country, and engage with policy makers and the industry to rethink and adjust the drug development agenda accordingly.

AC: *Is progress being held back by a culture emphasising competition over collaboration within the academic community?*

JT: The most pioneering research of excellence in biomedicine, and particularly in oncology, is recognised and supported by competitive grants, including funding from the European Research Council (ERC) and the European Commission Horizon 2020 calls. That's a fact. Many of these projects involve multicentre partnerships and promote strong collaboration across borders. As long as research institutions can apply for these opportunities, which are awarded based on the promise and quality of proposed projects, then worthy academic groups will continue to advance the oncology field.

In terms of equal access to funding programmes, the uncertain climate triggered by Britain's vote to exit the EU is a cause for concern. We must stand together to protect cross-border partnerships and projects, strengthen our cancer science through continued funding, and defend the mobility and exchange of talent throughout our laboratories and hospitals.

AC: *How do you manage to lead the VHIO at the same time as playing a very active role in clinical/translational research, and soon taking on the presidency of ESMO?*

JT: I am very lucky to be supported by many superb teams and flanked by dedicated and talented colleagues. Without them, I couldn't possibly hope to do what I do – there simply wouldn't be enough hours in the day! I am honoured and privileged to work alongside so many exceptionally gifted individuals who uphold the same ethos as me: there is no 'I' in team.

AC: *How do you see the future of ESMO, and what would you like to achieve during your tenure as President?*

JT: ESMO has both the responsibility and the will to move multidisciplinarity in oncology forward. While medical oncology will rightly remain at the core of its activities, our Society must continue to foster, nurture and develop essential strategic partnerships with other specialties and target groups, collaborating to speed up progress, with the interests of patients at the centre of everything we do.

I will seek to better respond to the growing needs, pressures and daily obstacles faced by medical oncologists – within Europe and beyond – and tailor specific actions matched to the regional needs. I want to help alleviate some of the pressures on the up-and-coming generation, who face heavy burdens and burn-out that could cost our specialty dearly if not addressed.

ESMO is perfectly equipped to provide critical intelligence aimed at better guiding policy makers and government authorities in their priority setting towards sustainable healthcare systems. As a future ESMO President, I will strongly support actions led by our Cancer Medicines Working Group, together with ESMO's policy committees, to identify and act on these region-based realities and promote a multi-stakeholder rethink of reimbursement policies, cost settings and pricing.

Josep Tabernero is Director of the Vall d'Hebron Institute of Oncology, in Barcelona, and head of Medical Oncology at Vall d'Hebron University Hospital. He is very active in translational research and phase I studies, with a special focus on EGFR-family inhibitors and IGFR-PI3K-Akt-mTOR pathway inhibitors, and is also involved in phase II and III studies with new chemotherapy agents in gastrointestinal tumours.

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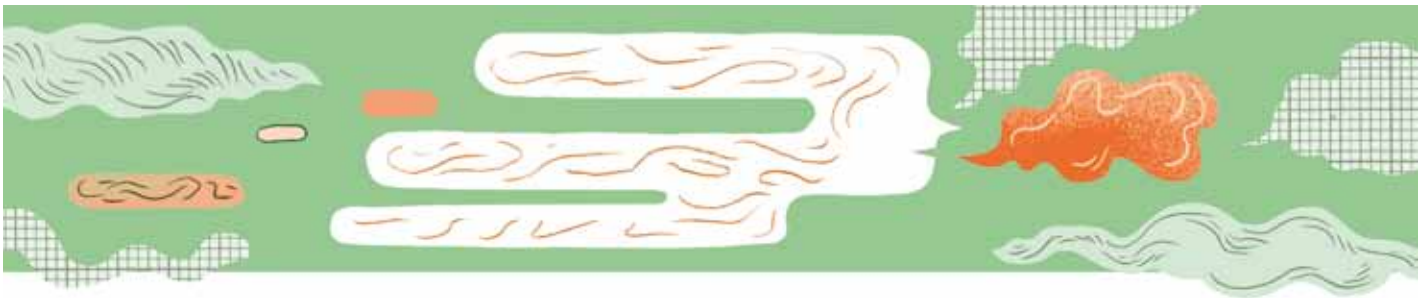

Lisa Hutchinson: teasing out the signal from the noise

The explosion of new information in the era of personalised medicine has created a headache for busy clinicians. Lisa Hutchinson has spent the past 13 years helping them keep abreast of developments by sifting, sorting and summarising the clinical research findings that matter most. She talked to **Anna Wagstaff** about the joys of her job as Chief Editor of *Nature Reviews Clinical Oncology*.

Every month, Lisa Hutchinson and three colleagues scan more than 3,500 abstracts published in 70–80 medical and cancer journals to keep abreast of the latest advances and discoveries that could be of value and interest to practising oncologists. She attends cancer conferences and talks to her wide network of people who are pursuing interesting research or have new and thought-provoking things to say.

Together with her team, she filters the information and works out how to present it all in 64 pages.

Hutchinson is just reaching the end of an almost 14-year stint as Chief Editor of *Nature Reviews Clinical Oncology* (NRCO). It's a position she has held since the title was launched in November 2004, as part of *Nature's* first foray into the clinical arena and, despite the long hours, as far as she's concerned it's been nothing but a privilege and a pleasure.

"I think I've got the nicest job of anybody in this room," is how she opened a talk to a group of cancer researchers last year. "I don't have to worry about getting funding, or design fancy experiments. I've still got the enormous privilege and luxury of knowing what's going on in the cancer world from the people who are the main influencers, and are educating me in the process, and I get a publication at the end of it – and there's the kudos that goes with that, particularly as it's *Nature* branded." As she adds, "It doesn't get better than that!"

Do we need yet another journal?

By the time *Nature* launched its monthly review publication for oncologists, the explosion in medical publishing was already well under way. "Do we need yet another journal?" was the question posed in the launch issue by the journal's external Editor-in-Chief – and former head of the US National Cancer Institute – Vincent DeVita, who went on to argue that it was precisely because of the overload of new information that this new monthly clinical oncology review was needed. "This journal has some unique editorial features that will ease your workload and help you interpret and put into practice the enormous amount of published research," he wrote.

A great job. Lisa Hutchinson at *Nature's* London publishing centre, where she has worked as Chief Editor of *Nature Reviews Clinical Oncology* since its launch in 2004

The concept, explains Hutchinson, was "to filter and tease apart the signal from the noise for busy clinicians, so that we can provide a chronology of the medical research applications that are being reported on, and add an interpretation as well as an informed opinion." The new journal was to carry no primary data, but provide expert commentaries, short articles, and research highlights written in-house, "crossing the breadth of the literature," and then the more lengthy reviews and perspectives, which are all commissioned and peer reviewed.

The latter, which make up the 'back half' of each issue, provide background to a given topic, but then take an original look at the timeline of recent developments, controversies, where progress is being made, and where once promising research is failing to deliver. "We are proactive as well as reactive to the literature," says Hutchinson.

Thirteen years on, she feels the journal is needed more than ever. At the start it was a question of keeping abreast of 20–30 journals, but that number has now increased almost four-fold. And it isn't just the number of journals, she adds. "They are publishing more frequently, so there is more content coming out on a daily basis, especially as we have advance online publication."

She admits to being "in awe" of the way clinicians keep on top of the ever-accelerating pace of new information. "I struggle and it's my day job. I don't have patients to treat and ward rounds to do."

Loving science, but not the lab work

A biochemist by training, Hutchinson did her PhD at the UK's Institute of Cancer Research, starting in 1994, as molecular biology techniques were just beginning to take off. "That was studying Wnt signal transduction in mouse fibroblasts relating to breast cancer. Very preclinical. At the time we did not know or understand the biochemical pathways, our knowledge was based on clonal epistasis analysis."

All the technologies referred to in *Nature* journals now, she says, are way beyond anything she ever did in a lab.

Microarrays, she remembers, were just being introduced in the last year or so of her PhD, "and were considered a massive thing". The second *BRCA* gene was cloned at the Institute, and the findings were published in 1995, "I remember the *Nature* paper coming out on that."

So why leave research, with all this going on? "I probably didn't have quite the nurturing environment with my first supervisor during the early part of my PhD," Hutchinson speculates, "and I thought: gosh, this is a treadmill. I could work for another 5–10 years doing a post doc. Do I want to do a team-leader role as a lab researcher, having to get funding to support four or five people in a lab? And after all, even though science is extraordinarily exciting and interesting, it is the 99% perspiration 1% inspiration rule. I remember the times I was stuck in a lab trying to get minipreps to work for months on end. Trying to clone certain things, get antibodies, and I just thought: I'm not sure I'm in this for the long run – but I loved science."

Having taken the decision to leave research, a career in science publishing seemed an appealing alternative. An opening for an Assistant Editor arose at *Breast Cancer Research*, where Bruce Ponder was Editor-in-Chief. With her newly minted PhD, Hutchinson got the job, and within a year was promoted to a journal Editor role.

She enjoyed the work, but was soon lured away by a medical communications company, which offered her the chance to do something different, on better pay and a varied role. Her new job gave Hutchinson an insight into the world of product life cycles and pharmaceutical company messaging, which she says has proved invaluable in her current position.

The insight she gained into pharmaceutical company messaging proved invaluable in her current position

"I got experience in writing and communicating and working as the middle man; the pharmaceutical companies were writing abstracts for conferences, and we would essentially ghostwrite them. We also put together a publication plan for an insulin sensitiser drug. I got to see how you analyse all the key marketing messages in manuscripts, and try to come up with an editorial strategy to publish and get across those marketing messages of certain products, such as how they compare themselves to competitors."

When *Nature* then advertised for a Chief Editor to launch a new oncology review journal, Hutchinson believes her experience working within the medical communications industry helped her clinch the position – as 'poacher turned gamekeeper', she knew all the tricks.

"If you understand how the process of a formulation of a manuscript works, you can start to tease apart articles that might not be written first hand by the authors, and see influences that have been exerted by pharma companies. When I'm reading papers I do notice things like that."

How far does she think the hidden hand of industry really threatens the integrity of the academic literature? "I think it is more prevalent in the literature than people realise," says Hutchinson. She mentions a study presented at the 2017 ECCO, where 300 corresponding authors were randomised to read abstracts of a key trial that had been written either with or without spin, and were then asked to rank whether they felt those treatments made a difference. "The scoring they got at the end with spin was about 6/10 – 10 being that they thought the drug was really great, and 0 being the opposite. And it was around the 2–4 range without spin. Even experts are being influenced, and these were corresponding authors who had written several similar papers."

She adds, however, that industry is by no means the only culprit here. "A conflict of interest isn't always financial. There are other pressures to get a positive result on a research paper, because you are more likely to induce people to read it and to cite it, and it might further research funding."

Hutchinson wonders, too, about why she keeps coming across the same type of phrasing in a lot of abstracts. "I'm seeing a trend of how things are phrased where there is almost a template, and buzzwords have been inserted – almost like you've got to have that in there. It's got to have 'multidisciplinary', it's got to have 'translational' or 'immunotherapy' for you to have a chance of getting into the top-tier journals. It's the same for grant tenure and further funding, they also stipulate that people have got to be publishing in these type of areas with these type of outputs."

She feels research funding is too bound up with publication track records. It's not wrong to insist that people have to publish, she argues, but the lack of focus on negative trials does raise questions about the reproducibility of published results. She also feels that promising initial scientific findings are too often allowed to advance into clinical publications without enough attention being paid to issues of clinical utility or benefit for those findings to change practice or influence care. "The pathway for assessing preliminary scientific promise to advance to the clinic is not as well created as it should be."

She worries too about the "disturbing increase" seen in retractions and falsification of data, and about the increasing numbers of papers that include large sections cut and pasted from other articles. *Nature* is one of many academic publishers who have signed up to the Committee on Publication Ethics (COPE) guidelines, "and we as a company are educating our own staff in-house across the board about integrity issues," she says.

Broadening readers' horizons

In her 13 years scrutinising every aspect of clinical oncology, and trying to make sense of it for busy practitioners, Hutchinson has seen some big changes.

"We're all looking much more at health policy, societal challenges, sustainable healthcare models," she says, and at a clinical level, as oncology has become more complex, care has become much more multidisciplinary, and there are more pressures to super specialise – though some clinicians don't want to go down that road, says Hutchinson.

"I get the impression that people are trying to not be too siloed because it's not in their career interests. They want to be broader, and they are finding avenues to do that, even if it means moving to other institutions."

She notes also a trend towards horizontal linkages between specialties that used to be more distinct. Molecular biology is no longer just the preserve of clinical oncology – it has a role to play in imaging, radiotherapy, and even surgical oncology. Learning more about other specialities can help people deepen their understanding of their own, and she adds that publishing can play a role in that.

She cites as an example a recent article about the career path of a radiation interventional oncologist, which looked at the interfaces between radiotherapy, radiology and clinical oncology, and where education and training could be improved. "That article was more on the educational side than on the hard core business coverage we typically cover, and it came about through anecdotal conversation. I said, 'If people don't know this is a problem, but that there are actually ways this can be achieved by different interactions within departments, getting better internships, things like that could really help.' Even if this article doesn't attract high citations, we wanted to cover it because there's a need."

The rise of the personalised/precision medicine paradigm happened largely during her editorship. Hutchinson is cautious about the benefits, and devoted one of her editorials to the topic. "The reality is that the clinical benefits of precision medicine, as currently practised, are quite limited.

Well connected. *Nature's* offices are part of the King's Cross Science Hub, which now includes the Francis Crick Institute – the largest biomedical research facility under a single roof in Europe. King's Cross St Pancras station, seen on the skyline, gives rail access to Brussels in less than two hours

"Evidence-based medicine is the opposite paradigm to precision medicine, so the field is at a bit of a crossroads"

"We are trying to look at how you can get data that will inform clinical practice, but the paradox is that evidence-based medicine is the opposite paradigm to precision medicine. So the field is at a bit of a crossroads – heterogeneity of the tumour, clonal evolution, the snapshot of the tumour, liquid biopsies, how that is helping – or not helping in some cases – inform on disease progression. There are uncomfortable truths in terms of health spending pressures, uncertainty of the precision medicine era, and the billions

being invested in it that we can't just throw away."

Hutchinson's own best guess is that a better overall understanding of the tumour microenvironment and stromal tumour interactions may be among the more fruitful places to look for answers. "For me, understanding how cancer starts, understanding more about the metastatic process, along this continuum, is going to be the really important thing in the next 10 years."

As she points out, cancer is not like any other speciality, in that it has no organ or system base to it. "It's not like cardiology, where you understand the functioning of the heart and the supply structure intricately in and out." Cancer experts are therefore generalists to a degree, she argues. "We still don't have an essential understanding of how, on the molecular level, the disease starts. The stem cell model – sometimes it's in, sometimes out of favour. That for me is quite interesting."

"There are uncomfortable truths in terms of uncertainty of the precision medicine era, and the billions being invested in it"

Also intriguing is how little we know about 'normal' cells, says Hutchinson, who feels this is an area that deserves far more attention – an issue she first raised five years ago in a conversation with Roger Stupp, now President of the European Organisation for Research and Treatment of Cancer. "We'd been assessing the cancer cell in isolation in cancer patients, without considering the mutations or alterations or influences in the surrounding 'normal' cells. The point I made was that we need to consider the so-called 'normal' or non-cancerous tissue changes, otherwise we lack a baseline comparison, which inevitably is influenced by the cancer cells, and vice versa."

And sure enough, says Hutchinson, "It turns out that there are many mutations in 'normal' surrounding tissue, which has been pre-programmed to some extent by the latent dormant cancer cell. Failure to appreciate this has been providing a bit of a red herring when it comes to drug discovery, which is to some extent why we are in the mess we are in."

