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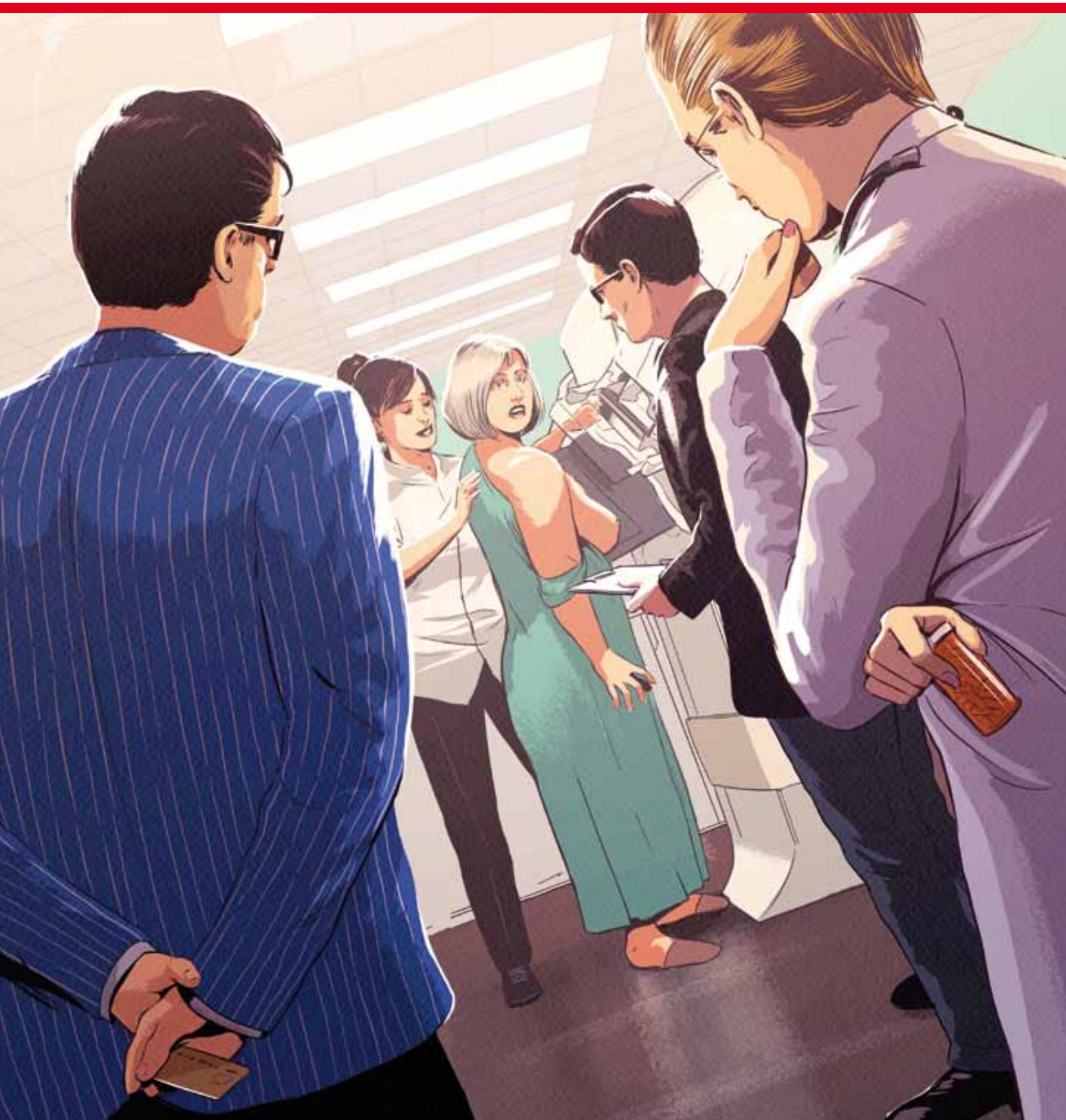
n° 76 January / February 2017



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Contents

Printed by
Grafiche Ambert, Verolengo (TO)

Cover by
Guy Shield

Illustrations by
Maddalena Carrai, Elisa Macellari, Nicolò Assirelli

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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European School of Oncology

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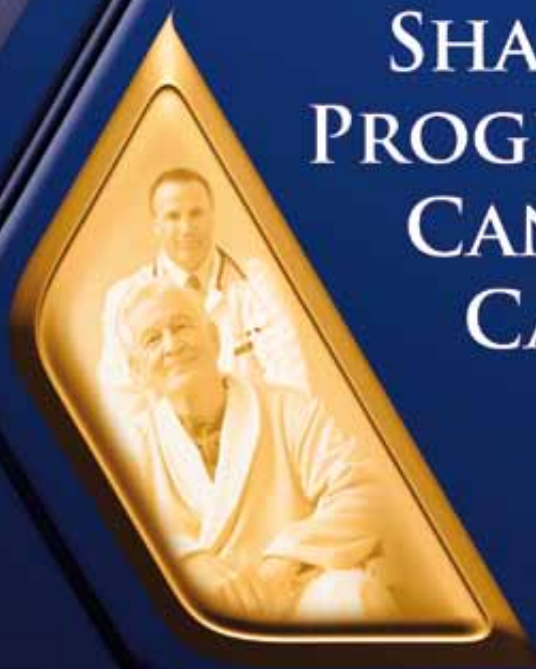
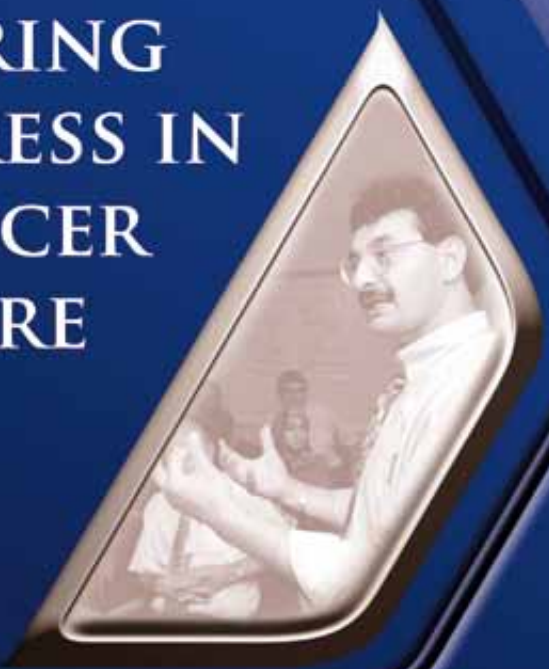
Sharing Progress in Cancer Care





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Umberto Veronesi's legacy

Alberto Costa, Editor

With the death of Umberto Veronesi last November, the cancer world has lost one of its great leaders, and we at the European School of Oncology have lost our inspiration and founder. In this issue we remember his achievements as a visionary surgeon, whose pioneering development of breast conserving therapy and adjuvant therapy led to a paradigm change in our approach to cancer care.

We also look ahead, in our Cover Story, to see how Veronesi's guiding principle of finding the least harmful way of safely treating each breast cancer is now also starting to be applied to screening and prevention. Specifically, we explore the work being done by a number of groups to define and measure women's individual risk, which is adding a new dimension to the long-running debate about the risks and benefits of 'one size fits all' mammography programmes, and beginning to map out a new field of population-based risk-stratified prevention.

In opening up the potential for personalising breast screening schedules, as well as prevention advice and interventions, this research may eventually lead to another paradigm change for which Veronesi was an early and lifelong advocate, namely rebalancing cancer control efforts to focus on intervening at the earliest possible stage.

We know, for instance, that tamoxifen can halve the chances of getting breast cancer in many women at high risk, just as we know that low-dose aspirin can dramatically reduce the risk of colorectal cancer. Using our growing knowledge of risk factors to introduce population-based risk screening with tailored detection and prevention packages for those at highest risk could be one of the most powerful strategies we currently have to cut deaths and suffering from cancer, and would be a great way to carry forward Veronesi's legacy.

In this issue we also say Happy New Year to all our readers, and a special greeting to everyone who will be gathering in Amsterdam for the new ECCO conference – four intense days of presentations and debates that will set the framework for how we tackle the big challenges of delivering patient-centred quality care to everyone who needs it.

ECCO, and each one of its member societies, deserve recognition for this innovative conference, which is looking outward to engage more in discussions about the non-medical aspects of providing sustainable best-quality care, while also focusing down on the multidisciplinary collaboration that will be essential to delivering that care.

With the number of patients, and the complexity of their care steadily rising, and little sign of better times for European economies, challenges undoubtedly lie ahead, some of which are reported in our Systems & Services article, 'No time!', which looks at the impact of growing staff shortages in cancer care. For this issue's 'In the Hot Seat', meanwhile, we present ECCO's new President-elect, Philip Poortmans, who answers our questions about his vision for helping ECCO's member societies work to a common goal to meet those challenges in the best interests of all patients.