She is betting on the potential of 'omics technologies and systems biology to reveal more about how cancer starts and spreads, which would then lead to how to apply "what we have in our armamentarium to treat the patients". But her best guess for the timescale for reaching a 'biological cure' is measured in centuries rather than years or decades.

"Clinical cure is different. We've reduced colorectal cancer mortality by 40% in the past 30 years. But you are never going to get a full cure. If one in two of us is going to get a diagnosis of cancer, which is what the estimate is, this is here to stay. It is an adaptive complex disease that has had millions of years to use its biological circulatory to its advantage.

"The way I see it, in England we have a map of every single road and we know every single registered car on that road, and have high levels of CCTV [traffic monitoring cameras]. Are we able to predict which accidents happen on the A roads and the motorways? No. With cancer we haven't even got the road map done yet, let alone all the cars on it. So in some ways our progress is quite incredible given the lack of all that knowledge."

Hutchinson is clearly not worried that her journal will become redundant anytime soon, but she herself now feels it is time to move on. Having had the privilege of following at close quarters the explosion of new knowledge about cancer, and been part of efforts to translate that into better outcomes for patients, she is leaving NRCO to follow her interest in exploring the biological commonalities between non-communicable diseases, such as metabolism and inflammatory processes.

"I've had conversations with people at conferences, and we are starting to see this appearing in clinical oncology. Even cancer is not as distinct at a molecular level from other diseases that we've studied as completely separate entities. We are starting to see them interacting more. Biology does that. So understanding biology will help us understand disease pathway roadmaps better, not just oncology but other areas."

It's exciting stuff, but after almost 14 years working with and for clinicians, Hutchinson is clear that she does not want to return to basic science. "For me, the molecular era opens up a vista on how we view diseases on a fundamental level. We are starting to see more synergies about how non-communicable diseases develop and evolve to become incurable. I would love to use my oncology background to help find solutions for many of the key global healthcare problems. For instance, diabetes is a ticking time bomb, with more than 415 million people worldwide living with this disease, with millions more undiagnosed.

"We need to provide a sustainable framework for healthcare globally and tackle the top non-communicable diseases. To be part of this endeavour would be extraordinarily rewarding."

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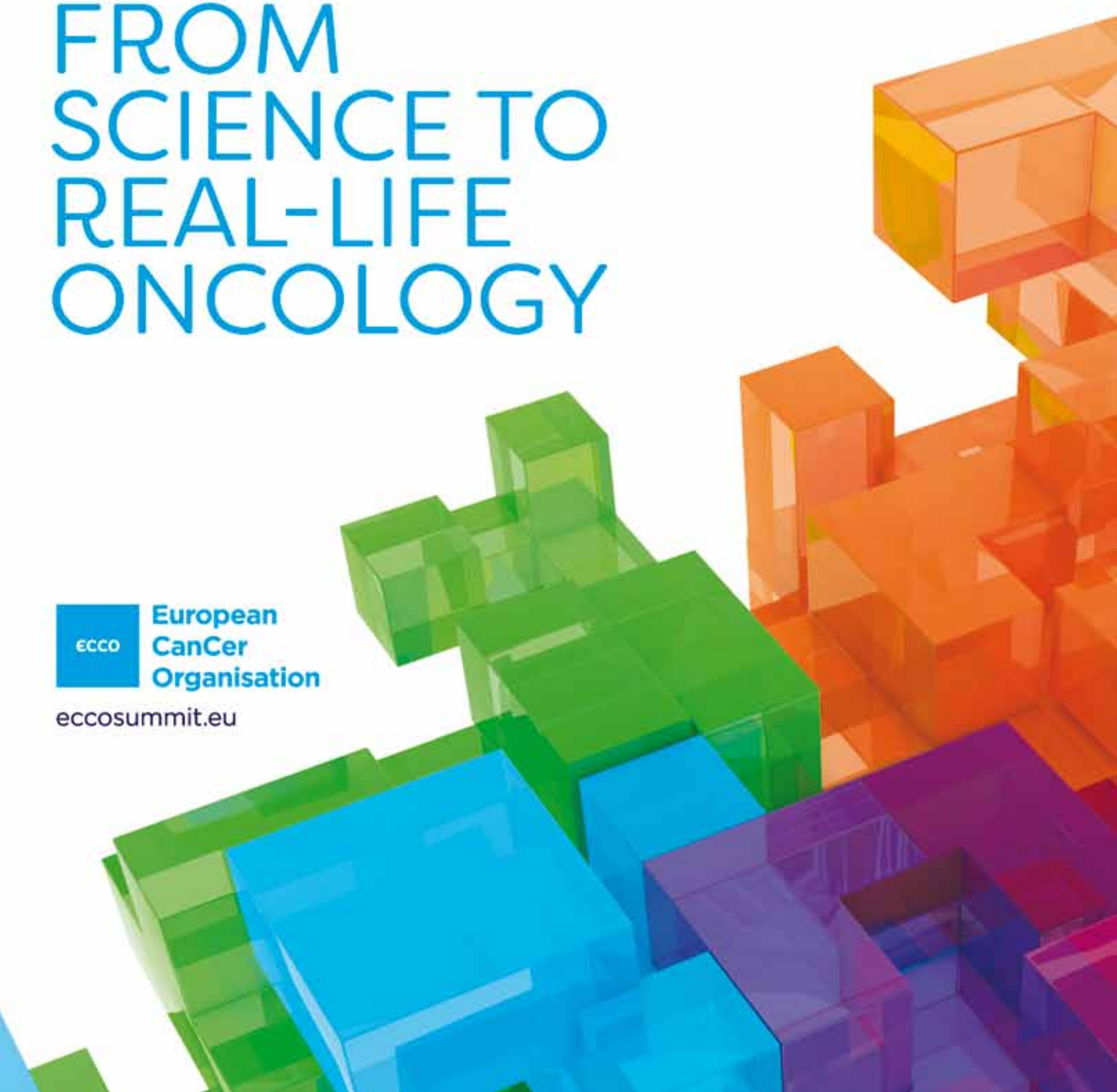

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EUROPEAN ACCREDITATION AND DESIGNATION PROGRAMME FOR CANCER INSTITUTES

OECI
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Simon Oberst
Accreditation and Designation Chairperson

The **Accreditation/Designation (A&D) Programme** has developed consensus European quality standards and criteria to support the growth of Comprehensive and Clinical Cancer Centres in Europe which integrate care, research and education.

This tool enables the performance of cancer centres to be assessed, benchmarked, and improvements planned, to increase the quality of centres across Europe.

As at June 2017, about half of the 82 OECI members are participating in the A&D Programme. 17 have been certified as Comprehensive Cancer Centres, 12 as Clinical Cancer Centres, and among them 3 centres have received a second certification.

Centres who take part in the programme report that the A&D Programme helps them to identify their key strengths and opportunities for improvement, and to further improve the integration of care, research and education within a strong governance structure.

OECI COMPREHENSIVE Cancer Centre

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Use of PARP inhibitors in ovarian cancer

PARP inhibitors are the first class of drugs to exploit a new concept in oncology – synthetic lethality. **Alexandra Leary** explains the rationale, reviews the trial evidence and clinical experience, and looks to their future possible use in subsets of ovarian cancers without the *BRCA* germline mutation.

This grandround was first presented by Alexandra Leary, from the Gustave Roussy Cancer Centre, Villejuif, France, as a live webcast for the European School of Oncology. Margaret Hutka, from St George's University Hospital NHS Foundation Trust, London, posed questions raised during the presentation It was edited by Susan Mayor. The webcast of this and other e-sessions can be accessed at e-eso.net.

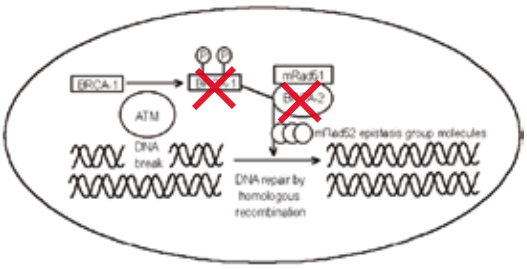
Ovarian cancer is a rare disease, and yet it is the fourth leading cause of cancer-related death among women, after breast, lung and colon cancers, which are much more common. The reason for the high mortality rate is that ovarian cancers tend to be picked up at an advanced stage. One of the enigmas associated with ovarian cancers is that they are initially very sensitive to chemotherapy, with response rates to first-line platinum of 70–80%. However, the prognosis is poor, with half of patients relapsing within two years. Until recently, the only 'targeted' therapy available was the anti-angiogenic agent bevacizumab, for which there are no predictive biomarkers.

An important point about ovarian cancers is that 12–15% are associated with germline mutations in either *BRCA1* or *BRCA2*. The Cancer Genome Atlas (TCGA) has provided more information, showing that, beyond these two germline mutations there are also somatic mutations that are acquired uniquely in tumours, occurring in 5–7%. The *BRCA1* and *BRCA2* genes can also be lost due to epigenetic silencing via hypermethylation (11–13%). In total, this means that around 30% of ovarian cancers may have alterations in *BRCA1* or *BRCA2* (*Nature* 2011, 474:609–15).

This finding is important because BRCA1 and 2 are key effectors in DNA repair, as downstream proteins involved in the repair of double-strand breaks in DNA, mainly via homologous recombination. *BRCA1*- or *BRCA2*-mutated tumours lose one of these proteins, and their homologous recombination DNA repair system no longer works effectively, so double-strand breaks accumulate in the genome of the tumour cells. The impaired DNA repair mechanism probably explains

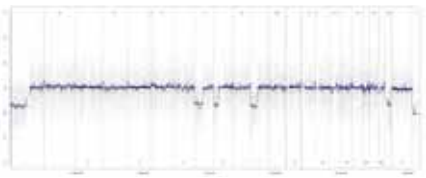
DNA repair deficiency in high-grade serous ovarian cancer

Inactivating mutations in *BRCA* results in homologous recombination deficiency

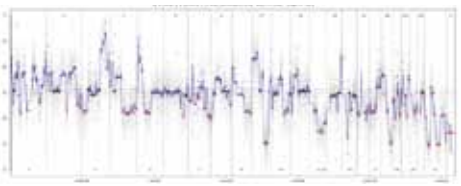


Probably explains chemo-sensitivity (unable to repair the DNA damaging effects of platinum)

CGH profile of a genomically stable ovarian cancer



CGH of a high-grade serous ovarian cancer, showing many gains and losses throughout the genome



High-grade serous ovarian cancer is genomically unstable due to DNA repair deficiency via homologous recombination (*above*). Comparative genome hybridisation (CGH) profiles show multiple gains and losses through the genome of unstable high-grade serous ovarian cancers (*bottom right*) compared with a genomically stable ovarian cancer (*bottom left*)
Source: Courtesy of Alexandra Leary, Gustave Roussy Institute

their sensitivity to platinum-induced DNA damage. It also affects the genomic profile: the figure above contrasts the comparative genome hybridisation (CGH) profile of a genomically stable ovarian cancer with the multiple gains and losses throughout the genome in genomically unstable high-grade serous ovarian cancer.

BRCA mutations result in loss of expression or function of BRCA, affecting its role as a major DNA repair effector of homologous recombination. This poses the question of how to target the loss of a protein to treat a cancer. In other cancers, drugs have been developed to inhibit *EGFR* mutations, but these are oncogenic gain-of-function mutations, in contrast to the loss of function in *BRCA*-mutated ovarian cancers.

Ovarian cancer is the first cancer to exploit a new concept in oncology – synthetic lethality – which targets the loss of an entity. This is illustrated in the mechanism of action of PARP inhibitors in *BRCA*-mutated tumours (see figure p35). Cells have many ways of repairing their DNA. Homologous recombination is one of the major DNA repair mechanisms, but there are others, such as base-excision repair. This explains how mutated cancer cells survive, because they switch to another mechanism to repair their DNA.

PARP1 is a major mediator of base-excision repair. Blocking PARP1 in normal cells has no effect, because they switch to homologous recombination to repair DNA. Cells with *BRCA* mutations have lost homologous recombination, so blocking base-excision repair with a PARP1 inhibitor results in loss of DNA repair and cell death, or synthetic lethality. PARP inhibitors are the first example of drugs that target the loss of a gene suppressor. *BRCA*-mutated tumours are dependent on other DNA repair pathways, so PARP inhibition becomes synthetically lethal in the context of an inactivating *BRCA* mutation.

Olaparib in ovarian cancer

Olaparib was one of the first PARP inhibitors to be developed. Early studies in *BRCA*-mutated ovarian

cancer demonstrated olaparib's efficacy, with objective response rates (*Lancet* 2010, 376:245–51). Phase I and II studies showed clear olaparib activity, principally in ovarian cancers that were *BRCA*-mutated and/or tumours showing platinum-sensitive relapses (>6 months). These findings prompted the first large trial in patients with high-grade serous ovarian cancers with platinum-sensitive relapse responding to re-challenge with platinum-based chemotherapy (*NEJM* 2012, 366:1382–92). They were randomised at this point to maintenance olaparib or placebo. Overall results were positive, regardless of *BRCA* status, with a median progression-free survival (PFS) of 8.4 months with olaparib compared to 4.8 months with placebo (HR=0.35, $P<0.001$) (see figure overleaf *top*).

A subgroup analysis of patients with *BRCA*-mutated tumours (germline or somatic) showed even greater benefit with olaparib (median PFS 11.2 months vs 4.3 months, HR=0.18, $P<0.0001$) (see figure overleaf *bottom*). It was previously very rare to see such a dramatic impact with drug treatment in ovarian cancer. These results led to approval by the European Medicines Agency of olaparib for patients with platinum-sensitive relapsed high-grade serous ovarian, fallopian tube or primary peritoneal cancer associated with a deleterious *BRCA1* or *2* mutation, which can be germline or somatic. One of the remarkable consequences was that somatic mutation analysis entered routine practice. Olaparib was the first targeted therapy associated with a genomic predictive biomarker approved in gynaecological cancers, representing a major step forward.

Olaparib is given as monotherapy at a dose of 400 mg twice daily, starting within eight weeks of the last platinum chemotherapy, avoiding too short an interval, to reduce the risk of cumulative toxicity. Patients should have monthly blood cell counts for the first 12 months and then periodically.

Olaparib is relatively well tolerated. The main side-effects are fatigue, nausea and vomiting, and anaemia. One factor that is problematic is that patients have to take eight capsules twice a day, giving a total of 16 per day. The first dose reduction is to 200 mg twice daily, followed by a second reduction to 100 mg twice daily.

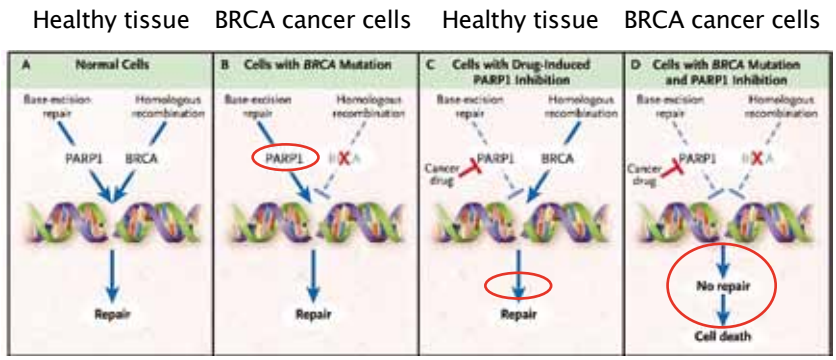
An important message to give patients is that, unlike chemotherapy, the side-effects with olaparib are at their worst during the first three months of treatment, and then often improve. They are not cumulative. When patients start olaparib they may experience nausea and not feel very well, but reassuring them that these side effects should improve can help them continue with treatment, which is important for a drug that is taken long term. Efficacy is dose-sensitive, so it is important to support patients to maintain dose intensity.

The European approval of olaparib for use in platinum-sensitive, relapsed high-grade ovarian cancers in patients with *BRCA* mutations was given on the basis of a phase II study, conditional on completion of a second, larger phase III confirmatory study.

This was recently achieved in the SOLO 2 trial, which randomised patients with a germline or tumour *BRCA* mutation to olaparib or placebo maintenance therapy for two years following response to platinum-based chemotherapy.

Results reported at the Society of Gynecologic Oncology meeting (12–15 March, 2017) showed this much larger study confirmed previous findings, with a significant 14-month increase in median progression-free survival with maintenance olaparib, compared to placebo, based on

Synthetic lethality of PARP inhibitors in *BRCA*–mutated tumours

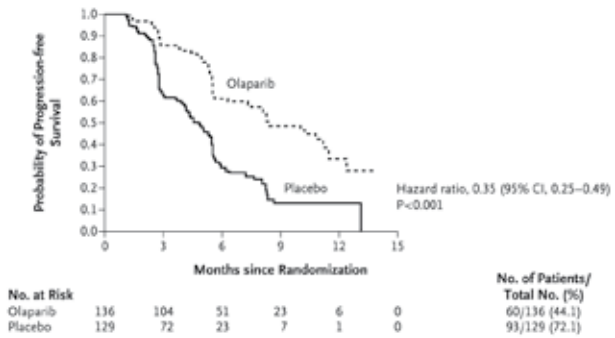


Inhibition of PARP becomes synthetically lethal in the context of an inactivating *BRCA* mutation, because homologous recombination defects make *BRCA*–mutated tumours 'addicted to' (dependent on) other DNA repair pathways

Source: JD Iglehart and DP Silver. (2009) *NEJM* 361:189–191, © 2009 Massachusetts Medical Society, reprinted with permission

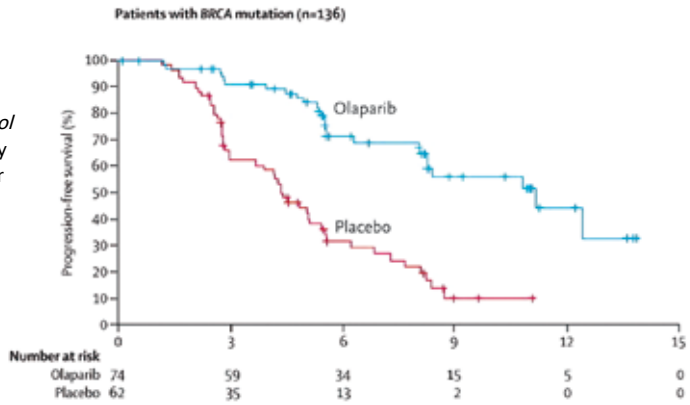
Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer

PFS for all patients



Source: J Ledermann et al. (2012) *NEJM* 366:1382–92, © Massachusetts Medical Society 2012, reprinted with permission

PFS in BRCA-mutated subset



Source: J Ledermann et al. (2014) *Lancet Oncol* 15:852–61. Reprinted by permission from Elsevier

The first large trial investigating the use of a PARP inhibitor in platinum-sensitive, relapsed, high-grade serous ovarian cancer showed a median progression-free survival (PFS) of 8.4 months with olaparib compared to 4.8 months with placebo (*top*). A subgroup analysis (*bottom*) showed greatest benefit in patients with *BRCA*-mutated tumours (median PFS 11.2 vs 4.3 months)

investigator assessment (see figure p 37). The central radiological review showed even more positive results.

When should we test for *BRCA* mutations?

In the past, *BRCA* testing was used only for hereditary cancers and testing family members for mutations. This has changed following the recognition that *BRCA* status can have a therapeutic implication. We now know that 20% of high-grade ovarian cancer is associated with germline or somatic *BRCA* mutations.

Germline testing

BRCA germline testing was previously carried out based on family history, but would now be recommended in all high-grade ovarian cancers regardless of family history. We know that women without family history can be the index case, and have a *BRCA* germline mutation. It is important to test as early as possible, ideally at diagnosis, because we know that once the patients relapse, their *BRCA* status could have therapeutic implications.

Tumour BRCA testing

Tumour *BRCA* testing is beginning to be introduced into routine care. It may become a therapeutic emergency to test patients with confirmed *BRCA* germline wild-type status who relapse. Academic centres now do targeted next generation sequencing for *BRCA* on tumours. This should be considered in patients without germline mutations who relapse, to look for the 7% who have somatic mutations.

PARP inhibitors: beyond *BRCA*-mutated ovarian cancer?

Clinicians now have a drug that is rationally designed to target patients with ovarian cancer who have a deficiency in homologous recombination, identified by a mutation in *BRCA*. The next question is whether these agents could be used in patients with ovarian cancer beyond those with *BRCA* mutations. Impetus for this comes from early studies showing responses to olaparib in *BRCA* wild-type ovarian cancer. Some of the studies, although small, showed an overall response of 25%, but the question remains as to how to identify these patients.

The Cancer Genome Atlas also showed that, in addition to the 30% of patients with high-grade serous ovarian cancer who lose BRCA due to germline or somatic mutations or hypermethylation, there is a further subset of around 20% who have rare alterations in various other members of the homologous

recombination DNA repair pathway, such as EMSY amplification (5–17%) or RAD51 loss (3–5%). Although these are all quite rare, together they account for a further 20% of high-grade serous ovarian cancers that could have deficiency in homologous recombination.

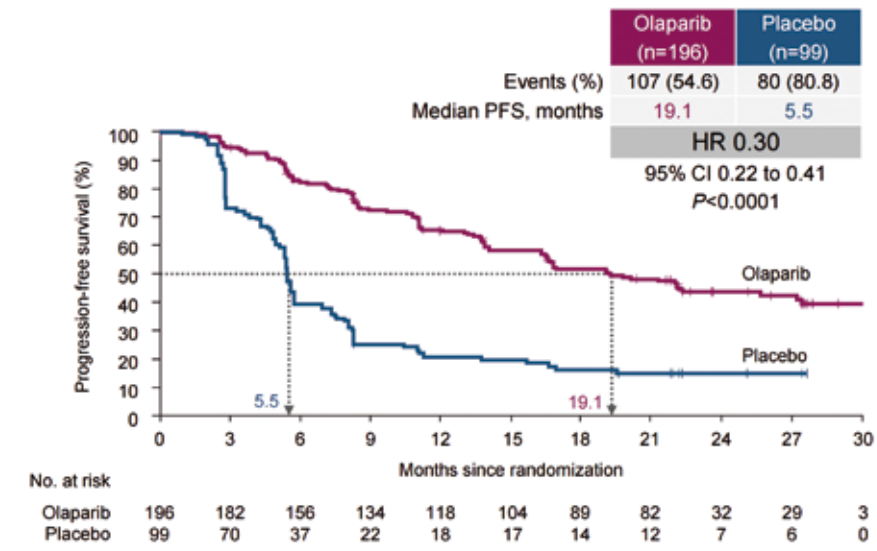
This may mean that the germline *BRCA* mutation is just the tip of the iceberg. We have now proved that somatic mutations occur as well, and now there is a wide range of other rare mutations that we can identify.

There are two methods of identifying *BRCA* wild-type ovarian cancers with homologous recombination deficiency: looking for rare mutations by carrying out targeted sequencing, or assessing the DNA damage scar of a tumour as a reflection of homologous recombination deficiency regardless of cause. A tumour that is unable to repair single- and double-strand DNA breaks accumulates DNA damage and has a very erratic genomic profile, in contrast to a tumour that is homologous recombination competent.

Identifying this profile would reveal tumours unable to repair DNA with deficiency in homologous recombination, which might respond to a PARP inhibitor regardless of the underlying cause.

Several studies have investigated this approach. ARIEL-2 set out to identify patients with *BRCA* wild-type ovarian cancer with defective homologous recombination that was sensitive to PARP inhibitors. Patients with relapsed high-grade ovarian cancer, regardless of *BRCA* mutation status, were biopsied before being treated with the PARP inhibitor rucaparib. The biopsy tissue was scored for homologous recombination deficiency, and the scores in patients responding to PARP inhibitors were compared with those in patients showing no response.

Benefit of PARP inhibitors in relapsed BRCA-mutated ovarian cancer



The SOLO 2 phase III trial showed that median progression-free survival for patients with platinum-sensitive, relapsed, *BRCA*-mutant ovarian cancer was 14 months longer for those randomised to the PARP inhibitor olaparib compared with placebo

Source: E Pujade-Lauraine et al. (2017) Late-breaking abstract. Society of Gynecologic Oncology 2017, figure courtesy of Eric Pujade-Lauraine , Hôpital Hôtel Dieu, Paris

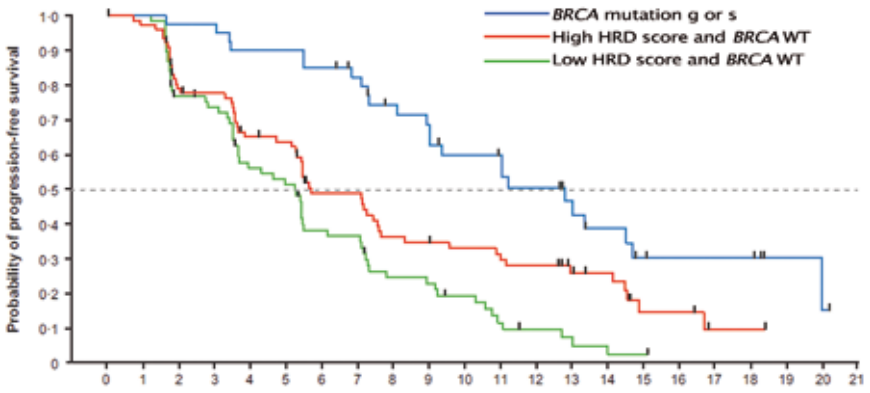
Results showed highest progression-free survival in patients with *BRCA* mutations (see figure p 38). There was some benefit in *BRCA* wild-type tumours with homologous recombination deficiency, with a response rate of 30%, but this was lower than that seen in *BRCA*-mutated cancers. Lowest response was found in those with low homologous recombination deficiency and *BRCA* wild-type tumours.

A second study with similar design, NOVA, also looked at this question with another PARP inhibitor, niraparib, in two groups of patients: those with germline *BRCA* mutations and those without (*NEJM* 2016, 375:2154–64). Results showed a benefit in progression-free survival of more than 15 months in patients with germline *BRCA*-mutated cancers treated with niraparib compared to those randomised to placebo (median PFS 21.0 vs 5.5 months, $P<0.0001$). Patients without germline *BRCA* mutations showed a six-month benefit (median PFS 9.3 vs 3.9 months, $P<0.0001$). Overall, the study showed that non-germline-mutated ovarian cancer also benefited from PARP inhibitors.

The remaining question is how to identify the subset of non-germline-mutated patients who benefit most from PARP inhibitors. An exploratory analysis of the NOVA study showed that, among patients with homologous recombination deficiency (as assessed by the Myriad HRD test), those with a somatic *BRCA* mutation had a progression-free survival hazard ratio of 0.27 with niraparib, compared with 0.38 in those who were *BRCA* wild type.

Interestingly, even patients without homologous recombination deficiency

PARP inhibitors can benefit some patients without BRCA mutations

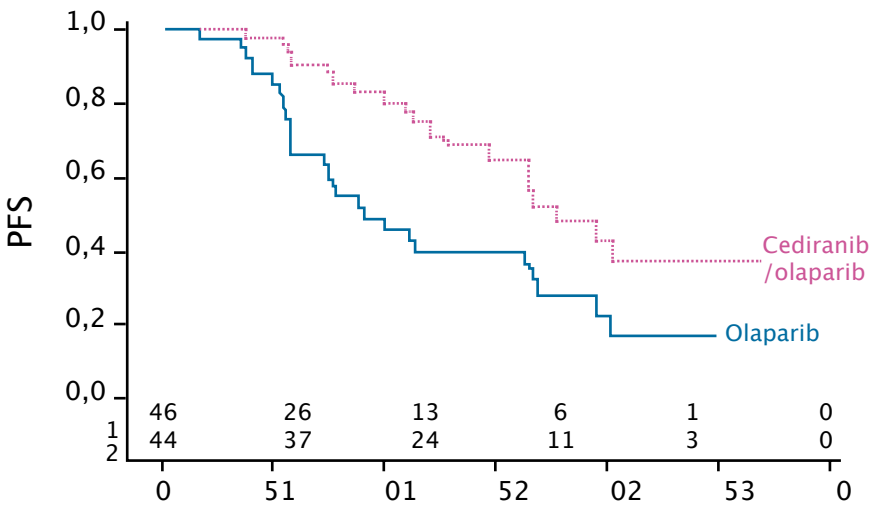


The ARIEL 2 international, multicentre, open-label, phase II trial showed that the PARP inhibitor rucaparib extended progression-free survival in patients with relapsed, platinum-sensitive high-grade serous ovarian cancers whose tumours showed homologous recombination deficiency not due to *BRCA* mutation, though the benefit was greater in patients with *BRCA* mutations

g – germline, s – somatic; HRD – homologous recombination deficiency; WT – wild type

Source: EM Swisher et al. (2017) *Lancet Oncol* 18:75–87. Reprinted with permission from Elsevier

PARP and VEGF inhibitor combination therapy in platinum-sensitive relapsed ovarian cancer



Adding the anti-angiogenic VEGF inhibitor cediranib to the PARP inhibitor olaparib improved median progression free survival in patients with platinum-sensitive relapsed ovarian cancer regardless of *BRCA* status (17.7 vs 9.0 months; P=0.005)

Source: J Liu et al. (2014) *Lancet Oncol* 15:1207–14. Reprinted by permission from Elsevier

benefited, although the hazard ratio was less marked, at 0.58 (*NEJM* 2016, 375:2154–64). The authors came to the provocative conclusion that all ovarian cancer patients benefit from niraparib maintenance therapy, regardless of *BRCA* mutation status or HRD status (as measured by currently available tests).

In fact, the results of the NOVA trial suggest that expensive genomic characterisation may not be needed, as platinum sensitivity is a valid predictor of benefit from PARP inhibitors. The FDA has recently approved niraparib in this indication.

Summing this up, homologous recombination deficiency occurs in 50% of patients with high-grade serous ovarian cancers. The development of PARP inhibitors has resulted in the first targeted therapy in this cancer associated with a genomic biomarker – germline or somatic *BRCA* mutations – with a response rate of 50% to 80%.

Several PARP inhibitors have now been shown to be active in ovarian cancers: olaparib, rucaparib and niraparib. Recent studies have suggested PARP inhibitor activity is not limited to *BRCA*-mutated ovarian cancers, and work is underway to identify the subset of patients with *BRCA* wild-type and homologous recombination deficiency who could benefit from these agents, with potential factors being: high homologous recombination deficiency score, mutations in non-*BRCA* homologous recombination genes and platinum sensitivity.

PARP inhibitors in combination?

PARP inhibitors have been tried in combination with chemotherapy, but this proved difficult because of cumulative toxicities. Remarkable

activity has been seen combining a PARP inhibitor plus an anti-angiogenic agent. A small phase II study of olaparib in combination with the VEGF inhibitor cediranib in patients with platinum-sensitive ovarian cancer showed high response rates and a median progression-free survival of 17.7 months with the combination, compared to 9.0 months with olaparib alone (*Lancet Oncol* 15:1207–14; see figure p 38 *bottom*). Subgroup analysis suggested the benefit of the combination was greatest in *BRCA* wild-type patients, indicating some synergy between these two approaches.