Population screening in the age of personalised medicine

The risk of developing breast cancer varies widely from woman to woman in ways we are increasingly able to define. **Marc Beishon** asks: Is it time to move to population screening for risk, and tailor mammography schedules – and prevention advice – to each individual?

The past few years have arguably given us the most controversial, long-running dispute in healthcare – whether the benefits of mammography screening outweigh the harms. There is much at stake – not least the cost of running population screening programmes for many millions of women in the western world, and potentially in less well-off countries as well. Public health officials have been grappling with conflicting evidence about the merit of screening, and what to tell women who are invited to take part in one of the centrepieces of cancer control policy.

The prospect of finding some common ground may now be emerging thanks to work being done by a variety of groups to replace the traditional 'one size fits all' approach with one that personalises screening according to how each woman scores on a set of risk factors.

This could have profound implications, as women in low-risk groups could drop out of programmes after one or two screens, which could go some way towards satisfying those who argue strongly against routine population screening. More likely, for the next 10 to 20 years, screening will remain a regular event, but with screening intervals adjusted for risk. This would still be a radical change given that it is hard to turn around major public health programmes that have considerable bureaucracy and investment in certain IT systems and core beliefs.

There is a race of sorts to establish the evidence that a risk-stratification approach will work. Ahead is a group in Manchester, England, while others in the Netherlands and Sweden are following. A group in Italy is preparing a study on three regions in the country. These are cohort studies, not randomised controlled trials (RCTs), but in the US the first RCT on risk stratification is taking shape, which could be the precursor to a round of such trials, and which could mark the point at which screening practices change, given that the RCTs that support current programmes are now old and were carried out when treatments were different.

"Screening and prevention go together beautifully – but there is currently no attempt to do this"

But it is the opportunity that such a risk-stratified approach offers for linking screening with prevention that is causing the greatest excitement among some in this field. As Jack Cuzick, an epidemiologist and prevention specialist at the Wolfson Institute in London, comments: "Screening and prevention go together beautifully, but there is currently no attempt to do this."

Some women, mainly those with a high family risk, are already offered earlier and more frequent screening, but a big step would be intervening with a prevention strategy for all women attending screening, especially those at moderate to high risk.

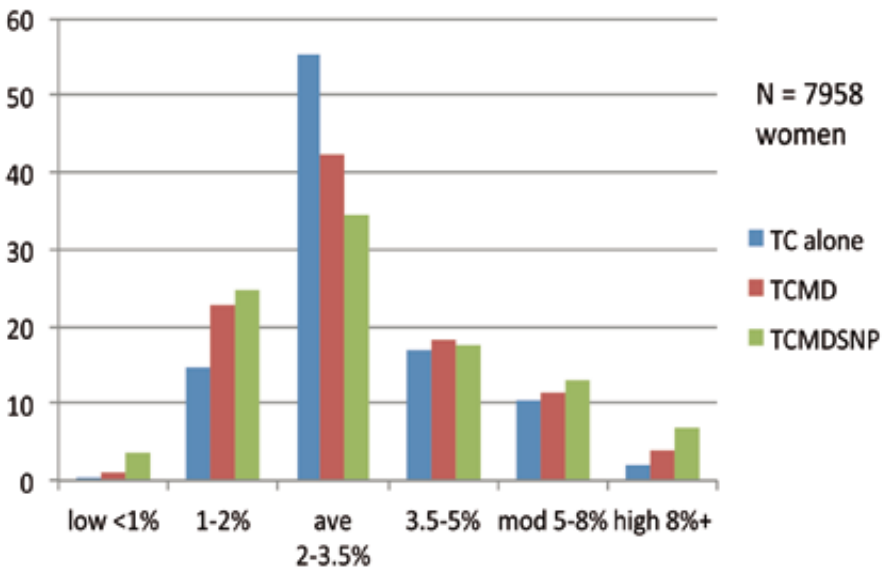
"If we can find 20% of the population who will get 40% of cancers, we have the means to reduce their risk by about 50% with preventive therapy," says Cuzick. "That could reduce breast cancer incidence by 20% if all high-risk women were identified and took up preventive therapy. Combined with lifestyle changes in the rest of the population, this offers a way to reduce overall incidence by as much as 25%."

Andrea De Censi, director of medical oncology at Ospedali Galliera in Genoa, Italy, has been championing preventive strategies in breast cancer for nearly three decades, and sees moves towards risk-stratified screening as an important opportunity. "We know women at low risk do not want to abandon screening at present. The debate is how to focus on those at high risk to try to prevent cancers," he says. Once this group has been identified, they may then want to collaborate on risk reduction, although De Censi is not sure all women actually want to know their risk – like smokers who avoid going to the doctor.

Stratifying by risk

There are three main steps researchers are now combining to better stratify risk, says De Censi. The first is to apply a well-studied risk tool, such as the Tyrer–Cuzick model (Jack Cuzick is the co-developer), or one of a number of others (the Gail model is widely used in the US, for example). Tyrer-Cuzick, part of IBIS (the International Breast Cancer Intervention Study), estimates the likelihood of a woman developing the disease within 10 years and during her lifetime, and takes into account factors such as age and weight, age of first menstrual period, whether she has had children, whether she has gone through the menopause, and if she is a current or past user

Risk stratification models



The PROCAS (Predicting Risk of Cancer At Screening) trial is investigating a breast cancer risk stratification model that starts with factors such as age, weight, and hormone-related factors (the Tyrer–Cuzick model), and then adds information about breast density and the presence of any of 18 SNPs associated with higher risk of breast cancer. The figure above shows how risk estimated according to the Tyrer–Cuzick model (*the blue bars*) changes when information about breast density (adjusted for age and body mass index, *shown in brown)* and SNPs (*green*) is added, with many women's risk levels being either upgraded or downgraded.

Source: Genesis Breast Cancer Prevention Centre: Research Overview 2014/15. (2015) Genesis Breast Cancer Prevention Appeal, Manchester

of hormone replacement therapy (HRT).

Some of these may not remain constant: age of course, but also weight gain – which is now known to be a much more important factor than alcohol intake (which is not included in the models) – HRT use, and family history (which is a major predictor and can change as new events may occur in a family).

Already, these models can stratify women into those at high and moderate risk, and they have been validated, says De Censi.

A second step is breast density, which does not just mask lesions in dense tissue, but is associated with cancer risk, and is an ongoing field of study. "Density has been measured fairly subjectively, but now there are ways to apply computerised methods that will probably be more accurate," he says. Importantly, density is also a surrogate biomarker in trials of prevention drugs like tamoxifen, he adds – a decrease in density is a sign that the drug is working.

The third step is to take a genomic profile from a blood or saliva sample – this is to assess frequency of common variations (single nucleotide polymorphisms, or 'SNPs') related to risk, but not the *BRCA1/2* mutations that give rise to major risk (these are taken into account in Tyrer–Cuzick, but affect only relatively few women). Again, this is ongoing research.

Evans hopes that risk profiling will eventually start at entry to the screening programme

One of the leading trials of this three-pronged risk-stratification model is an ongoing study called PROCAS ('Predicting Risk Of Cancer At Screening'), led by Gareth Evans, professor of medical genetics and cancer epidemiology at the University of Manchester, UK. It's part of a programme now called Prevent Breast Cancer, which aims to fill knowledge gaps on risk estimation, prevention strategies (both medical therapy and lifestyle changes) and the biology of breast cancer risk. The first phase of PROCAS ran from 2009 to 2015. It recruited more than 57,000 women who were invited for screening in a certain area, and the

group has published data showing how the distribution of risk changes as first breast density and then SNPs information is added to the Tyrer-Cuzick model (see opposite).

Evans stresses that his team is yet to publish recent results from the latest phase of the project, but says they are close to being able to confirm from data on nearly 10,000 women who have provided DNA samples that about one in six (17%) are at moderate to high risk, of whom 6% are in the high-risk group, and have a 10-year risk of more than 8% of having breast cancer (moderate is 5–8%). That high risk doubles to 16% for the 20 years of the UK's screening programme, which runs from age 50 to 70. Then there is 30% at below 2% risk – women who have a low incidence of breast cancer – and the remainder are in a 2–5% average risk group.

"Importantly in the high and moderate groups, we are not just detecting what we would call overdiagnosis – there is less as a proportion of indolent DCIS [ductal carcinoma *in situ*] and grade I type cancers, and also more interval cancers [breast cancers diagnosed in the interval between scheduled screening episodes in women screened and given a 'normal' screening], which could justify more frequent screening for these women," says Evans. "And we would potentially pay for this by reducing screening in the lower risk group."

Stratified risk management

Evans adds that the 30% low risk group could be advised that their risk/benefit ratio is not enough to justify ongoing screening. The UK, he adds, is also in a unique position with three-year screening intervals, which would work well for the 2–5% risk group, while women classified as at moderate to high risk could move to two-year or annual screening, and possibly chemoprevention with tamoxifen or other drugs. The UK's NHS, he adds, could at least set a benchmark for the rest of the developed world to move to three-year intervals for a large number of women, although again he emphasises that this is a preliminary indication.