A large phase III European study, PAOLA 1, is currently investigating first-line maintenance therapy with bevacizumab alone or in combination with olaparib, regardless of *BRCA* status, in patients with high-grade ovarian cancer following first-line treatment with surgery and chemotherapy plus bevacizumab. More than 600 patients have been recruited and results are eagerly awaited.

Question & Answer session with Alexandra Leary

Margaret Hutka from St George's Hospital, London posed the questions.

Question: How do you think testing for homologous repair deficiency (HRD) will be used in the future? Will this take over from BRCA testing?

Answer: For now, I don't think the HRD scores that have been tested in studies are convincing enough to go into routine practice. While they are somewhat discriminating, they are probably not discriminating enough between responders and non-responders.

Q: Based on the ARIEL-2 study, considering HRD scores, how will we predict the effect of PARP inhibitors? What type of testing would you envisage at this point, as we have various options – BRCA, HRD or no testing at all?

A: I think we have to continue working on this in the current randomised studies that include a PARP inhibitor. Testing has to be both sensitive and specific. We want to make sure we include all potential responders. We need to analyse our data and compare tests until we find one that's good enough for practice. For now we don't have anything apart from BRCA testing that we can use in clinical practice.

Q: If a patient progresses while on a PARP inhibitor, do you stop the PARP inhibitor or continue?

A: Stop, as there is no data to support continued PARP inhibition with a subsequent line of chemotherapy, especially given overlapping toxicity concerns. The real question is whether there would be value to the re-introduction of a PARP inhibitor as maintenance in a patient previously exposed to a PARP inhibitor. A clinical trial opening very soon – OREO – will be asking exactly this question. Continuing treatment should only be considered in a patient who has shown a response initially. I wouldn't re-use a PARP inhibitor in a patient who has progressed within three or six months. It will be interesting to know whether you can resensitise a patient with chemotherapy and then re-introduce a PARP inhibitor.

Q: What would you add to a PARP inhibitor after progression? Maybe an antiangiogenic?

A: Without a doubt, the antiangiogenic combination with a PARP inhibitor is very encouraging. We only have results from one study, but they were very positive. Is there a rationale for combining a PARP inhibitor with immunotherapy? There probably is. We don't yet know whether or not BRCA mutated tumours are going to be the ones that are most sensitive to immunotherapy, but biologically there are some suggestions this could be possible, because they frequently demonstrate lymphocytic infiltration, are genomically unstable and may produce more neoantigens. Combining a PARP inhibitor with immunotherapy might enhance the antigenicity of a tumour; there might be a rationale for combining PARP inhibitors with immune checkpoint inhibitors.

Q: What about PD-L1 testing?

A: For now I wouldn't consider PD-L1 expression as a predictor of response in ovarian cancer.

Q: Can you comment on predictive markers for antiangiogenic therapy?

A: I don't think we have any. We keep searching for them and there has been a lot of work on circulating biomarkers, but they haven't given reproducible results. We may have biomarkers for the combinations but that's a different question.

Q: Thinking beyond ovarian cancer, endometrial cancer is increasing in incidence, it seems interesting to have results with PARP inhibitors in this tumour site?

A: Given the homology in the genomic profile of high-grade serous ovarian cancer, triple-negative breast cancer and serous endometrial cancer or certain grade 3 serous-like endometrial cancers, some endometrial cancers probably have HD deficiency and may respond to PARP inhibitors. We know that endometrial cancer can be associated with BRCA mutations. I think the next step will be to consider PARP inhibitors in the treatment of serous-like endometrial cancers.

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2005-2015 DECADE REPORT

GLOBAL STATUS OF mBC DECADE REPORT

A comprehensive, 10-year review examining the global landscape of advanced/ metastatic breast cancer (mBC)

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January 2016

Pfizer Oncology

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The JARC brings together thousands of players among 18 Member States and the European Commission. Health professionals, universities, public health institutions, cancer institutes, patients' associations, policy makers, have an aim to improve health outcomes and to decrease health inequalities for patients with rare cancers across Europe.

We work together to reach a consensus across borders and different professional groups, to bring together different areas of expertise, to share knowledge.

You are invited to see more at www.jointactionrarecancers.eu and transform this bold initiative into an outstanding success.

JARC
JOINT ACTION ON RARE CANCERS

Dissemination by School of Medicine, National and Kapodistrian University of Athens, Greece

The JARC is coordinated by the Fondazione IRCCS Istituto Nazionale dei Tumori of Milan (Italy)

This leaflet is part of the project / joint action '724161 / JARC' which has received funding from the European Union's Health Programme (2014-2020)

esso
THE EUROPEAN SOCIETY OF SURGICAL ONCOLOGY

Lynda Wyld – Chair of ESSO's Education and Training Committee, and President of the British Association for Surgical Oncology

Every cancer surgeon should be a specialist in surgical oncology

One of the main aims of our Society is to facilitate the training and education of surgical oncologists across Europe, so that a cancer patient can have the same expectation of excellent treatments, care and outcomes anywhere in the region.

ESSO has been working to achieve this in a number of ways, by raising the quality of the education provided in our area of expertise, which is critically important in the multidisciplinary management of cancers.

We currently provide up to 20 high-level courses and Masterclasses every year at various European locations. These cover a range of surgical disciplines, with a faculty that features world leaders in the field, showcasing advanced surgical techniques and multidisciplinary practice. Details of these courses can be found on the ESSO website (www.essoweb.org/courses).

ESSO's Education and Training committee offers a range of fellowships to support young trainees in our discipline, allowing them to visit centres of oncological excellence, within and outside Europe, and sponsoring their attendance at hands-on training workshops and high-level congresses, including ESSO's own congress, which features a strong educational programme.

Together with our sister organisation, the US Society for Surgical Oncology, we have also been working to develop a global curriculum for surgical oncology, aiming to create a robust workforce of highly-skilled surgical oncologists through applying uniform standards of training at the global level. Designed to serve as a template for the minimum knowledge that all surgical oncologists should possess, the outcome of this common effort was published jointly in the *European Journal of Surgical Oncology* and the *Annals of Surgical Oncology* in 2016.

We are also involved in two examinations, in collaboration with the European Union of Medical Specialists (UEMS) – the European Board of Surgery Qualification (EBSQ) exams in Breast Surgery and Surgical Oncology – both of which confer the official title of Fellow of the European Board of Surgery.

The Surgical Oncology exam is designed to test basic knowledge of oncology as well as high-level applied clinical decision-making, and is set at the level of a newly appointed consultant. This exam was first run in 2002, and the current ESSO President, Santiago González-Moreno, was one of its first Fellows.

The Breast Surgery exam, which is run jointly by ESSO, the European Society of Breast Cancer Specialists (EUSOMA) and the UEMS, also tests advanced competencies in the field.

ESSO has also been working in partnership with other organisations to provide advanced training in managing particularly challenging tumours, and helped initiate the European School of Peritoneal Surface Oncology, in collaboration with the Peritoneal Surface Oncology Group International and the European School of Soft Tissue Sarcoma Surgery, together with the Connective Tissue Oncology Society.

We hope by these means, alongside our yearly scientific conference, to help surgical oncologists achieve their full potential and help them to practise state-of-the-art surgical treatments.

We sincerely hope you will join us in our mission.

www.essoweb.org/education/

All.Can Changing cancer care together

All.Can is a multi-stakeholder initiative set up to engage policymakers on the need to improve the efficiency of cancer care, focusing on better outcomes for patients.

Why All.Can?
With the growing prevalence of cancer and ongoing pressures on limited healthcare budgets, we need to find new ways to make the most of the resources we have.

Waste must be challenged:

20% of healthcare spending is wasted on ineffective interventions

Waste is not just money, but time, quality of life, and missed opportunities for patients and their families

Efficiency ≠ cutting costs

...it's about continuously ensuring resources are focused on delivering what matters most to patients

Improving efficiency is about re-focusing resources on delivering what matters most to patients, and it requires a long term vision.

We need a longer-term vision which takes a whole system view of cancer care and is focused on four key areas:

1

Patient-relevant outcomes at the heart of cancer planning, delivery and evaluation

2

Investment in data to create a continuous cycle of improvement

3

Concrete mechanisms to create **accountability** across the entire care pathway

4

Political will to focus on better outcomes for patients

To learn more about All.Can and read our policy report, visit www.all-can.org

All.Can comprises leading representatives from patient organisations, policymakers, healthcare professionals, research and industry. All members contribute their time for free to the initiative, and all publications from the group reflect consensus of the members, who hold full editorial control. The All.Can initiative is made possible with financial support from Bristol-Myers Squibb (lead sponsor), Amgen and MSD (co-sponsors).

Do I refer this patient on?

European family doctors swap notes on how they decide who should be tested for cancer

Symptomatic cancers are diagnosed quicker in some countries than others. A group of European primary care physicians recently set out to discover why this is, by gathering information about the different factors that influence decision-making. **Janet Fricker** talked to one of them, to find out what they learned.

For the great majority of cancers, diagnosing early is the single most important factor in determining whether the patient survives, and does so with a good quality of life. It might be seen as somewhat surprising, therefore, that more effort has not been put into learning how to configure primary healthcare systems in a way most likely to facilitate early diagnosis.

Important new information that could throw a light on this topic is now beginning to make its way into the literature thanks to the determined efforts of Michael Harris, a now-retired English primary care physician (PCP), together with a group of European colleagues.

Harris remembers that his 'Road-to-Damascus' moment occurred in 2011 when reading a paper in the *British Journal of General Practice*. The study, by Peter Vedsted and Frede Olesen from Aarhus University, Denmark, suggested that European countries with strong primary care gatekeeping systems had much poorer one-year relative cancer survival than countries with weaker gatekeeping systems (*Br J Gen Pract* 2011, 61:512–3).

Gatekeeping is about controlling referral to specialist services, and the results showed that, for the 12 countries with gatekeeping roles for PCPs, the one-year relative cancer survival was 67.8%, compared with 73.4% for the seven countries that did not have gatekeeping (P= 0.004).

The study used data taken from the EUROCARE-5 study, which had demonstrated wide disparities in one-year cancer survival rates across Europe, ranging from 81.1% in Sweden to 58.2% in Bulgaria.

"For me the publication really struck home, because up until that point I had been telling my European colleagues how marvellous the UK gatekeeping system was," said Harris, who at the time was a PCP in Bath, England, with a visiting academic post in Bern, Switzerland, advising on PCP training.

Gatekeepers, typically PCPs, are the doctor of first contact for patients, coordinating the care of their patients and controlling their access to secondary care.

What had particularly appealed to Harris about the gatekeeping system was that it helped prevent over-investigation of patients, and identified

The Swedish system

"In Sweden, although the primary care practitioner (PCP) has no formal gatekeeping role, two-thirds of cancer patients present first to general practice. The Swedish system allows patients to write their own referral letters directly to the hospital, although of course such patients will not be prioritised for appointments.

"The reality of the Swedish system is, perhaps, that the gatekeeping role is undertaken by the practice nurse, who 'triages' which patients should be seen by the PCP. This can lead to delays of a few days before patients are able to get an appointment with their PCP.

"Swedish PCPs don't use any cut-off values for deciding who to refer for cancer testing, and can directly arrange their own tests, including CT and MRI scans, without going through the hospital.

"Despite Sweden's cancer survival rates being among the highest in the world, long waiting times still exist. In 2015 the Swedish government started a new national programme to standardise cancer care pathways, with the aim of reducing waiting times, increasing patient satisfaction and reducing regional inequalities. Once cancer is suspected, the PCP can tick a box on a form that directs patients along up to 20 different 'standard care pathways'.

"The biggest bottleneck for cancer diagnosis is in pathology departments"

"Maximum waiting times are specified for every step along these pathways, from specialist appointments, to each pre-treatment diagnostic procedure, the pathological and other analysis and multidisciplinary team meetings. The idea is that providers should stick to each 'time slot', creating 'time-bound' clinical guidelines.

"In Sweden, the biggest bottleneck for cancer diagnosis is in pathology departments, where tissue specimens are processed for histopathological analysis for all cancers, to help plan treatment."

Hans Thulesius, Associate Professor of Family Medicine, Lund University, Malmö, Sweden

the most appropriate management and specialist care – and in doing so controlled healthcare costs. "I was shocked to discover that, while the gatekeeping system may well ensure optimal care for most patients, it appears to work badly for patients whose symptoms are due to cancer," said Harris, who now undertakes primary care research at the University of Bath.

The need for action was further brought home to him when he saw that more than 6,000 premature deaths from cancer – i.e. 6–7% of cancer-related mortality – would have been avoided each year, if Britain had achieved the mean survival rate in Europe.

For Harris, the Vedsted and Olesen study was a 'call to arms' to undertake research to see how different healthcare structures in countries across Europe impact on timeliness of cancer diagnosis. He decided to enlist collaborative help from European partners, which he did by 'googling' for primary care researchers exploring cancer disparities.

There were clear differences between where PCPs do diagnostic investigations, such as ultrasound, and where access is solely by referral

In 2012 Harris secured an EU grant of €11,000 to run an exploratory three-day workshop with 18 colleagues from 12 different European countries. From the workshop, which was hosted at Örenäs Castle, Sweden, they established the Örenäs Research Group, with the remit to investigate how health system factors affect the timeliness of cancer diagnosis in primary care.

Achieving more timely cancer diagnoses in primary care poses considerable challenges, said Harris, as PCPs only see a small number of new cancers each year, and half of patients with malignancies present with evolving and undifferentiated symptoms

that can be interpreted as something other than cancer.

At another Örenäs workshop, held in 2014, eight PCP researchers from six European countries came together

How easy it is to telephone or email a specialist for informal discussion and advice was key

to identify system-related and other non-clinical factors that could affect a PCP's decision-making when faced with a patient who might have cancer. The workshop identified 50 different system factors that could have an effect (*J Cancer Res Ther* 2016, 4:7–10).

Notably, the group highlighted clear differences in decision-making between systems that have some special investigations done by PCPs themselves, for instance diagnostic ultrasound, and those that have access to them solely by referral. When investigations are undertaken by PCPs "the investigation is facilitated because it is seen as a quick, easy, and possibly income-generating way of making (or ruling out) a sinister diagnosis."

The Örenäs group also found that relationships with specialist colleagues, including how easy it is to telephone or email a specialist for informal discussion and advice, was key. Systems where the PCP is prevented from referring to a named specialist – which is the case in countries such as Croatia, Slovenia, Spain and the UK – may have an inhibitory effect on referrals, the group suggested.

The intensity of PCP workload was also seen as an important factor, with high workloads potentially making PCPs more likely to refer, in an attempt to reduce follow-up appointments. However, if there is an expectation that the PCP will write detailed referral letters (as in the UK), the time taken to do this may discourage the PCP from making that referral.

"Overall, the workshop gave us an awareness of the range of factors that may influence how PCPs act on concerns that cancer may be present, and it helped us to highlight future studies," said Harris.

Next, came the 'vignettes' study, with the Örenäs group aiming to find out where patients with possible cancer

The Dutch system

"In The Netherlands we have a really strict gatekeeping system, where the primary care physician (PCP) decides who should be referred to secondary care. The PCP does not use risk-assessment tools, but instead uses guidelines developed by the Dutch College of General Practice. Overall, we have 110 guidelines on different clinical areas that flag alarm symptoms known to indicate an increased risk of cancer.

"I would like a model where a number of PCP practices come together to form community diagnostic centres"

"PCPs feel real ownership of these guidelines, because they know that they were written by PCP colleagues, and were not just imposed upon them.

"An important aspect of the Dutch system is that PCPs have really good personal communications with their secondary care colleagues. If I suspect cancer in a patient, I will pick up the phone to my specialist colleagues and ask them to see the patient within a week.

"In The Netherlands we have a system of practice assistants, who answer the telephones and triage how quickly patients should see the PCP. The practice assistant has the flexibility to book longer appointments if they feel this will be necessary. In some areas PCPs can order MRI scans, colonoscopies, or other imaging tests directly, but this is by no means universal.

"The patients who concern me most are those with 'low risk', but not 'no risk' symptoms, who can get lost in the system. I would like to see a new model where a number of PCP practices come together to form community diagnostic centres. Such centres would give PCPs easy access to all testing, and allow consultants to hold regular sessions to advise on results. People considered to be at high risk of cancer would still go directly to the hospital."

Niek de Wit, Professor of General Practice at the University of Utrecht, The Netherlands

The Spanish system

"Primary care practitioners (PCPs) in Spain use their clinical judgement to decide when to refer patients for cancer testing, and don't use tables for determining risk. No guidelines are available systematically across all regions to say how quickly patients with suspected cancer should be seen."

"Several years ago there was an initiative to develop fast-track pathways for breast and colon cancer, where patients were expected to be seen within 15 days. The system was abandoned, however, due to lack of funding.

"Much of the current variability in waiting times for cancer diagnosis in Spain is due to hospitals rather than PCPs, as most of the tests and diagnostic imaging are done in hospitals. There are also delays for outpatient appointments.

"The thing that works well in the Spanish system is that PCPs are very available, and keep free appointments during the day for emergency consultations. But to arrange for most cancer tests, PCPs then need to go through hospitals, and this is where the delays come in. "It helps when the PCP knows the hospital specialists personally and can pick up the phone to flag up that it is important to see the patient urgently. Otherwise, it is common for hospital clerks (who are not medically qualified) to undertake the medical triage, and decide how quickly patients should be seen. Sometimes PCPs refer patients to emergency services to get around waiting lists.

> "Sometimes PCPs refer patients to emergency services to get around waiting lists"

There are multiple delays in the Spanish cancer diagnosis system, but this is not completely reflected in our cancer survival statistics, which are comparatively good compared to other countries in Europe. It seems that we manage to compensate by giving our patients good access to treatment once diagnosed."

Magdalena Esteva, primary care researcher, from Mallorca, Spain

symptoms would be most likely to make initial contact with the health service in different European countries, and how this correlated with national one-year relative cancer survival (*Scand J Primary Health Care* 2017, 35:1–8).

For the study, 78 PCPs from 14 countries were given 'vignettes' of a symptomatic patient with possible lung cancer, one with possible ovarian cancer, another patient with possible breast cancer, and one with possible colorectal cancer.

In contrast to Vedsted and Olesen's findings, the Örenäs analysis found no significant correlation between overall national one-year relative cancer survival rates and the probability of initial presentation to a PCP (r= –0.16, 95%CI = –0.39 to 0.08). There was, however, poorer lung cancer survival in countries where patients were more likely to initially present to a PCP (r= –0.57, 95%CI = –0.83 to –0.12). "Our hypothesis was that most primary care doctors don't have in-house access to radiology, so if people see a specialist first they may be more likely to get an immediate chest X-ray," said Harris.

Next, Örenäs members delved more deeply into the 50 system factors that had been identified in the exploratory workshop as affecting decision-making by PCPs in relation to patients who may have cancer. After a pilot study had identified the 20 factors that varied most across Europe, 2,086 PCPs from 20 European countries took part in an online survey using a Likert scale (with answers ranging from 'strongly disagree' to 'strongly agree'), to rate how each of those factors influenced their referral decisions for the four clinical vignettes.

Such European surveys are laborious, explained Harris, as they involve collaborators translating questionnaires into each local language, with linguistic validation undertaken by independent 'back-translation' into English, to identify and then correct any important differences from the original.

From the results, a statistical 'exploratory factor analysis' identified that five factors between them explained half the variation in the survey responses:

- Ability to refer (this factor was about barriers to specialist referral),
- Patient access (financial and geographical barriers to healthcare),
- Pressure on the PCP from outside (workload, demands from patient,

The UK system

"In the UK most patients with cancer present first to primary care, with no direct access to specialists, although a proportion of them are so ill that they take themselves to A&E.

"In 2015 the National Institute for Health and Care Excellence (NICE) developed a cancer risk threshold of 3% (calculated from tables based on the patient's symptoms) for entry into a fast-track scheme where patients would be seen by consultants in two weeks.

"The cut-off value of 3% was a complex judgement that took into account the needs of patients and the risks of over-investigation. Children are deemed to be a special case, although no special cut-offs were specified for them.

"In the UK, when deciding who to refer outside of the fast-track system, PCPs can use these risk assessment tools to alert them to the possibility of cancer, and then add in their own clinical judgement. Medical delays most commonly occur for patients with low-risk symptoms, where the PCP initially decides against investigation, only to refer later for testing, when the situation is unresolved or has worsened.

"Oddly, the people who tend to do worst in the UK system are those with conditions other than cancer, since the system deprioritises them once cancer is ruled out.

> "Expanding access to cancer testing remains key for improving cancer survival in the UK"

"PCPs in the UK increasingly have direct access to testing such brain scans, CT scans, endoscopy and blood tests. The CanTest programme, funded by Cancer Research UK, is looking into how this can be expanded. Expanding access to cancer testing remains key for improving cancer survival in the UK."

Willie Hamilton, Professor of Primary Care Diagnostics at University of Exeter, UK

public or health system),

- Role of the PCP (level of expectations of PCP-centred care), and
- Quality versus cost (influence of financial aspects on decision-making by PCPs).

The results, presented at the 2017 European General Practitioner Research Network (EGPRN) meeting in Riga, Latvia, in May, revealed positive correlations between better one-year relative cancer survival and systems that focus on quality rather than cost (r=0.65) and lower barriers to specialist referral (r=0.46), and a negative association between one-year relative cancer survival and systems in which there is higher pressure on primary care (r= –0.40).

However, further analysis showed that these factors varied according to national healthcare spend per capita. For those European countries in the highest national healthcare spend tercile (Denmark, France, Germany, the Netherlands, Norway, Sweden and Switzerland), better national cancer survival was associated with closer relationships between PCPs and specialists, and less of a gatekeeping role and less pressure on primary care.

For countries in the middle tercile for per capita healthcare spend (Finland, Italy, Portugal, Slovenia, Spain and the United Kingdom), better national cancer survival was also associated with less of a PCP-as-gatekeeper role and with less pressure on primary care, but also with a higher likelihood of PCPs organising investigations at the initial consultation.

Conversely, for the lowest tercile (Bulgaria, Poland and Croatia), better national cancer survival was associated with being more PCP-centred: more active PCP involvement in referral decision-making, with less easy access to specialists.

"These data suggest that how system factors affect PCP decision-making varies according to the level of national per capita healthcare spend. It seems that poorer countries have better cancer survival when GPs [PCPs] have stronger decision-making roles, but in wealthier countries the opposite is true," said Harris.

The Örenäs Research Group now plans a health systems analysis, so that it can explore in more detail how each European country's health system affects cancer survival. It also plans qualitative work to compare decision-making in different European countries by PCPs when faced with patients who could have cancer.

Why is specialist cancer nursing important? Because quality matters

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

How do I get quality when I want plans for a new building? I go to a qualified and registered architect, confident that their education and training is regulated at a national and EU level. How do I get quality if I have a dental problem? I go to a qualified and registered dentist, knowing again that there is EU agreement on the education and training required by all who use that title.

Of course, in reality, few of us really think about these matters. Somehow citizens just *know* these professions are well regulated. The details of *how* need not concern us – unless a problem arises.

As a medic myself, I am happy to belong to a professional group that has resolved its major questions of regulation and education. Our common medical education pathway at undergraduate level opens into the full variety of medical specialties, including those within the ECCO umbrella, such as surgery, radiotherapy, medical oncology and many others.

However, not all of my health professional colleagues have yet gained the regulatory pathway towards specialisation that their skills and contribution to treating patients call for. Among them are our crucial caregivers: the specialist cancer nurses.

The need for specialisation in cancer nursing has arisen to address requirements such as coordinating care and providing patients with information that is specific to their condition. Different countries have responded with their own forms of specialist cancer nursing education and certification, in much the same way as happened for medicine and other professions and specialties before international coordination efforts were made.

So this is the situation that cancer nursing in Europe now faces: there are fantastic developments in some countries, but a lack of uniform approach impedes the spread of specialist cancer nursing across Europe.

ECCO is the voice of multidisciplinarity across the cancer continuum in Europe. Therefore, without hesitation we are fully supporting the Recognising European Cancer Nursing (RECaN) project, set up to increase recognition of the value of oncology nursing. With the input of our members and Patient Advisory Committee, ECCO recently published a consensus position statement highlighting the evidence for specialist cancer nursing and the need for their presence in the care pathway (bit.ly/ECCO-specialist-nurses).

Yet, all the while, we have the perversity of an EU not only making noises about downsizing its health ambitions, but also promoting a professional deregulation agenda, including in the safety-critical area of healthcare (see also my ECCO comment, *Cancer World* 78, May 2017).

These factors make the coming together of cancer professionals in common cause for oncology nursing very important.

Nobody wants to turn the clock back on the achievement of EU-level regulation of the medical profession and its specialisms. Achieving the RECaN goals of European coordination of specialist cancer nursing would never be regretted either. ECCO's latest position statement for cancer nursing is a powerful message. It is not just cancer nurses wanting a European approach to their specialty, it is also their fellow healthcare professionals, and the patients they serve so well – two groups who know best of all what cancer nurses have to offer.

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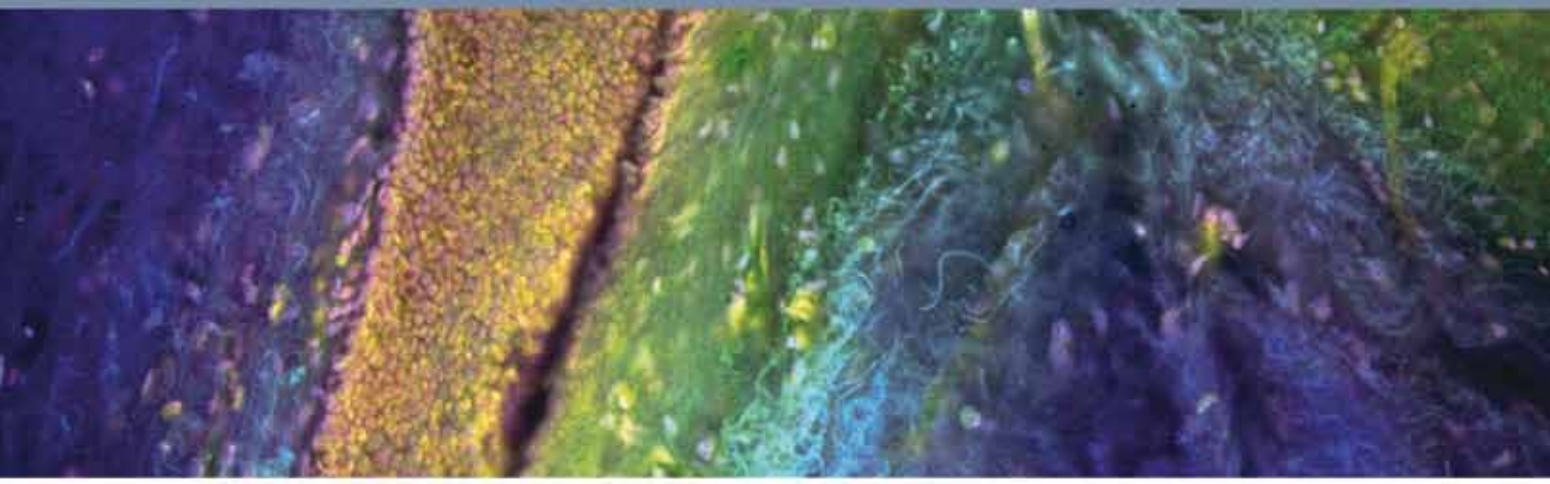

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Improving early diagnosis of symptomatic cancer

Focusing on the UK situation, **Willie Hamilton** and colleagues investigate *why* speeding up diagnosis of symptomatic cancers may be important, *how* to achieve it, *who* to focus on and *where*, and finally *how much* such strategies could cost/save in economic terms.

This is an abridged version of Willie Hamilton et al. (2016) Improving early diagnosis of symptomatic cancer. ***Nat Rev Clin Oncol*** *13: 740–749, doi:10.1038/nrclinonc.2016.109. It was edited by Janet Fricker and is published with permission* © *Macmillan Publishers Ltd.*

nature REVIEWS CLINICAL ONCOLOGY

In all developed countries, much time, effort and finance is spent on cancer diagnosis, on the expectation that this approach brings clinical benefits. Before reviewing the evidence regarding how the diagnosis of symptomatic cancer can be improved, it is important to look at why the diagnosis of symptomatic cancer is necessary and should be improved. Only by being explicit about what we are hoping to achieve can we design services to meet our needs optimally.

Benefits of more rapid diagnosis

Types of evidence

Few randomised controlled trials have investigated whether speeding up symptomatic cancer diagnosis improves patient outcomes, as it is hard to get ethical approval for trials where one group has delayed diagnosis. Trials comparing different diagnostic modalities have, however, been performed. The SIGGAR trial, for instance, compared the effectiveness of CT colonography versus colonoscopy for colorectal cancer symptoms (*Lancet* 2013, 381:1194–202).

An alternative has been to perform trials of cancer diagnostics (promoting earlier presentation of potential symptoms) in community care settings. Examples include computerised decision-support tools in primary care cancer diagnosis (*Trials* 2016, 17:184) and lower symptomatic thresholds for urgent chest radiography (*Trials* 2013, 14:405). However, no trial has included sufficiently large cohorts

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to address whether speeding up cancer diagnosis in primary care benefits mortality or morbidity.

Survival and diagnostic activity

Survival benefit provides the main rationale for speeding up cancer diagnosis. Among European countries with a higher income, the UK and Denmark regularly appear at the bottom of tables ranking cancer survival (*Lancet Oncol* 2013, 15: 23–34). Poorer outcomes relative to countries at a similar level of economic development are considered to arise from differences in availability of, and willingness to use, cancer diagnostic investigations, augmented by English patients being less willing to seek medical care. One study reported inverse relationships between cancer survival and degrees of separation of primary care from specialist care, where specialist care requires referral from primary care (*Br J Gen Pract* 2011, 61:512–13). The association could be accounted for by unwillingness of 'gatekeeper' GPs to test for cancer when risks are small [see also 'Should I refer this patient? p 44]. An 'international vignette study' asking GPs from 12 different geographical areas across three continents about fictitious patients revealed highly significant relationships between willingness to investigate cancer and national cancer survival ($P<0.05$ for four of five scenarios tested; *BMJ Open* 2015, 5:e007212).

An English study showed that patients undergoing upper gastrointestinal endoscopy at general practices that ranked in the top third for endoscopy rates had better overall survival ($P<0.001$) and fewer emergency admissions ($P<0.001$) than patients who were investigated at general practices ranking in the bottom third (*Gut* 2014, 63:250–61).

Considerable variations exist in use of cancer diagnostics in the UK. For example, in 2012–13, a 3.6-fold difference in CT use was observed between primary care trusts with the highest and those with the lowest CT use. Disparities also exist in terms of referral, with a three-fold difference between practices in the lowest and highest deciles for referral rate. In an English study (including 8,049 practices with 215,284 patients) cancer patients from general practices with lowest use of urgent cancer referral pathways showed excess mortality compared with intermediate use (HR=1.07; *BMJ* 2015, 351:h5102).