"We have found that women are ten times more likely to be motivated when advised in a risk management approach"

Like Cuzick, Evans hopes that risk profiling will eventually start at entry to the screening programme, which could be earlier in the UK than the current age 50. PROCAS has an 'extension' trial looking at starting at 47 and going up to age 73, although in the older age group, while risk continues to rise, there is more chance of overdiagnosis. But importantly, says Evans, women often believe wrongly that their risk disappears once they are no longer offered screening (and generally there is a poor understanding of breast cancer risk among women).

He is also of the view that the evidence supports the effectiveness of the current screening programme, but that informing women of their risk will give them a more informed choice on whether to attend screening or not, while those at higher risk could not only have more regular screens and chemoprevention, but could also take steps to cut their risk through modifying their lifestyles. "We have found that if you tell women they are at moderate or high risk, they are more likely to come for their following screening, and they will also take steps to cut their risk.

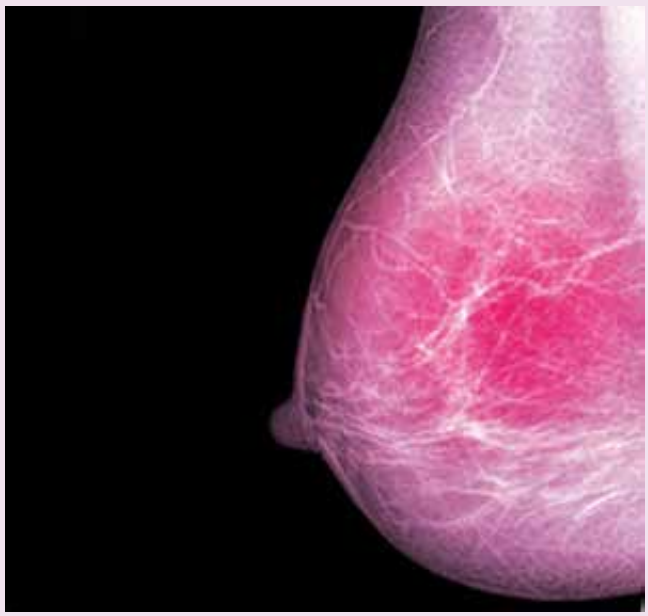
"Cynics say that identifying risks does not mean people will act, as we are bad at taking advice on our weight, and sticking to diets and exercising more – but we have found that women are ten times more likely to be motivated when advised in a risk management approach." Further, the vast majority (95%) of women in PROCAS wanted to know their risk, although there may be cultural barriers elsewhere, as De Censi suggests may be the case in Italy. Being given a high risk score can also be distressing, and Evans says his team is doing formal assessment of this, but he feels it can be counterbalanced by the benefits of more frequent screening and motivation to reduce risk.

As Evans points out, these sorts of risk-stratified prevention strategies could not only cut the incidence of breast cancers but also save the £20,000 [€22,000] or so it costs to treat a cancer. It's also important that any intervention is at least cost neutral, he adds, given pressures on health spending and the budget allocated to screening.

Refining the models, building the evidence

Refining risk models with underlying genetic predisposition is also likely to improve, as more data emerges from even larger studies,

Mammography: the latest evidence



Do the risk reduction benefits of mammography outweigh the harms? In September, Harry de Koning, professor of public health and screening evaluation at Erasmus University in Rotterdam, summed up the evidence and the points of contention at a meeting convened by University College London as part of its Frontiers in Oncology series.

Mortality benefit

In 2015 an expert group convened by the International Agency for Research on Cancer (IARC) concluded that there is sufficient evidence to show screening is effective in reducing mortality from breast cancer in the age groups 50 to 69, and 70 to 74, but evidence of effectiveness in younger age groups is limited (*NEJM* 2015, 372:2353–58).

The risk reduction among women aged 50–69 was estimated at 23% among those invited to screening and 40% among those who actually attended. The research was done to update IARC's handbook on mammography screening, first issued in 2002, and takes account of 40 case–control and cohort studies conducted in the interim.

Further, the last update of the influential Cochrane review says that screening is likely to reduce breast cancer mortality.

A 2014 Netherlands' case control study of screening attenders versus non–attenders showed that screening halves the risk of dying from breast cancer, and Dutch women are currently informed that about 775 fewer women die from the disease each year thanks to screening.

The proportion of cancers picked up at an advanced or metastatic stage in six European countries, including the Netherlands, was 42% in 1990/91 without screening but by 2013 this was much lower in the Netherlands, at 23%.

Earlier detection or better treatment?

Critics have argued that mortality reductions have come mainly from new treatments and better organisation of breast services.

A number of recent studies have looked back at the data in various ways. A recent paper in the *New England Journal of Medicine* (vol 375, pp1438–47), for instance, questions evidence about the drop in the proportion of larger tumours detected with the introduction of

such as the Breakthrough Generations Study, which is following more than 113,000 women across the UK for 40 years, and which in 2015 reported two new breast cancer susceptibility 'loci' (there are many SNPs associated with risk – PROCAS has been using a panel of 18).

"The next step with PROCAS is to do it live – if we can show it's feasible and doesn't cause harm, then we would also want to do a large RCT, where you offer one population the full risk strategy approach and compare mortality with a group that has screening as usual," says Evans. The live version of PROCAS will provide rapid feedback of risk to women – in the first phase this was a lengthy process.

Other groups in Europe working on risk stratification include the Karma project at the Karolinska in Sweden, which has a range of studies in train, including on prevention, breast density and cancer detection, and the Prisma team at Radboud University Nijmegen Medical Centre in the Netherlands. The latter institute is also coordinating the EU-funded ASSURE ('Adapting

mammography, arguing that "the more favourable size distribution was primarily the result of the additional detection of small tumours."

De Koning replies that the study only looked at data up to the year 2000, and has an arbitrary cut-off point for looking at tumour size.

There is also evidence to show that screen-detected cancers are independently associated with better prognosis (see for example *JNCI* 2011, 103:1-13), he notes. Another paper examined mortality from ER (oestrogen receptor) positive and negative cancers according to the relative contributions of adjuvant therapy and screening. Adjuvant therapy had a bigger impact than screening in ER positive cancers, but about the same in ER negative ones (*JNCI* 2014, 106:dju289).

Overdiagnosis

Estimating the extent of overdiagnosis is difficult, and studies that fail to adjust for breast cancer risk and/or lead time tend to overestimate the problem.

The 2015 IARC expert review did confirm that there is sufficient evidence that screening does detect cancers that would never have been diagnosed otherwise.

But it is the extent of this overdiagnosis that is crucial, and there has been much debate about how to explain the excess incidence in screened populations. In 1994, de Koning and colleagues put forward a model that predicted that there would be a big (temporary) drop in incidence – well below the unscreened incidence rates – when women leave the screening programme at the upper age limit, because their cancers had already been detected. Critics have said this has not been observed, but de Koning has now produced data from the Netherlands that does indeed show quite a close fit with the predictive model (see the graph in *The Breast* 2016, 27:182-83).

A modelling technique called 'age-period-cohort' is also being used to quantify the impact of screening mammography on incidence of DCIS (ductal carcinoma *in situ*), and early and late stage cancers, accounting for influences of birth cohort and changes in secular risk factors (ie risk factors associated with a particular period).

One such study found that, while mammography contributes to 'markedly elevated' rates of DCIS, it also contributes to substantial reductions in the incidence of metastatic breast cancer (*Cancer Epidemiol Biomarkers Prev* 2015, 24:905-12).

De Koning himself estimates the overdiagnosis rate at between 1% and 11%, and points to a model on the Netherlands that shows that, of 1,000 women aged 40 or over, who are invited to screening and followed over their lifetime, it is estimated that 124 will have a false-positive screening result, but only three will be unnecessarily diagnosed and treated. He adds though that: "Without diagnosis there is no benefit – for every three breast cancer deaths prevented, one woman is overdiagnosed."

De Koning is currently coordinating a new EU-funded programme, EU-topia (eu-topia.org), which aims to measure the impact of screening for breast, cervical, and colorectal cancer and provide countries with tools to manage their own programmes in terms of health outcomes and cost-effectiveness, and also aims to identify inequalities across Europe.

breast cancer Screening Strategy Using personalised Risk Estimation') project, which has several academic and commercial partners around Europe, and which has a particular focus on breast density and tools such as MRI and ultrasound to personalise screening and increase sensitivity.

As Nico Karssemeijer at Radboud notes, about 30% of breast cancers are detected between screening rounds, and a retrospective review has shown that almost a third of these could have been picked up in an earlier screening round, had the then-present signs of cancers been spotted at the time.

De Censi says he is helping to put forward a proposal in Italy to start a risk stratification study in three regions, and it will add insulin resistance to the factors taken into account in the PROCAS project.

Meanwhile in the US the first RCT of risk-based screening is underway, called WISDOM – 'Women Informed to Screen Depending On Measures of risk'), and funded by the Patient-Centered Outcomes Research Institute (PCORI). It addresses the more aggressive approach to

screening in the US, in which many women have annual screening starting at age 40, despite mortality rates being no lower than in Western Europe (and despite recent changes in recommendations to start screening later). The trial aims to randomise 100,000 women between the ages of 40 and 74 into a risk-based screening protocol (including a genomic profile of more than 150 SNPs), or annual screening as usual. The primary outcome measures are the proportion of cancers diagnosed at stage IIB or higher, and the rate of biopsies performed.

The ASSURE project focuses on tools such as MRI and ultrasound to personalise screening and increase sensitivity

The principal investigator of WISDOM is Laura Esserman, a breast surgeon and head of the Carol Franc Buck Breast Care Center at the University of California, San Francisco. She is known as a 'rebel' in the US for combating overdiagnosis and overtreatment, particularly of DCIS, which has soared in incidence since screening started, but also overuse of treatments such as radiation therapy. As an indication of her status, she has been recognised by *Time* magazine as one of the 100 most influential people in the world. While she believes that personalised screening could be the way to go, the study protocol rather gives the game away: "The investigators believe this study has the potential to transform breast cancer screening in America." But there will be a lot of work to do in building the evidence to a level that will dispel the fear that Esserman says many American women feel if they were to forego the current regime.

Evans is somewhat sceptical about WISDOM, as he expects confounding from women who will go for annual screenings anyway, given the easy access in the US. The WISDOM group has though done a pilot that has shown that randomisation is feasible. Evans also makes the point that this study is really only comparing variations in screening, and not the merit of screening *per se* – but concedes that carrying out a new RCT on screening vs no screening to update the evidence base in a fundamental way is not likely to happen soon.

Policy and practice

Whether the risk/prevention advocates can actually make headway against the breast screening 'machine' is a moot point, as Cuzick reiterates. There will need to be substantial changes to IT systems and processes to incorporate risk data, nurses will need training in the approach, and counselling will be needed for women at high risk, he says. He also questions how far women will act to reduce their risk, despite the evidence from PROCAS (with which he is also involved). He would like to see primary care doctors do more to support patients to take action – a new study shows that even a very brief referral to a weight management group is effective (*Lancet* 2016, http://bit.ly/obesity_intervention).

"Substantial changes to IT systems will be needed, nurses will need training, counselling will be needed for women at high risk"

Cuzick also points out that a risk-stratified approach to screening is not new: it is already applied in cervical cancer, where in the UK the younger age group of 25–49 is invited every three years, in contrast to every five years for the 50–64 age group, because the disease develops more rapidly in younger women.

Mortality from breast cancer has been declining in most developed countries, and the arguments will no doubt continue about the extent to which screening can take the credit for this drop and for lowering the incidence of metastatic disease. Advances in understanding of cancer biology raise challenging questions about the reliance on the size of a tumour, the mainstay in screening, and even lymph node status, in prognosis, as some cancers are molecularly more aggressive, which is why groups such as Prevent Breast Cancer, in Manchester, are trying to do much more than just improve conventional screening.

However, as De Censi comments, wearing his 'prevention hat', mortality is only part of the picture, as preventing an invasive cancer that would not have metastasised, subject to standard treatment, also gives substantial gains in quality of life and wellbeing – and cost savings.

Preventive strategies for women at high risk

Women are not all the same – and nor is their risk of breast cancer. Screening women for risk levels can not only reduce unnecessary testing in women at low risk, but also give women at high risk the information they need to take informed decisions about taking steps to lower their risk. These include lifestyle changes and, in those at highest risk, chemoprevention.

Currently, two selective oestrogen receptor modulators (SERMs), tamoxifen and raloxifene, are approved in the US and recommended by NICE in the UK for those at moderate to high risk (in the UK for those with familial breast cancer history). Take-up rates, however, are reported to be quite low – one in six.

Aromatase inhibitors such as exemestane and anastrozole are also being trialled for postmenopausal women (raloxifene is also only for postmenopausal use – only tamoxifen is approved for premenopausal chemoprevention). NICE recently recommended anastrozole rather than tamoxifen for women with a family history of breast cancer.

The data from trials of all these agents are good in terms of reducing breast cancer incidence of ER+ tumours, although there are side effects. Studies show that tamoxifen taken for five years decreases invasive breast cancer risk by 30–40%, and exemestane reduces incidence by 65%. However, mortality benefit has not yet been shown, even after long follow-up in one tamoxifen study. Some commentators are asking whether chemoprevention has now reached the end of the road (*JAMA Oncology* 2015, 1:1033–4).

Proponents of chemoprevention, including Jack Cuzick, argue that follow-up is not yet long enough to evaluate mortality, and there simply haven't been enough deaths in the study groups to show a mortality reduction. Nevertheless, he notes a projection of an 18% mortality reduction in ER+ disease (*Lancet Oncol* 2015, 16:67–75).

Other compounds being studied for potential benefits in women at high risk of breast cancer include genistein (a component of soy), omega 3 fatty acids, vitamin D, bisphosphonates, statins, metformin, and even some vaccines. None of these have yet been shown to be preventive in RCTs (*Trends in Breast Cancer Prevention* Springer, Switzerland, 2016).

As a medical oncologist, he says his prevention interest is not widely shared with colleagues immersed in the world of anti-cancer drug treatments, while the screening side is dominated by epidemiologists. "Prevention is in its infancy," he laments. But the signs are that the wheels are turning slowly towards seeing risk-stratified screening in the prevention field – although as well as professional collaboration, there may also have to be much better awareness of the concept of risk among the public.

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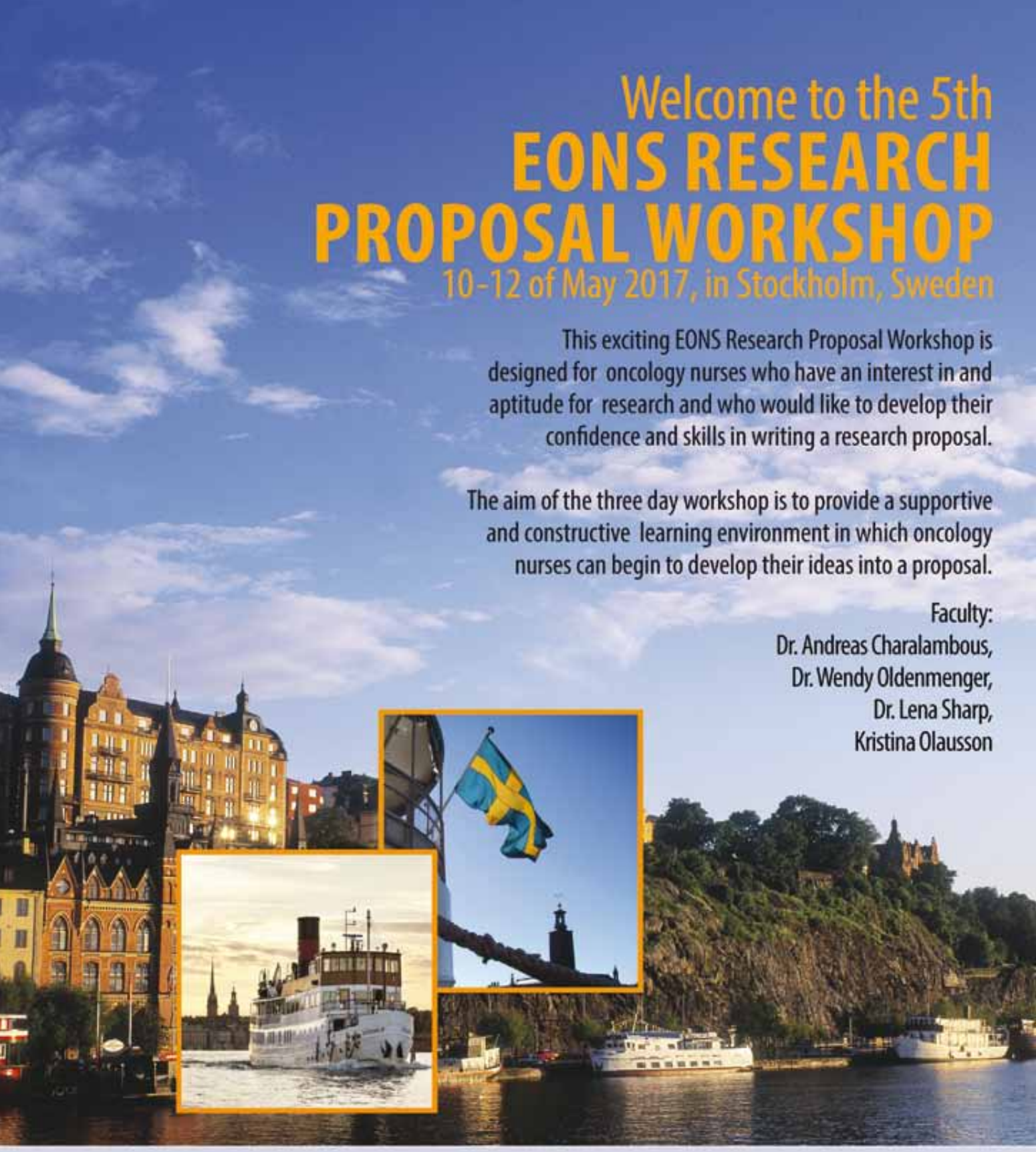