Findings from observational studies support the hypothesis that increased use of cancer diagnostics improves survival. This underpins the recommendation made by England's Independent Cancer Taskforce that, by 2020, 95% of GP referrals for cancer testing should receive a definitive investigation and results within four weeks. Nevertheless, patients with one of six common cancers offered initial primary care diagnostic testing had a median time to referral of 16 days compared to zero days for those not offered primary care investigations (*Br J Cancer* 2015, 112:676–87). If suspected cancer investigations are used by GPs, diagnostic services need to be more responsive.

Time to diagnosis and survival

Time to diagnosis incorporates three elements: patient interval (beginning when bodily change is detected); primary care interval (beginning at first presentation to primary care); and secondary care interval (beginning with specialist referral). The diagnostic interval is the sum of the last two elements.

In a landmark systematic review of 87 breast cancer studies, clear relationships for worse survival were found for patients with delays of three months or more compared to shorter delays (OR=1.47; *Lancet* 1999, 353:2155–62).

For colorectal cancer, diagnostic interval and survival studies reveal J-shaped curves. In patients presenting with symptoms suggestive of cancer or any other serious illness, the risk of dying within three years decreased with diagnostic intervals up to five weeks and then increased (*Br J Cancer* 2011, 104:934–40). The explanation suggested for the poorer survival among patients diagnosed very rapidly is that these patients will be the ones who present with the most aggressive disease with obvious symptoms, or who present as emergencies.

Morbidity and time to diagnosis

Reduced morbidity and improved symptom relief are possible benefits for quicker diagnosis. A study of 263 patients in Denmark showed significant associations between reported psychological distress and time to diagnosis ($P<0.005$; *Anticancer Res* 1996, 16:995–99). Another study among patients with colorectal cancer found no association between symptom duration and satisfaction with care (*Can Fam Physician* 2012, 58:e495–e501). A third study, in endometrial and ovarian cancer, revealed that total diagnostic intervals negatively correlate with quality of life (*Qual Life Res* 2012, 21:1519–25).

Separating distress of diagnosis from additional anxiety from diagnostic delays is difficult. Initial distress resulting from the discovery of a symptom of breast cancer (measured on an emotional distress scale) negatively correlates with delays in presentation to healthcare systems ($P=0.01$; *Prev Med* 2003, 36:374–8). Associations may be

complicated by a tendency for clinicians to investigate patients with anxiety or depression less rapidly.

Achieving quicker diagnosis

Pre-presentation factors

For most cancers, the time between first detection of potential symptoms by the patient and subsequent presentation to healthcare systems represents the greatest proportion of total time to diagnosis (*Br J Cancer* 2005, 92:1959–70). One study showed patients with oropharyngeal and oesophageal cancers were most likely to present 15 days or more after noticing an initial symptom, while another showed patients with prostate and rectal cancer were most likely to delay consultations by three months or more.

To speed up diagnosis, it is essential to understand how patients recognise possible symptoms and the decisions they make regarding seeking help. Symptom appraisal and help-seeking are influenced by psychosocial and cultural contexts, including fear of stigma, cancer diagnosis and treatment, and a belief in fatalism, as well as practical barriers to help seeking, such as a lack of access to health care, and sufficient time / transport to attend consultations.

Symptom awareness campaigns

Public campaigns raising symptom awareness might educate and empower people to hasten earlier presentation (*Br J Cancer* 2009, 101:S31–9). For example, between 2011 and 2012, Public Health England's 'Be Clear on Cancer' campaigns increased attendance for lung cancer symptoms by 29% and bowel [colorectal] cancer symptoms by 63%. Notably, the percentage of lung cancers diagnosed at stage I (amenable to surgical resection) rose from 14.1% before the campaign to 17.3% after ($P<0.001$).

Cancer awareness campaigns need to address the health literacy level of their target audience, with lower health literacy strongly associated with disadvantaged socioeconomic and ethnic minority groups (*BMC Health Serv Res* 2008, 8:49).

Few studies of interventions specifically targeting individuals at increased risk of cancer have been conducted. However, a Scottish study on people at high risk of lung cancer (smokers and former smokers) provides preliminary evidence of altered consulting patterns following a single nurse consultation and provision of a symptom self-help manual (*Br J Gen Pract* 2013, 63:e47–54).

In primary care

In most countries, symptomatic patients initially present to primary care, although some healthcare systems allow direct access to specialists. Clinicians must first think of cancer as a possibility and then decide whether testing is required. Some cancers are difficult to suspect, particularly when symptoms share common features with benign conditions. For example, although backache is the most frequent symptom of myeloma, only one in 1,000 adults reporting backache will turn out to have myeloma (*Br J Gen Pract* 2015, 65:e106–13). Such 'difficult to diagnose' cancers are characterised by three or more primary care visits before diagnosis. Consulting with the same clinician in the practice has only a very small effect on the rapidity of cancer diagnosis (*Br J Gen Pract* 2014, 65:e305–12).

Clinical decision support

Insights into the epidemiology of primary care cancer symptoms, including estimates of positive predictive value, have enabled development of risk assessment tools predicting likelihood of cancer. Systematic reviews have indicated that clinical decision support improves physician performance and ordering of diagnostic tests.

The first evaluation of a risk assessment tool for patients with suspected lung or colorectal cancers found use increased two-week referral rates by 31% for lung cancer and 26% for colorectal cancers; and increased chest radiography by 4% and colonoscopy by 15%. It also resulted in increased cancer diagnoses by 37% for lung cancer and 76% for colorectal cancer (*Br J Gen Pract* 2013, 63:e30–6).

Risk algorithms include electronic tools interacting with patients' individual clinical records, which involve doctors entering symptoms and calculating risk, with prompts to consider a cancer diagnosis when the combined features add up to a 2% or greater cancer risk. In an evaluation involving more than 500 UK general practices, use of tools increased urgent referrals by 19%. No studies have examined diagnostic utility of clinical judgement compared with evidence-based tools, although 2015 guidance from NICE [England's National Institute for Health and Care Excellence] allows clinicians to override recommendations from decision support tools when there are good reasons

to do so. More sophisticated artificial intelligence systems are currently in development and may be implemented in routine practice in the next few years (*Br J Cancer* 2015, 113:1645–50). In the latest revision of NICE guidance for suspected cancer, tools were not made the subject of recommendations as they had not been sufficiently studied.

Policy-driven initiatives

Early national intervention strategies designed to improve cancer outcomes prioritised treatment advances. By the early 2000s, however, some jurisdictions were seeking to speed up referrals of patients with high-risk symptoms, with the UK setting a two-week time frame.

The responsibility for cancer diagnosis could be extended beyond general practice to other providers of primary care, such as dentists and opticians, who identify oral and uveal cancers. At present, outside pilot studies, pharmacists have no access to diagnostic testing, and often have to refer symptomatic patients to GPs.

Patient and population aspects

Many cancer risk factors have been identified, but arguably risk factors other than age, sex and smoking should only be used in the selection of patients for screening, not for clinical assessment of symptomatic patients. Patients from ethnic minorities generally have worse cancer survival than prevalent majorities, but also experience more diagnostic delay (*BMC Fam Pract* 2013, 14:197).

NICE guidance on patient selection

In 2015 NICE guidance on selecting patients for cancer investigations was based on a cancer risk threshold of 3% or more, also allowing investigation for risks of less than 3% for children (who experience survival benefits long-term) and for widely available primary care tests, such as PSA testing. The decision to use a cancer risk threshold and the specific cut-off for referral were both contentious.

Alternatives include giving priority to cancers known to result in better patient outcomes from faster diagnosis and availability of diagnostic resources.

The decision to use positive predictive values (PPVs) for symptomatic cancer derived from primary care populations, as thresholds bring equity across cancers, and can be numerically integrated into general practice software, enabling automated calculations of risk based on symptoms.

PPVs derived from primary care, however, differ from those derived from referred populations, due to referral creating populations with substantially higher disease prevalence, which has led some specialists to express concerns that the recommendations fail to match their personal experience of cancer symptomatology (*Lancet* 2002, 360:2080).

Thresholds for cancer investigation

The final decision by NICE to recommend urgent investigation once cancer risk was 3% or more was a compromise between liberalisation of previous guidance and recognition that many people would opt for investigations on the basis of a risk as low as 1% (*Lancet Oncol* 2014, 15:232–40). Liberalisation to a 3% threshold should theoretically lead to expansion in testing. Between 2006 and 2015, imaging activity increased at 5.7% per year, and the number of urgent referrals made under the National Health Service's (NHS's) 'two-week wait' system passed one million referrals in 2012. At the same time as attempts have been made to speed up NHS cancer diagnosis, cancer survival in the UK has improved, narrowing the gap with other European countries (*Br J Cancer* 2015, 113:848–60).

Internationally, new referral pathways have been developed to support guidelines, enabling rapid assessment of patients with symptoms of concern. In the UK, Australia and Canada, patients referred using these pathways are seen by specialists within 14 days, while in Denmark patients are seen within four working days (*Health Policy*, 2012, 105:65–70).

Referral pathways have been criticised for restricting use to patients with specific – generally high-risk – symptoms (*Br J Cancer* 2014, 110:584–92), excluding around one-half of symptomatic patients. Consequently, in 2013 only 34% of all cancers in England were diagnosed as a result of referral pathways, resulting in recognition of a need for development of rapid assessment models for patients with less-specific or lower-risk symptoms (*Br J Cancer* 2015, 112: S65–9).

Influence of diagnostic programmes

Any symptom investigation programme, as well as identifying patients with non-malignant conditions, will also identify patients in whom the cancer was causing symptoms as well as patients with comorbidities where cancer was an unrelated finding (e.g. people with chronic obstructive pulmonary disease are at higher risk of lung cancer from past or current smoking).

Overdiagnosis

Overdiagnosis describes diagnosis in an asymptomatic person that does not result in a net benefit. While overdiagnosis is of more concern with screening programmes, expansion of diagnostic activity means there is also a possibility with symptomatic cancer.

Currently, thyroid cancer, prostate cancer, and melanoma are the most likely to be overdiagnosed – e.g. thyroid cancer incidence rose 15-fold between 1993 and 2011 in South Korea, with no change in mortality observed (*NEJM* 2014, 371:1765–7). While evidence is limited, the authors suspect risks of overdiagnosis from expediting symptomatic diagnosis are small relative to possible benefits.

Health economics

Health economic analyses of costs versus benefits of expedited cancer diagnosis in symptomatic patients are less advanced than analyses of cancer screening performance. Diagnostic costs should include costs of negative results.

Comparisons of alternative diagnostic strategy costs are possible, with 2015 NICE guidance finding that faecal occult blood testing was the most effective approach for colorectal cancer (NICE 2015, http://www.nice.org.uk/guidance/NG12).

Data on cancer investigation performance in primary care populations, however, are rarely available, with little known about adverse events.

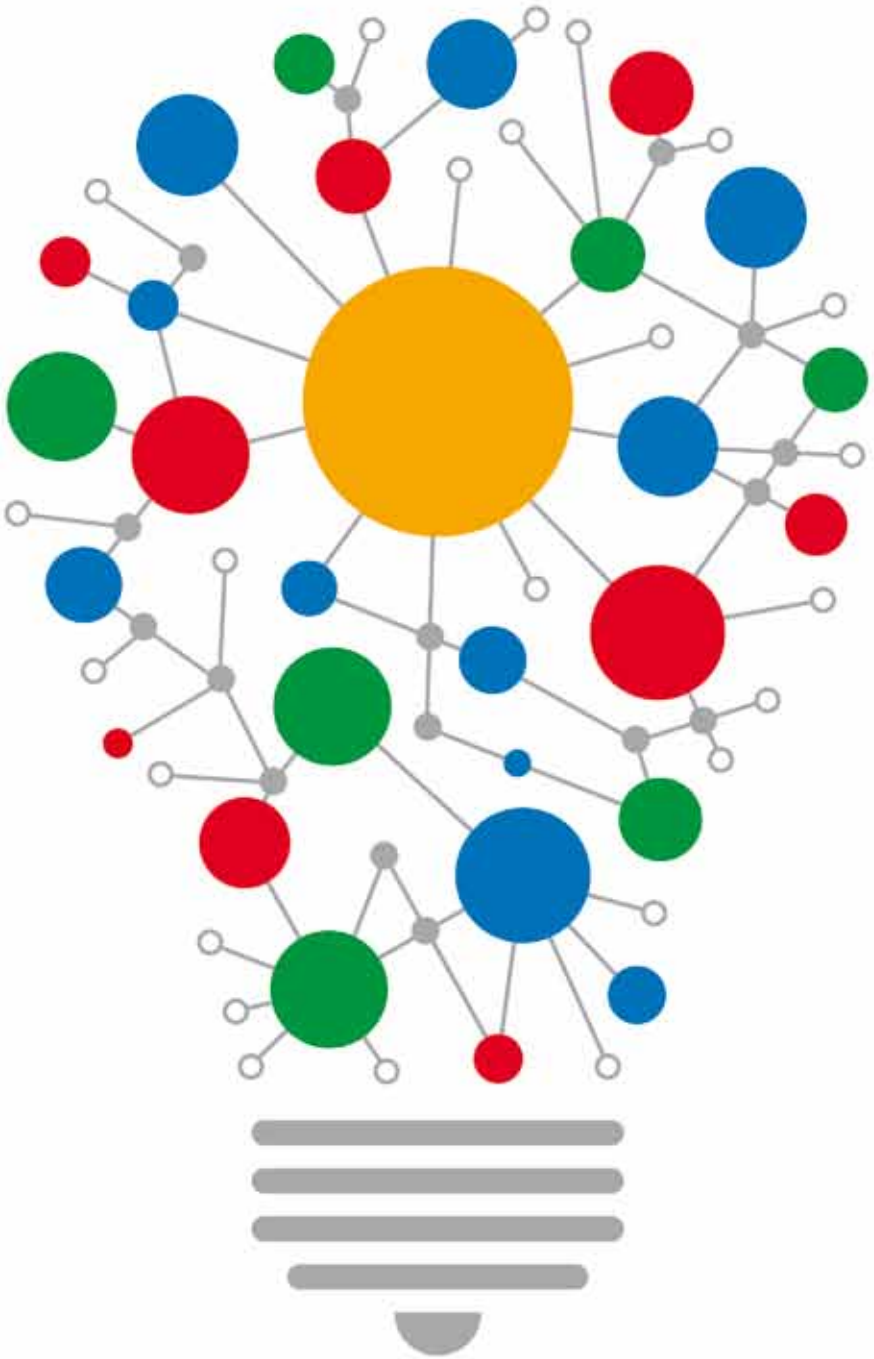
Estimating the benefits of more rapid cancer diagnosis is more difficult than estimating the costs of implementing such strategies. Establishing costs of treatment for various stages of cancer would be possible, with less advanced cancers cheaper to treat. Reporting stage shifts (if any) following cancer awareness campaigns would allow more informative health economic analysis.

Conclusions

In the UK, times to cancer diagnoses have fallen, as has the proportion of patients presenting with cancer as an emergency. Such progress is almost certainly a sign of improved diagnostics and have happened contemporaneously with liberalisation of the criteria for cancer investigation coupled with better identification of individuals most at risk. However, we do not yet know whether such attempts at early diagnosis are cost effective.