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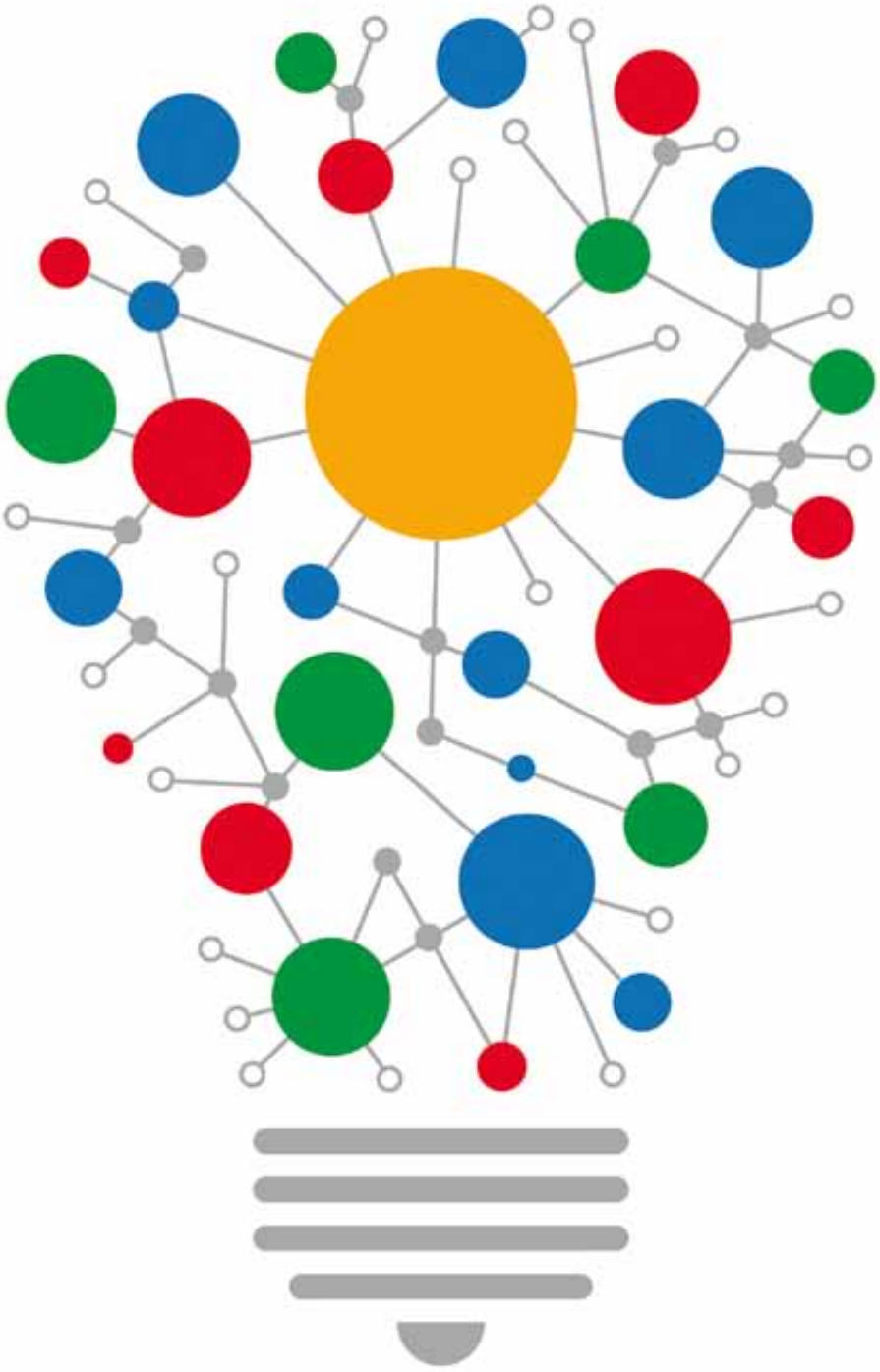

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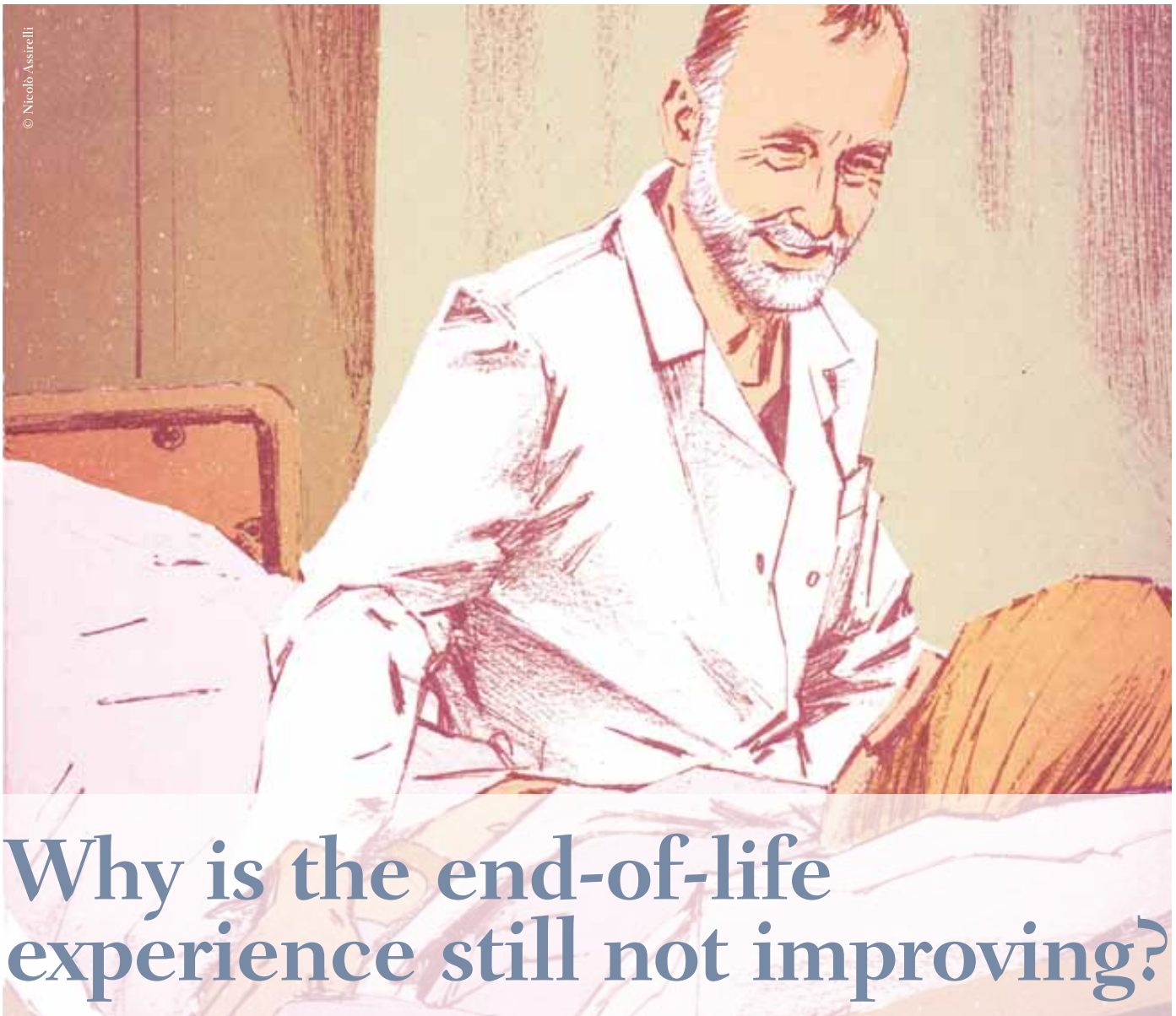
Boehringer Ingelheim



Why is the end-of-life experience still not improving?

Efforts to improve symptom control near the end of life have received more attention in recent years, but the impact is often frustratingly small. **Simon Crompton** asks where we are going wrong.

Seven years ago, Neil Bonser died from a sarcoma, aged 35. He was at home with his family, where he wanted to be, relatively free of pain, and supported by a Macmillan nurse. Neil's father, Tony, knows that the family got considerably better end-of-life care than many people. But there are still regrets.

No health professional mentioned the prospect of Neil dying from the point of his diagnosis until two days before this death, five years later.

"Because of this, we lived in hope, probably long after there was, in fact, no hope," says Tony. "Most of his last six months were spent in a fruitless search for a cure, which denied him the opportunity to enjoy the time he had

left. It also meant that all of us suffered high levels of anger, as his health steadily declined."

Tony, from Lancashire in the UK, is now a key figure in campaigns to improve end-of-life care. Would things be any better for Neil today? A lot has changed in the UK, says Tony, who has travelled around the country looking at examples of best practice: more people are able to die at home; there's greater awareness of and knowledge about symptom control and patient comfort; more professionals are trained to administer pain relief in the community.

But beyond the best practice, are people always getting access to the right medications at the right time as death approaches? Are they getting information and consultation when they need it? Are they being helped to the right balance between consciousness and pain? And is the quality of death actually improving? He's not so sure.

"There's still a lack of awareness of the dying process," he says. "And my experience is that, at home, it's still difficult to get the drugs and people with appropriate training at the right time."

Tony Bonser's experience reflects a contradictory situation that applies through much of Europe. On the one hand, awareness of the importance of palliative care is growing in health systems, and end-of-life care is improving in some countries. But there are still massive gaps and failings.

True, palliative care is no longer the 'Cinderella service' it once was in much of the world. A major step forward occurred in 2014 when the World Health Assembly adopted a resolution urging member states to integrate palliative care services into the continuum of care. And a wave of surveys and studies have indicated recent international progress.

A 2015 analysis of quality of death by The Economist Intelligence Unit concluded: "it is clear that some countries are stepping up their efforts to ensure all citizens have access to palliative care." The European Association for Palliative Care's *Atlas of Palliative Care in Europe* in 2005 and 2012 has shown that there has been significant development of at least one type of palliative care service in 21 of 46 European countries.

"At home, it's still difficult to get the drugs and people with appropriate training at the right time"

Yet the variations from country to country are still astounding. Carlos Centeno, who has headed work on the European Association for Palliative Care's (EAPC's) atlas says: "In western Europe we've seen some development of palliative care in in-patient units, but in central and eastern Europe, nothing. I don't know how western Europe can forget the other parts of Europe."

What's more, it's not always clear that development of palliative care services actually results in more people having better deaths.

Research from the David Geffen School of Medicine, University of California, has indicated that, despite national efforts to improve end-of-life care in the United States, proxy reports of pain and other alarming symptoms in the last year of life increased between 1998 to 2010. Reports of pain rose from 54.3% to 60.8%, and reports of depression and confusion from 26.6% to 31.3%.

The study was in the United States, but Stein Kaasa, Professor of Oncology and Palliative Medicine at the University of Oslo and Head of the Department of Oncology, says that studies on pain intensity in Norway have similar findings. Two evaluations over five years found that, despite more resources and training being poured into pain and symptom management, there was no improvement in patient-reported pain scores.

Disappointing results

"It's very disappointing," says Kaasa. He believes one explanation may be that improvement programmes aren't sufficiently focused and reaching into the clinical decision making process. "Pain control is still not central to decision making in oncology. The focus is still too often on the tumour and saving life, and that's why I strongly argue for integrating palliative care into the care pathway for all patients."

Small studies of proxy and patient reported scores of pain and other symptoms may be flawed, but in the absence of population-based data on end of life, they deserve attention. Research into national trends in palliative care at end of life has been extensive over the past five years, but it uses indicators that can provide international comparisons. These demonstrate how patchy services are from nation to nation, but do not necessarily reflect patient experience.

The indicators roughly fall into two categories: availability of symptom-relieving drugs, and availability of palliative care services. On drugs, for example, the WHO Collaborating Center for Pain Policy and Palliative Care publishes global data for total opioid consumption, which shows that people in Austria, Germany, Denmark, Switzerland and the UK are consuming

twice the amount of opioids per capita as Portugal, Slovenia, France, Iceland and Italy.

"If you look over the past 30 years, global consumption of morphine has increased considerably, although the increase has been much larger in higher-income countries," says Liliana De Lima, Executive Director of the International Association for Hospice and Palliative Care. "But it's a very raw indicator, because it may be being over used or figures may include non-palliative use."

The other basic indicator is the number of palliative care services. This forms the basis of European rankings produced by the EAPC in its atlas. The 2013 statistics show that the highest concentration of palliative care units can be found in Ireland, Iceland and Belgium, with almost 18–20 units per million inhabitants. The UK, Sweden, The Netherlands, Poland and Austria have 12–16 units per million.

But although comparisons between the data from 2005 and 2012 suggest that there has been overall growth, services in most countries are still inadequate to meet the needs of the population.

Most of the evolution is characterised by expanding in-patient palliative care services, but development of home care and hospital support teams has been slow. Carlos Centeno, who is clinical consultant at the Department of Palliative Medicine of the University of Navarra, Spain, says the lack of hospital support teams is particularly disappointing, given the impact they can have on integrating palliative considerations into all aspects of care.

"Does having more palliative care services result in more people having a better end-of-life experience? I don't have the answer to that, but many studies and all my experience over 20 years suggest this is the case."

Flexibility is important

But Kaasa believes it's more complex than that. Yes, certainly, having access to competent healthcare providers and home care nurses at end of life is vitally important. But equally important, as far as the end-of-life experience is concerned, is having sufficient flexibility within systems so that access to and transfers between hospitals, hospices and home care teams can occur at the right time for the patient and family.

"Access to hospitals, hospices and home care, and transfers between them, should be possible at the right time"

"Most patients want to stay at home as long as possible at the end of life, and it's important that this is made possible," says Kaasa. "But that shouldn't be the only benchmark for good end-of-life care. Death at home can be very hard for the family, and it should be one option, not the only one."

Kaasa is concerned that end-of-life experiences may not significantly improve as long as medical systems allow treatment to take priority over symptom management long after they should – as Tony Bonser and his family found out. "It's become more and more evident that symptom management should be in clinical pathways long before end of life is considered," says Kaasa. "And when a patient is getting to the stage where therapy isn't having any effect, then you need to start talking to the patient about end of life."

In Germany, there have been recent advances in access to palliative care, with state funding available since 2007 for outpatient end-of-life care provided by qualified carers. Yet the culture of treatment still dominates, according to Jutta Hubner, a German palliative care doctor and currently head of the database project at the German Cancer Society.

"We are a long way from early integration and a more 'normal' contact with the palliative care. I think no active anti-tumour therapy within the last four weeks of life is an important marker of high-quality cancer care. But it's my impression that patients are still being treated nearly until their death, especially in highly specialised clinics."

"Mostly the oncologist and the palliative care physician are different people – but I think that every oncologist and every other specialist caring for cancer patients should have a foundation in palliative care and communication."