Key points

- Very few randomised controlled trials have investigated whether speeding up the diagnosis of symptomatic cancer improves the outcomes of patients; however, observational evidence is indicative of clinical benefit for some patients.
- Awareness campaigns often prompt earlier presentation of patients with cancer to the healthcare system, although the long-term effect of this earlier presentation is largely unknown.
- Rapid access to specialist expertise, coupled with national guidance for selection of patients for investigation of possible cancer – and, subsequently, clinical decision support – might result in shorter times to diagnosis.
- The UK National Institute of Health and Care Excellence recommend an explicit risk threshold of 3% for investigation of cancer in symptomatic patients; this liberalisation will influence the spectrum of patients seen by specialists.
- The cost-effectiveness of initiatives to speed up diagnosis of symptomatic cancer is markedly under-researched.



Thousands of researchers are collaborating together around the world. When it comes to generating ideas to help cancer patients, the lights are always on.

LET'S COLLABORATE
ONCOLOGY FROM BOEHRINGER INGELHEIM

Boehringer Ingelheim

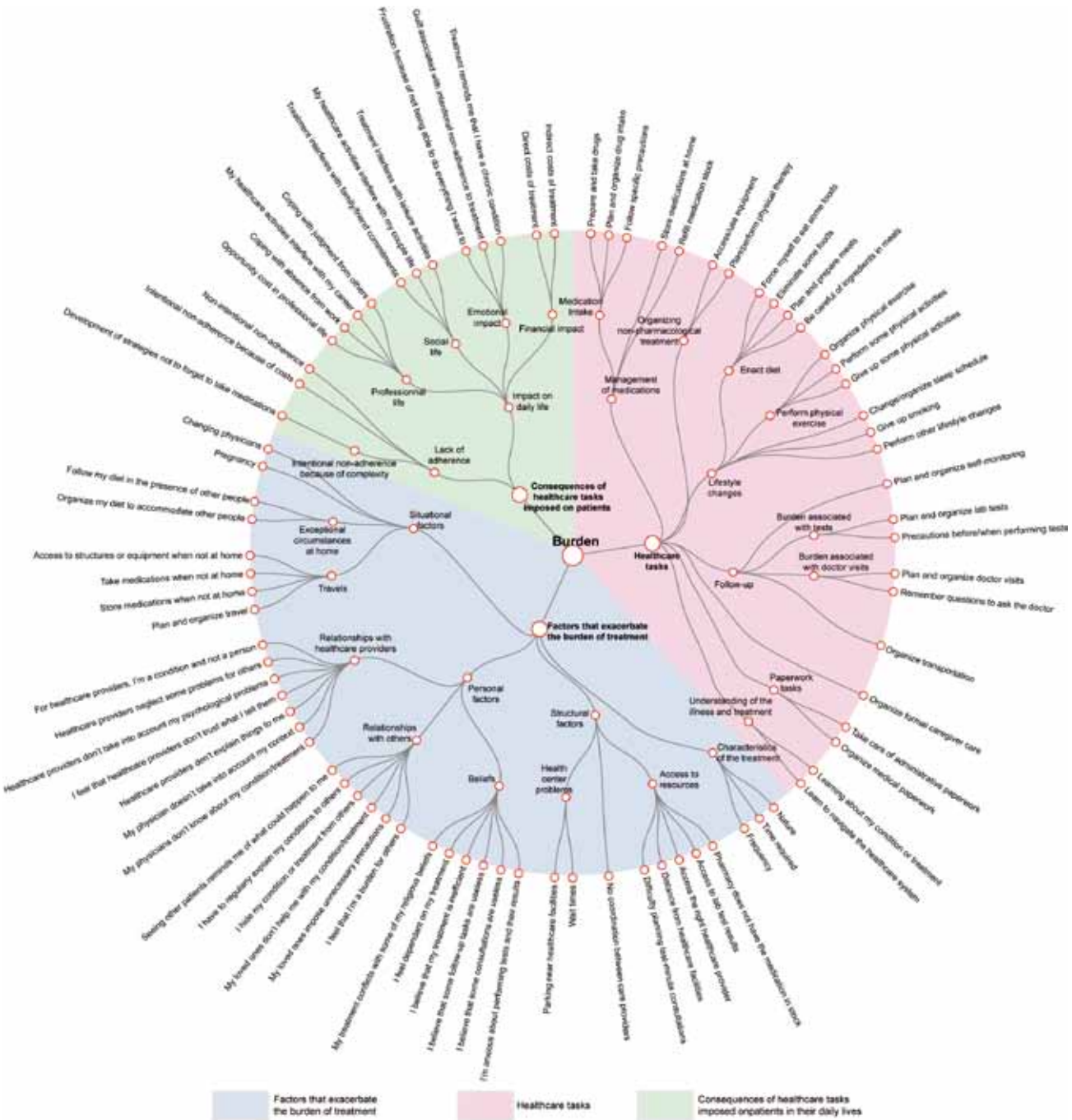
Does being a patient have to be a full-time job?

Most doctors believe in holistic care, yet the clinical guidelines they use, and the way they discuss and deliver care, rarely take into account the demands that a given treatment option will make on the patient and their daily life. **Anna Wagstaff** reports on calls for this to change. Additional reporting by **Peter McIntyre**.

A patient with advanced melanoma on clinical trials and a standard plan occupies roughly 50 hours a year of health professional time spread across all the multidisciplinary teams responsible for their care. That same patient, if they are fully adherent and engaged, will spend around 900 hours of their own time doing the best they can to support their own health and give their treatment the best chance of success.

These calculations were drawn up by Gilly Spurrier, who has become a bit of an expert in what it takes to be a 'successful patient' since her husband was diagnosed with advanced melanoma in 2010. For the past eight years, she has taken on organising every possible aspect of her husband's life as patient, to free him up to focus on his 'real' life.

Taxonomy of the burden of treatment



This figure shows the results of a survey about the burden of treatment which was completed by of 1,053 patients with a variety of chronic diseases. The survey was available in English, French and Spanish, and was conducted, as part of an effort to promote a minimally disruptive approach to healthcare.

Source: V-T Tran et al. (2015) Taxonomy of the burden of treatment: a multi-country web-based qualitative study of patients with chronic conditions *BMC Medicine* 13:115, reprinted under a Creative Commons licence

The 900 hours, she explains, gets eaten up by time spent ensuring the right medicines are in the right place and taken at the right time; travelling to and from consultations; undergoing treatments, blood tests, imaging; filling out forms; reporting side effects; setting up, changing and waiting for appointments; chasing results, liaising between different parts of their healthcare team; keeping up with the scientific and clinical trial developments; changing lifestyles; exploring how to control or adapt to side-effects, and sharing with other patients. And all this while sustaining a life beyond being a cancer patient.

"Being a cancer patient is a full time job," says Spurrier. "If you want some normality, like non-patients have, then you have to be extremely organised and knowledgeable… Patients invest everything in their treatment and survival, much of which is unrecorded and unevaluated, but we are not nearly as good at managing and optimising the impact of it on our lives as engaged, chronic patients sometimes are."

She is not complaining. Spurrier knows full well that had her husband been diagnosed only a couple of years earlier, his prognosis would have been counted in months. Her aim is rather to flag up an under-documented consequence of cancer moving from an acute to a chronic disease, because she believes that acknowledging the increasing role patients have to play in their own care is the first step in enabling patients to work with the healthcare providers to plan and organise well enough to "live lives they would be happy with".

Hans Scheurer, president of Myeloma Patients Europe, who was diagnosed with the disease aged 40, understands exactly where Spurrier is coming from. Changes in life expectancy may not have been quite as dramatic as in melanoma, but novel treatments and improved quality of care introduced in recent decades have seen 10-year survival rates in myeloma triple for women (from 9.8% to 28.1%) and quadruple for men (from 8.9% to 36.6%) between 1991–95 and 2010–11 (figures for England and Wales).

"There are so many new options, and we are very happy with those new treatments, but they give us a unique set of new challenges to living with cancer," he says. "You have to go to the hospital more often, and it is more disruptive in your daily life. It is certainly a big topic among cancer patients."

As Scheurer points out, and contrary to popular perceptions, many of the new drugs are not oral treatments, and need to be given in hospitals, and because oncologists are still learning about their impact, patients need more frequent check-ups to monitor the effects. They also come with new side effects, which then require further monitoring and treatment.

"Before you know it, you are living with cancer full time. For a lot of patients that is the reality"

"That gives new options, new treatments, new visits, and new things to make decisions about. Before you know it, you are living with cancer full time. For a lot of cancer patients that is the reality. You live longer with your disease, which we are very grateful for, but the challenge is: How do you do that? How do you live with your cancer when you want to work and you have a family and you want to go on holiday?"

Burden of treatment

The problems that Scheurer and Spurrier are alluding to have been given a name: the burden of treatment. The concept was first mentioned in the context of chronic conditions such as gastro-oesophageal reflux disease and diabetes. The challenge of meeting the needs of the growing number of patients, particularly elderly patients, with multiple chronic conditions, prompted a group of medical researchers in Paris to team up with a group at the Mayo Clinic in Minnesota, USA, to develop the concept and a tool to measure it.

A 2012 paper by Viet-Thi Tran (Paris Diderot University) and colleagues, presenting an 'instrument to assess treatment burden', defined it as "the impact of health care on patients' functioning and well-being, apart from specific treatment side effects" – a metric that "takes into account everything patients do to take care of their health".

The authors used the tool to describe and classify the components of the burden of treatment from the patient's perspective, based on survey responses from more than 1000 patients from 34 countries with different chronic conditions. The 'taxonomy' of burden of disease they came up with, shown opposite, is an impressive attempt to bring together the many different ways that 'the work of a being a patient' can impact on their daily lives.

It may be just a description/classification, but for patient advocate Gilly Spurrier, that study represents the first step in getting to grips with a burden that can make patients' lives a misery. "This is the starting point of learning to manage time and the disease more effectively, in times of rationed healthcare," she says. And so it is.

"Every second time I forget about the blood test, because you try to get on with your life"

"Every month when I have an injection I am meant to have a blood test a few days before. Every second time I forget about the blood test, because you try to get on with your life but you forget about the things you are meant to do.

"There are a lot of patients I know whose disease is very stable, but they might be on a watch and wait, they may have a scan every 6 or 12 months if they are lucky, whereas with me it is every three months.

"That takes a whole day, but I get anxious for days before, and then waiting for results. Often medical staff don't realise that once you've had a scan, you actually want to know what is happening. I'm very lucky that I have a great team of doctors looking after me. But I also learnt to ask the questions – if I don't hear anything, I'll chase it up.

"I'm lucky I don't have to work full time, because this cancer is like a part-time job anyway, with how much time it consumes, even in your thoughts.

I try not to let it stop me doing things, because it ends up consuming you."

Katie Golden, Australia, on being treated for neuro-endocrine tumour

Minimally disruptive treatment: the concept

Developing in parallel with the 'burden of treatment' concept and taxonomy, and also led from the Mayo Clinic, is the concept of 'minimally disruptive medicine'.

A 2015 paper published in a Scottish medical journal, with input from both the Mayo Clinic and the University of Glasgow, describes it in transformative terms as a concept that supports 'a new era of healthcare' (*J R Coll Physicians Edinb* 2015, 45:114–7).

"Minimally disruptive medicine," they say, "is a patient-centred approach that asks the question: what is the situation that demands medicine, and what is the medicine that the situation demands?"

Getting the right answer, they stress, requires understanding the burden and the patient's capacity, and crucially also, "reshaping the working relationship of patient and clinicians, adjusting goals, shared decision making, streamlining medications and strengthening relationship with the community."

Central to this is a recognition that clinical guidelines are developed with a focus purely on clinical outcomes, and fail to take into account either "the capacity, abilities and limitations of patients to manage their daily care," or the impact on their lives of the workload, demands and responsibilities that accompany these treatment regimens.

"Concepts such as workload, burden and capacity direct attention to the situation in which the patient and their carers exist while living with illness. Importantly, these concepts also direct our attention to issues which healthcare and clinicians are often blind – the extent to which healthcare-created burden inadvertently drags people down," say the authors.

Minimising disruption for cancer patients

The heavy demands that adhering to cancer care plans places on patients is a big concern for Helena Ullgren, a nurse specialised in head and neck cancers, based at Stockholm's Karolinska hospital. Ullgren is responsible for coordinating all the 'contact nurses' in her region, who are assigned to individual cancer patients to help them navigate through the complexities of their healthcare.

"The consequence of treatment is not just coming to hospital on the day," she says. "Aside from the side effects, it is all the practical stuff. We demand patients take blood tests; usually they have to go to hospital or their GP, or perhaps if they are lucky they have a homecare team that will cover blood tests. It's not that you can take them on a random day, you have to take it on an exact day."

There can also be a lot of anxiety

and disruption attached, she adds, because if their blood tests show they have not recovered sufficiently from the previous round of treatment, they may have to postpone the next one, "and then their whole schedule will be upset."

Many patients undergo regular X-rays to evaluate the impact of their treatment. "That can be a big thing, particularly if you are old, or you live maybe an hour away. To do the X-ray you have to first take a blood test, then you go and do the X-ray, which is another day of travel, and then you go back again to the physician to hear the results.

"I'd say some patients are overwhelmed by the practical stuff that treatment leads to."

The most disruptive thing of all, reckons Ullgren, is the poor coordination between the different elements involved in one patient's treatment, which are many, as she explains. "For instance, patients with head and neck cancers can go to both the outpatient and inpatient clinic, radiotherapy clinic, the dentist within the cancer care setting, the dietician, speech therapist and chemo clinic."

As she points out, that doesn't take account of any additional conditions the patient may be receiving treatment for. And the problem isn't only a failure to streamline different aspects of treatment, to minimise the number of locations and visits a patient has to make, says Ullgren. It is that the job of coordinating, to ensure that the right things happen in the right order, and that referrals actually turn into appointments, often falls to the patient themselves, adding substantially to their workload.

"Patients spend a lot of time calling first one care giver, and then the other. They are often the messenger between the two, and that is something we can improve in general," she says.

She feels that, within the cancer setting, cancer clinical nurse specialists have an important coordinating role, but that everyone involved in providing cancer treatment and care also has a responsibility to work in a coordinated way, rather than in silos. When it comes to patients also being treated for other chronic conditions, she feels a single primary care contact with responsibility to keep track of all the elements of their care could be helpful, and mentions the UK general practitioner system as particularly suitable for this role.

"Nothing was made easy… when you put these appointments together, it easily involved four days out of seven"

"Of course, chemo took a full day every time. There were additional appointments for bone scans as there was concern of the cancer having spread to the bones. There were plenty of CT scans to see whether the treatment was working. I also needed radiotherapy and visits to see my surgeon. These were in two different hospitals, quite a distance from my home. The addition of a biological drug also meant travelling to a private hospital as the NHS refused me this medication. Nothing was made easy and you can imagine that when you put these appointments together, it easily involved four days out of seven".

"I never attempted to work during my two years' of treatment. But my husband had to continue with his work while taking me to all these appointments. I think we should appreciate and care for the carer. They have to continue with their routine and often find themselves in an impossible position along with the worry and feeling of helplessness."

Barbara Moss, UK, on being treated for advanced colorectal cancer

Easing disruption, negotiating goals

Paul Cornes, an oncologist based in Bristol, England, has been a supporter of minimally disruptive medicine since before the concept was named. His interest in value-based medicine has led him to focus on key aspects of minimally disruptive medicine to improve adherence to care plans and improve quality of life.

He argues that, while evidence-based guidelines describe the most effective treatment for the disease, choosing the best option for an individual patient means offering them the

"Patients who have no support often abandon treatment rather than make the journey"

"Some patients are being asked to travel up to 100 kilometres for radiotherapy, and elderly patients who have no support often abandon treatment rather than make the journey. I completely understand that, in the middle of winter, if you are 75, immunosuppressed and receiving chemotherapy, and you need to go to take two buses and then walk 20 minutes, they say I won't do it, even if it is only 25 kilometres. In Spain the carer is usually a member of the family, and it is difficult for them to go because they need to keep working and pay the bills."