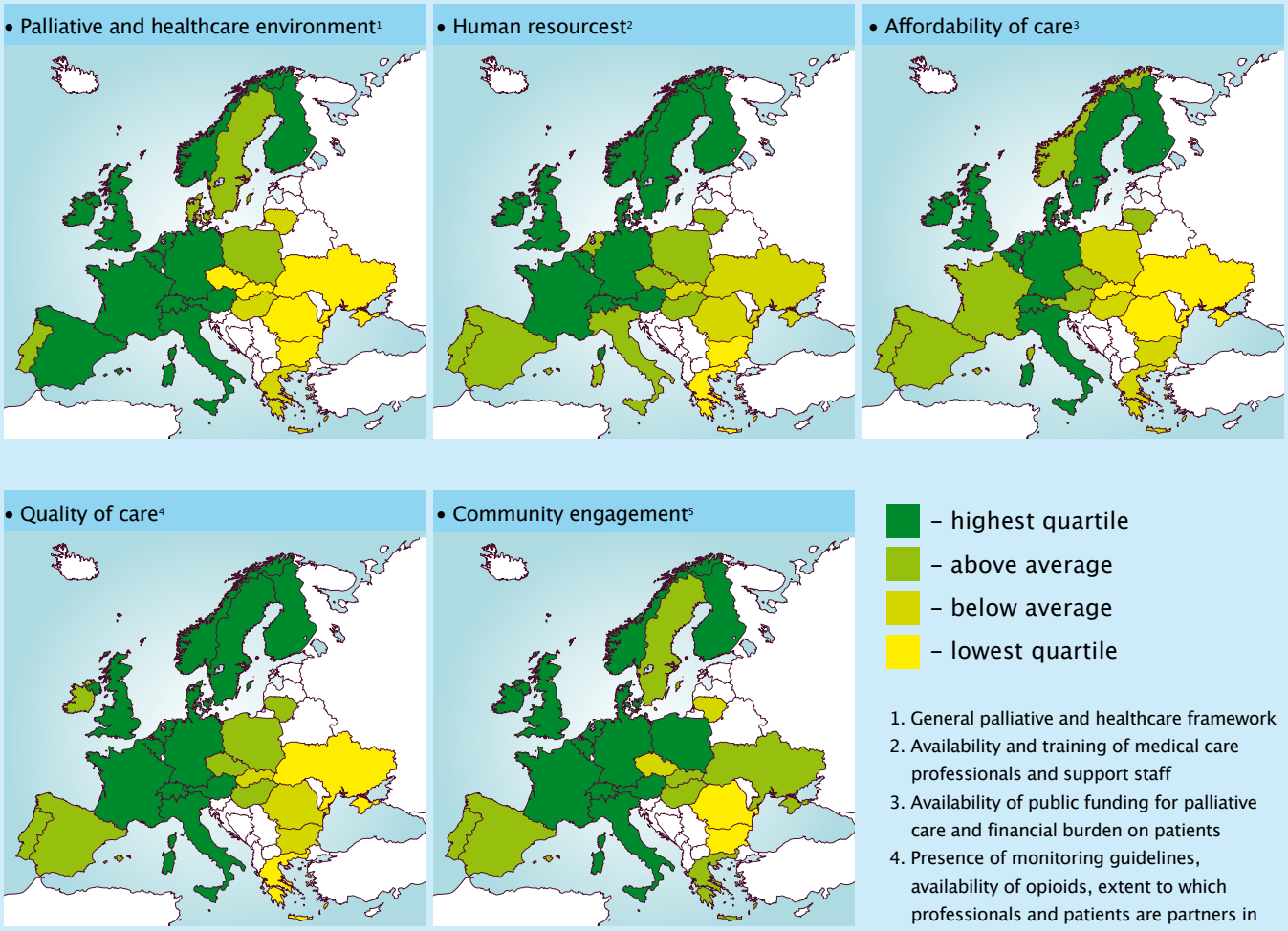
Integrating symptom control

Matti Aapro, a director of the Multidisciplinary Oncology Institute in Genolier, Switzerland, also believes the answer is integrating symptom management into a continuum of care. "Currently, when active treatment no longer works, patients are sometimes sent to another team entirely for end-of-life care," he says. "And they can feel they've been abandoned."

But though end-of-life care in western Europe is far from perfect, central and eastern Europe is in a completely lower league, whichever indicator you use. The Economist Intelligence Unit's 2015 Quality of Death Index ranked Ukraine, Romania and Bulgaria among the 20 worst performing countries in the world. The index was formed from scores of five indicators: palliative

Quality of death across Europe

The Economist Intelligence Unit ranked countries across the world according to the availability, affordability and quality of palliative care available to adults. Countries were scored according to 20 indicators, in five categories. These maps show the global quartile rankings for European countries



1. General palliative and healthcare framework
2. Availability and training of medical care professionals and support staff
3. Availability of public funding for palliative care and financial burden on patients
4. Presence of monitoring guidelines, availability of opioids, extent to which professionals and patients are partners in care
5. Availability of volunteers and public awareness of palliative care

Source: The 2015 Quality of Death Index (2015) The Economist Intelligence Unit Ltd

and healthcare environment; human resources; affordability; quality of care; and community engagement.

Equally, the European Association for Palliative Care (EAPC) survey of 53 countries shows that coverage of specialised palliative care services in central and eastern Europe is very limited – with just 14% coverage for home care teams, compared with 52% in western Europe.

Yet there are hopeful signs. The experience of Romania in the past five years, for example, provides not only the prospect of considerable improvements for cancer patients at the end of life in that country, but also a clear indication of what it takes to bring the kind of reform that Kaasa and Aapro believe is the long-term solution to improving patients' experience at end of life.

Hopeful signs

The EAPC atlas shows that Romania ranked 26th out of 28 European countries in terms of palliative care resources in 2013. Yet in terms of palliative care "vitality" – an EAPC index reflecting existence of a national association, directory of services available, existence of physician specialisation, level of attendance at conferences and level of publication – Romania ranked third, surpassed only by Germany and the UK.

Ten years ago, there were no in-patient palliative care services. Today there are 75.

Daniela Mosoiu, National Director for Education, Strategy and Development at the Hospice Casa Sperantei Foundation, Brasov, is excited at the development of palliative care in Romania. A national development strategy began in 2010 and now has backing from the World Bank.

"The state is becoming more aware of its responsibilities," says Mosoiu. And since the strategy coincides with a long-running health service reorganisation, new initiatives are being integrated into mainstream health systems. "The body responsible for hospital accreditation has now has put forward new standards for relieving suffering at end of life, and one of the criteria they are using is pain. Hospitals have to assess symptoms and have appropriate medications ready in the pharmacy. There will be an assessment system for hospitals from the beginning of next year."

There is also progress in education, with palliative care now recognised as a subspeciality, and a long waiting list of doctors waiting to enrol in training.

Use of opioids has not increased significantly over the past 10 years, she says, even though national regulations changed in 2007 to make them available to all doctors and pharmacies. "There's the question of whether clinicians are confident to use them, and there are also patient fears," she says. Interestingly, pilot studies examining the impact of symptom management by GPs in patients at home have indicated that it is counselling, emotional support and grief support that are most valued by patients and families, not pain relief.

But Mosoiu is hopeful that in five years' time, Romania will no longer be at the bottom of the palliative care rankings. What's been the main factor that has brought such vibrancy and willingness to change in both government and health systems? Mosoiu is clear. "The pressure has come from the grass roots – from people with knowledge in palliative care pushing authorities, putting forward proposals, persuading them of the need to change regulations. The programmes have been developed by local managers."

Pressure from below

That message – that the individuals with knowledge and passion about palliative care are the ones who can change healthcare systems to integrate it – is echoed by many others.

Liliana De Lima says the key ingredients for improving end-of-life care are political will and palliative care champions. "Each country needs people who are energised and keep pursuing their agenda to push it forward. People like Daniela Mosoiu."

Carlos Centeno believes you achieve that kind of energy by ensuring that as many people as possible are educated about symptom management and the potential of palliative care.

"The key to good end-of-life care is integration," he says. "If it's outside the health system in an independent hospice, it doesn't work. If it's just for cancer patients, it doesn't work. If it's in the last week rather than the last months, it doesn't work. It has to be part of a health system and part of a home care system. As I heard at a conference recently, palliative care has to be as the air that we breathe."

> **"It's people standing up locally and saying that palliative care is important that has brought real change"**

"How do you get that integration? If we started teaching palliative care to all medical and nursing students today, we would have integrated palliative care in 10 years. We need all physicians to know about symptom management, and then things will change."

And Tony Bonser is equally clear that yes, funding, infrastructure and political will are all important if end-of-life experience is to improve for patients and their families. But from what he's seen, it's people standing up locally and saying that palliative care is important that has brought real change.

"My impression is that improvements in experience at end of life are not driven by pathways, or schedules or inspections. They're driven by the right people saying: 'This is important.' We're still in the situation where we're having to convince doctors that a good death is a success, not a failure. There has to be a change of perspective among medics, so that palliative care becomes a fundamental part of what they do."

Cancer journalism awards shared across four continents

Journalists from Germany, India, Kenya and China have been recognised for their outstanding articles in the Cancer World Journalism Awards. The articles were judged best in their category out of a total of 145 entries – a record number, coming from a greater range of countries than ever before. Each winner receives a prize of €1500. The overall winner will be funded by *Cancer World* to attend the ECCO European Cancer Congress in Amsterdam in January 2017.

Patient access to gene testing in Germany

Pia Heinemann from Germany won the Research, Science and Treatment category, and the overall prize, for her article published in *Welt Am Sonntag* about the need for patients to have access to gene testing to protect them from unnecessary chemotherapy. Pia said: *"The current scientific advances in oncology are impressive. For me, as a journalist, it is very interesting to observe how difficult it can be to bring these advances to the patient."*

The state of cancer care in Kenya

The winner in the Patient and Carer Experience category was Pauline Kairu for her patient-centred investigation into the state of cancer care in Kenya for the *Daily Nation* newspaper. Pauline said she was delighted to win the award: "*It comes as such a gratifying affirmation that there's reward for hard work and focus.*"

No painkillers in India

The winner in the Policy, Services and Affordability category was Suman Naishadham for her article "Cancer with no pain meds? The tragedy of India's painkiller shortage", published by *The Influence*, a US journalistic website focused on stories about human relationships with drugs. *"This makes it all the more encouraging to be rewarded for an article on India's narcotics policy and its effects on the country's terminally ill*," said Suman.

Prevention in China

The winner in the Prevention category was Duanduan Yuan, a health and environmental journalist on *Southern Weekly* newspaper in China. The judges commended her responsible investigation into the alleged link between talcum powder use and ovarian cancer. "*This award not only encouraged me to write better stories, but is also a call for all people to be aware of the importance of cancer prevention*," she said.

The judging panel also gave a special commendation to a group of entrants who had used funding from the European Fund for Investigative Journalism to carry out an impressive cross-border investigation into why cancer patients in eastern European countries often cannot afford the newest therapies, and the role of the EU in setting the drug prices. These highly commended journalists are: Eric Breitinger (Switzerland), Aleksandra Jolkina (Latvia), Stanimir Vaglenov (Bulgaria), Cristian Niculescu (Romania), David Leloup (Belgium) and Dimitra Triantafillou (Greece).