Natacha Bolaños, advocate with GEPAC, an umbrella group for Cancer Patients, Spain

chance to trade-off a small percentage of efficacy for reduced side effects or reduced burden of treatment.

He mentions adjuvant radiotherapy in early breast cancer as an example. "You can have your conventional five or six weeks postoperative radiotherapy. You can have the short course as exemplified by the Royal Marsden and Canadian research – just two or three weeks' treatment. Or you can now have these intraoperative machines where you have the radiotherapy at the time of your operation, and if you have a low- or moderate-risk tumour, you can just stop there and say the extra advantage of another five weeks of treatment is so minimal that you probably won't want it." For a woman with lots of nodes that extra treatment might be very worthwhile. "You can have that discussion, but how many patients are offered that?"

Evidence from many countries shows that patients who live further from treatment centres are less likely to attend adjuvant radiotherapy, so offering a more practical alternative makes sense, says Cornes. "Would you rather that 100% of your patients get 90% of benefit, or will you try to strike 100% all the time, and leave lots of patients untreated?"

Treatment for women with endometrial cancer is another example, he says, where intravaginal brachytherapy can be an alternative to five weeks of pelvic external beam radiotherapy as adjuvant treatment, particularly for patients with comorbidities. "There's a simpler treatment that can give 95% of the benefit – would that do?"

He wonders too whether Herceptin-eligible patients are ever told that nine weeks' treatment (standard in Finland) is an option that has been shown to offer near enough the same benefit as the 52 weeks that is standard everywhere else.

Cornes would like to see changes in the way guidelines are developed and implemented, to include a range of options with information about pros and cons, to allow patients a real choice, and says this approach is backed by advocacy groups: "They don't say: 'our patients must have the very best,' they say 'the very best *for them*'."

One-stop clinics

Changing the way services are organised and delivered could also do a lot to lighten the burden of treatment, says Cornes. He points to the 'one-stop' bone pain clinics that have been running in Canada and Norway for many years, as good examples.

"There are few more successful things than a single dose of radiotherapy for bone pain," says Cornes. "You go into a clinic in the morning, you have all the scans, the treatment planning is done on the spot, you get your treatment, and go home at the end of the day with your post-treatment instructions."

There's no reason why something similar couldn't be done in other countries, he says, but it would require changing the way treatments are incentivised and rewarded.

If a patient of his mentions bone pain at a consultation, says Cornes, it would be logistically possible for that patient to be taken downstairs to get a scan on the spot, and have their one-off shot of radiotherapy planned and delivered there and then. But without the right procedures, staff

and budgetary mechanisms in place to make that happen, patients end up instead being referred to a separate imaging appointment, which would inevitably be followed by a further appointment for the treatment, possibly weeks later.

The future, he believes, is for more cancer services to be delivered at a community level, as is happening with cardiology services in his part of the UK.

With the right level of training, and access to local facilities, they could take care of routine tests, discuss the results, prescribe or adjust certain medications, and administer infusions or injections or supply oral treatments along with advice about how to take it and why – all within the same day.

The ageing population and the higher prevalence of multiple comorbid conditions, particularly among older patients, means that services are simply going to have to work out how to reduce the burden of treatment, says Cornes, because following evidence-based management guidelines for managing diabetes, high blood pressure and cancer is neither feasible nor desirable.

Signs of change

Patient advocates are already arguing for some of the changes Cornes is calling for, says myeloma advocate Hans Scheurer. He has been discussing with other European cancer groups and health professionals about how to press for more home-care options.

"There is a desire to look at alternatives. There are a lot of hospitals busy talking about how you can go with this, and we also stimulate patient organisations to do so, because it is absolutely of benefit to patients to have treatment at home. Blood tests could be at home.

"Maybe we can look at some kind of ambulance that can drive around with options to do chemotherapy at home, especially for frail patients. This is an idea we have discussed with health professionals."

One such service has been operating in the Netherlands since 2015, he says. Working in close cooperation with particular hospitals, it administers infusion therapy at home, including anti-cancer immunotherapy. "Of course you need specially trained nurses to provide this service, and they work closely with the doctor, as they would in the hospital. But this is absolutely a welcome tailor-made solution for a group of cancer patients – it is the future we are looking at."

Not all cancers are the same, however, and nor are all cancer patients. How much does the burden of treatment matter to people with advanced melanoma, whose priority will be staying alive long enough for the next experimental treatment to come along?

It matters, says Gilly Spurrier. "Clinicians and health systems expect patients to just accept that their lives must contain long periods of waiting and that they are resigned to the inefficiencies of healthcare which impact on their lives. There is an almost unspoken rule that a patient 'becomes their disease', and that patients should not be surprised that life is so heavily impacted. The assumption is that: 'Well, you are alive, be grateful for that.' For me, this is not acceptable."

As important as lightening that burden, she argues, is simply recognising and acknowledging the amount of time that patients spend on self-care, the contribution they make to their own health and disease outcomes, and above all the expertise that they build up on the way.

"I think it is important for patients to recognise this," says Spurrier, "as it shows them how much they have invested, how much they know, and hence why they should be drivers of their care… Now we ration healthcare and have more individualised treatment regimes, it is essential both for the patient and the healthcare systems that patients take charge."

> **"It is important to recognise the contribution patients make to their own disease outcomes, and the expertise they build up"**

It is also important for healthcare providers, researchers and administrators to recognise, she adds, because patients who invest the time and effort into adhering to their care plan, and doing everything they can to promote their health and wellbeing, not only save money, time and resources in relation to their own care, but they also represent "a hugely under-used expertise in research into improvements in healthcare," says Spurrier.

If health services are researching ways to improve the personalised treatment they deliver to growing numbers of patients needing complex care, why wouldn't they want to involve the people who devote half their lives to learning to live with and overcome their disease?

Efficacy in three indications

Metastatic pancreatic cancer
in combination with gemcitabine for first-line treatment of adult patients

Metastatic breast cancer
as monotherapy when first-line treatment fails and anthracycline containing therapy is not indicated

Non-small cell lung cancer
in combination with carboplatin for first-line treatment when surgery and/or radiotherapy are not indicated

Abraxane®
nanoparticle albumin bound paclitaxel

Prescribing Information: Abraxane® 5 mg/ml powder for suspension for infusion.
Refer to the Summary of Product Characteristics (SmPC) before prescribing.
Name of medicine: Abraxane 5 mg/ml powder for suspension for infusion **Active ingredients:** paclitaxel formulated as albumin bound nanoparticles. **List of excipients:** Human albumin solution (containing sodium, sodium caprylate and N-acetyl DL tryptophanate). **Available dosage form:** Powder for suspension for infusion. The reconstituted suspension has a pH of 6-7.5 and an osmolality of 300-360 mOsm/kg. The powder is white to yellow. **Authorised indication(s):** Abraxane monotherapy is indicated for the treatment of metastatic breast cancer in adult patients who have failed first-line treatment for metastatic disease and for whom standard, anthracycline containing therapy is not indicated. Abraxane in combination with gemcitabine is indicated for the first-line treatment of adult patients with metastatic adenocarcinoma of the pancreas. Abraxane in combination with carboplatin is indicated for the first line treatment of non-small cell lung cancer in adult patients who are not candidates for potentially curative surgery and/or radiation therapy. **Dosage regimens and routes of administration:** Breast Cancer - The recommended dose of Abraxane is 260 mg/m² administered intravenously over 30 minutes every 3 weeks. Pancreatic adenocarcinoma - The recommended dose of Abraxane in combination with gemcitabine is 125 mg/m² administered intravenously over 30 minutes on Days 1, 8 and 15 of each 28-day cycle. Non-small cell lung cancer: The recommended dose of Abraxane is 100 mg/m² administered as an intravenous infusion over 30 minutes on Days 1, 8 and 15 of each 21-day cycle. The recommended dose of carboplatin is AUC = 6 mg•min/ml, on Day 1 only of each 21-day cycle, beginning immediately after the end of Abraxane administration. Refer to the full prescribing information for dose adjustments during treatment in case of haematologic (neutropenia and/or thrombocytopenia) and other adverse reactions. Administer reconstituted Abraxane suspension intravenously using an infusion set incorporating a 15 µm filter. Following administration, it is recommended that the intravenous line be flushed with sodium chloride 9 mg/ml (0.9%) solution for injection to ensure administration of the complete dose. **Reference to special groups of patients:** Patients with hepatic impairment: For patients with mild hepatic impairment (total bilirubin > 1 to ≤ 1.5 x ULN and aspartate aminotransferase [AST] ≤ 10 x ULN), no dose adjustments are required, regardless of indication. Treat with same doses as patients with normal hepatic function. For metastatic breast cancer patients and non-small cell lung cancer patients with moderate to severe hepatic impairment (total bilirubin > 1.5 to ≤ 5 x ULN and AST ≤ 10 x ULN), a 20% reduction in dose is recommended. The reduced dose may be escalated to the dose for patients with normal hepatic function if the patient is tolerating the treatment for at least two cycles. For patients with metastatic adenocarcinoma of the pancreas that have moderate to severe hepatic impairment, there are insufficient data to permit dosage recommendations. For patients with total bilirubin > 5 x ULN or AST > 10 x ULN, there are insufficient data to permit dosage recommendations regardless of indication. Patients with renal impairment: Adjustment of the starting Abraxane dose is not required for patients with mild to moderate renal impairment (estimated creatinine clearance ≥30 to <90 ml/min). There are insufficient data available to recommend dose modifications of Abraxane in patients with severe renal impairment or end stage renal disease (estimated creatinine clearance <30 ml/min) Older people: No additional dosage reductions, other than those for all patients, are recommended for patients 65 years and older. Paediatric population: The safety and efficacy of Abraxane in children and adolescents aged 0-17 years has not been established. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. Lactation. Patients who have baseline neutrophil counts < 1500 cells/mm³. **Warnings:** Abraxane should not be substituted for or with other paclitaxel formulations. It is an albumin-bound nanoparticle formulation of paclitaxel, which may have substantially different pharmacological properties compared to other formulations of paclitaxel. Rare occurrences of severe hypersensitivity reactions, including very rare events of anaphylactic reactions with fatal outcome, have been reported. If a hypersensitivity reaction occurs, the medicinal product should be discontinued immediately, symptomatic treatment should be initiated, and the patient should not be rechallenged with paclitaxel. Bone marrow suppression (primarily neutropenia) occurs frequently with Abraxane. Neutropenia is dose dependent and a dose limiting toxicity. Frequent monitoring of blood cell counts should be performed during Abraxane therapy. Patients should not be retreated with subsequent cycles of Abraxane until neutrophils recover to >1500 cells/mm³ and platelets recover to >100,000 cells/mm³. Sensory neuropathy occurs frequently with Abraxane, although development of severe symptoms is less common. The occurrence of Grade 1 or 2 sensory neuropathy does not generally require dose reduction. If Grade 3 sensory neuropathy develops, treatment should be withheld until resolution to Grade 1 or 2 followed by a dose reduction for all subsequent courses of Abraxane is recommended. For combination use of Abraxane and gemcitabine, if Grade 3 or higher peripheral neuropathy develops, withhold Abraxane; continue treatment with gemcitabine at the same dose. Resume Abraxane at reduced dose when peripheral neuropathy improves to Grade 0 or 1. For combination use of Abraxane and carboplatin, if Grade 3 or higher peripheral neuropathy develops, treatment should be withheld until improvement to Grade 0 or 1 followed by a dose reduction for all subsequent courses of Abraxane and carboplatin. Sepsis was reported at a rate of 5% in patients with or without neutropenia who received Abraxane in combination with gemcitabine. Complications due to the underlying pancreatic cancer, especially biliary obstruction or presence of biliary stent, were identified as significant contributing factors. If a patient becomes febrile (regardless of neutrophil count), initiate treatment with broad spectrum antibiotics. For febrile neutropenia, withhold Abraxane and gemcitabine until fever resolves and ANC > 1500 cells/mm³, then resume treatment at reduced dose levels. Closely monitor all patients for signs and symptoms of pneumonitis. After ruling out infectious etiology and upon making a diagnosis of pneumonitis, permanently discontinue treatment with Abraxane and gemcitabine and promptly initiate appropriate treatment and supportive measures. Because the toxicity of paclitaxel can be increased with hepatic impairment, administration of Abraxane in patients with hepatic impairment should be performed with caution. Patients with hepatic impairment may be at increased risk of toxicity, particularly from myelosuppression, and such patients should be closely monitored for development of profound myelosuppression. Abraxane is not recommended in patients that have total bilirubin > 5 x ULN or AST > 10 x ULN. In addition, Abraxane is not recommended in patients with metastatic adenocarcinoma of the pancreas that have moderate to severe hepatic impairment (total bilirubin > 1.5 x ULN and AST <10 x ULN). Rare reports of congestive heart failure and left ventricular dysfunction have been observed among individuals receiving Abraxane. Most of the individuals were previously exposed to cardiotoxic medicinal products such as anthracyclines, or had underlying cardiac history. Thus patients receiving Abraxane should be vigilantly monitored by physicians for the occurrence of cardiac events. The effectiveness and safety of Abraxane in patients with central nervous system (CNS) metastases has not been established. CNS metastases are generally not well controlled by systemic chemotherapy. If patients experience nausea, vomiting and diarrhoea following the administration of Abraxane, they may be treated with commonly used anti-emetics and constipating agents. Carefully assess patients with pancreatic adenocarcinoma aged 75 years and older for their ability to tolerate Abraxane in combination with gemcitabine. Give special consideration to performance status, co-morbidities and increased risk of infections. When reconstituted, Abraxane contains 0.183 mmol sodium, which is 4.2 mg of sodium. To be taken into consideration by patients on a controlled sodium diet. **Clinically significant interactions:** Abraxane is indicated for as monotherapy for breast cancer in combination with gemcitabine for pancreatic adenocarcinoma, or in combination with carboplatin for non-small cell lung cancer. Abraxane should not be used in combination with other anticancer agents. Caution should be exercised when administering paclitaxel concomitantly with medicines known to inhibit either CYP2C8 or CYP3A4 (e.g. ketoconazole and other imidazole antifungals, erythromycin, fluoxetine, gemfibrozil, cioplidogrel, cimetidine, ritonavir, saquinavir, indinavir, and nelfinavir) because toxicity of paclitaxel may be increased due to higher paclitaxel exposure. Administering paclitaxel concomitantly with medicines known to induce either CYP2C8 or CYP3A4 (e.g. rifampicin, carbamazepine, phenytoin, efavirenz, nevirapine) is not recommended because efficacy may be compromised because of lower paclitaxel exposures. **Reported side effects:** The most common clinically significant adverse reactions associated with the use of Abraxane have been neutropenia, peripheral neuropathy, arthralgia/myalgia and gastrointestinal disorders. Prescribers should consult the summary of product characteristics in relation to other side-effects. **Storage conditions:** Keep the vial in the outer carton in order to protect from light. Neither freezing nor refrigeration adversely affects the stability of the product. This medicinal product does not require any special temperature storage conditions. **Price: Classification:** Medicinal product subject to medical prescription. **Marketing Authorisation Numbers:** EU/1/07/426/001, EU/1/07/426/002. **Marketing Authorisation Holder:** Celgene Europe Limited, 1 Longwalk Road, Stockley Park, Uxbridge, UB11 1DB, United Kingdom. **Date of last revision:** 11/2010. **Internal ID of the printed material: INT-ABR170002**
Date of preparation: February 2017

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