Alberto Costa, Editor of *Cancer World* and a member of the judging panel, said he was delighted that the new award had attracted so many high quality entries from all over the world, and in so many different media. *"This is an indication of the important role journalists are playing globally in highlighting cancer experience, inequalities and the need for service improvements," he said. "Cancer World and the European School of Oncology believe it is important to promote and support all they are achieving."*

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New award

The Cancer World Journalism Awards replaces the European School of Oncology's Best Cancer Reporter Awards, which have been run since 2006. The new award recognises individual works of cancer journalism rather than a journalist's overall contribution to covering cancer topics, and includes four categories for different article types. *Details about ESO's journalism programme can be found at www.cancerworld.net/media*

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George Pentheroudakis: blue-sky thinking in Greece

The head of Medical Oncology at Ioannina University Hospital not only oversees ESMO's prolific output of clinical guidelines, but also helps ensure that they can be sustainably delivered in his own country, where hospital budgets have never been so tight or doctors so few. **Peter McIntyre** asked him how he does it.

Since the start of the financial crisis in Greece, about 15,000 doctors have left to work in Germany, Sweden, the UK, France or the Middle East. Restrictions imposed by the troika that polices the Greek economy exert a tight grip on the Greek National Healthcare Service (ESY), and opportunities for doctors at home are limited.

The Department of Medical Oncology at the University Hospital of Ioannina in northern Greece is renowned across the country, providing state-of-the-art treatment and care, as well as access to innovative cancer therapies. However, the new head of department, George Pentheroudakis, finds himself at least four consultant oncologists short of what he needs to serve a population of more than half a million people.

Pentheroudakis has a vision for plugging the gap by developing research to improve care for patients, save the health service money, and attract back some of the talent that has left the country.

He is well placed to play a leadership role in Greece as chair of the Scientific Committee of the Hellenic Cooperative Oncology Group (HeCOG), and more broadly in Europe as chair of the guidelines committee of the European Society for Medical Oncology (ESMO), working to improve standards of care in EU countries.

HeCOG is a non-profit network of 15 regional tertiary cancer centres across the country, each serving 500,000–700,000 people (http://hecog.gr/en/). In the absence of government grants, research is funded by pharmaceutical companies, benefactors, European grants and income generated by investigator-initiated clinical trials.

In a country of 11 million people, phase III trials are beyond its scope, but HeCOG sponsors and manages phase I and phase II trials with a translational research component. Under Greek law, sponsors of clinical trials must fund not only the investigational medicinal products (IMPs) but also all other products in the trial, including standard chemotherapy on a comparator arm.

Pentheroudakis says: "We do the whole package: patient accrual, regulation, data management, pharmacovigilance, management of the tissue bank. If we or you have an idea, fine, we run the trial, and have ownership of the data, but we have to have a legal agreement with the pharmaceutical company to provide the investigational agents as well as some

financial support for the infrastructure of the trial. We use this income to survive and be active in the field of clinical research and translational cancer research."

Pentheroudakis sees this as an all-round win. "It is a definite benefit for the patient. Say 40–50% of our cancer patients are not going to do well so they need novel treatment options, and we provide these options within the context of the trial. It is a benefit for the scientific community, because we generate new data, even if they are not registration trials. It is a benefit for the state, because all these therapeutics are provided free to the hospital and to the patient – so you can imagine the saving."

He hopes to help reverse the brain-drain by opening up more posts for doctors using money raised for research

Research also boosts levels of care within the 15 centres. "Whenever you run trials, you set up mechanisms for quality control. Everybody is going to benefit – the patient inside or outside the trials, and the doctors, because they get to know the proper way to do things."

His hope is that it will also make a contribution to reversing the brain-drain, opening up more posts for doctors using money it raises for research. "The Greek NHS was created using the British NHS as a template, so you have to convince the government to advertise jobs, and this is currently difficult. Research is another way to do that, because you generate 'soft money' you may use to keep people here. Some Greek doctors would maybe return if you show them there is a network and structure where they can run clinical trials and have a forum in scientific congresses."

HeCOG runs its own biobank, with 14,000 formalin-fixed paraffin-embedded blocks, all fully annotated with clinical data from patients treated in network centres. There is a HeCOG molecular oncology laboratory in Thessaloniki, with a second smaller laboratory in Athens. Pentheroudakis has plans to set up a liquid biopsy laboratory in Ioannina in 2017.

ESMO guidelines

This strong background in research has given Pentheroudakis a foundation to work more broadly with ESMO. He was introduced to the ESMO clinical practice guidelines in 2007 by his predecessor Nicholas Pavlidis and Rolf Stahel, then chairman of the guidelines committee. Four years ago he became co-chair of the ESMO clinical practice guidelines committee and this year became the sole chair.

ESMO produces an astonishing range of consensus and clinical practice guidelines – 75 produced so far, with regular updates to keep practitioners abreast of new developments. Pentheroudakis works with the authors (medical oncologists, surgeons, radiation oncologists and others), and seven subject editors and deputies, who are all top specialists in their area of expertise. Each guideline is peer reviewed by five to seven independent ESMO members before it is approved by the committee.

In September 2016 alone, ESMO published new guidelines on acute lymphoblastic leukaemia in adults, B-cell lymphoma, and prevention and screening for BRCA mutation carriers, as well as updating eight other guidelines. October saw publication of consensus guidelines for care of patients with malignant lymphoma, and November publication of seven sets of 'pocket guidelines' – easily accessible abridged versions – for the ESMO cancer guidelines mobile app.

The guidelines team has to run fast just to keep up, says Pentheroudakis. "It is impossible to update 75 guidelines every year, so we produce or update 10–15 a year. Even so there may be a breakthrough which cannot wait for the update."

In such cases, subject editors, authors and Pentheroudakis as the chair of the

Peter McIntyre

guidelines committee, produce a brief e-update with the new data, a recommendation and a reference. This appears on the ESMO guidelines website, is circulated with the newsletter, and links to the full guideline in the website.

Pentheroudakis stresses that the guidelines are designed to aid practitioners in treatment decisions rather than for regulatory or funding decisions. "ESMO guidelines are produced by the cancer specialist for the cancer specialist, not by the authorities to be used for reimbursement or for health technology assessment. If you went down that way you would have to change the whole character of the guidelines. They would have to be hundreds of pages long with a systematic review of all the data, and you would have to put health economics in there."

By contrast, the ESMO guidelines are compact. Each has a management flow-chart by tumour and stage characteristics, and is colour coded: red for surgery, green for radiotherapy, blue for systemic therapy. Guidelines are freely available for download from the ESMO web site (www.esmo.org/) and the OncologyPro website (http://oncologypro.esmo.org/), and they are published every September in the *Annals of Oncology*.

The abridged pocket versions summarise the guidelines in three or four pages, with handy tables on staging, and bullet-point recommendations on therapy. Guideline sessions in every ESMO congress present real clinical cases.

Even so, the guidelines need something extra to help with priority setting, and they are now being linked to the ESMO Magnitude of Clinical Benefit Scale (MCBS), a tool to help clinicians choose the most effective anti-cancer drugs.

The MCBS assesses clinical benefit rather than statistical significance, scoring new therapies on a scale from A to C for curative therapies (A being highest) and 1 to 5 for non-curative therapies (5 being highest). MCBS scores are being added to the guidelines for all new drugs given EMA approval since January 2016. For example, the non-small-cell lung cancer guideline updated in September 2016 now includes a flow chart with MCBS scores for nivolumab, pembrolizumab, and afatinib.

"There is no cost data in there, because we are living in the European Union where there are 27 different pricing and reimbursement systems. We are saying that, if you have a new drug approved by the European Medicines Agency and it scores a 4 or a 5 for extra clinical benefit, then you have to provide the drug for your patient, even if you are bankrupt. If it scores 1, 2 or 3, you make up your own mind, depending on your financial situation.

"You have the ESMO guidelines, with state-of-the-art management, and you also have a tool that gives you information on whether a statistically significant difference is clinically meaningful. You can use that tool to make some decisions with your patient or with your funding body."

This is particularly helpful in countries like Greece, where there is no health technology assessment body to advise doctors and – in theory – an open door policy on drugs. "Every novel therapeutic agent approved by the EMA is approved by the Greek state and has to be provided to Greek patients. Nobody tells me that I should not prescribe bevacizumab in some cases because it is not cost-effective."

"How am I going to rationally decide which expensive drug to use? That is where the clinical benefit tool comes in handy"

Of course, behind the scenes there is a hospital administrator tearing their hair out. "Quite often there are indirect administrative or financial pressures about the annual drug budget finishing so I should try to rationalise my spending. How do I do that? Everything is approved, and the patient might sue me if I do not treat them with whatever is approved, so how am I going to rationally decide which expensive drug to use? That is where the MCBS tool comes in handy. I can use that as an argument, a reason for the administrator and for the patient."

Work-work-research-life balance

Pentheroudakis is associate professor of oncology with a full clinical workload. "I see patients every day. I have to be a physician. I have on-call duties and at the same time I have to be a teacher and a researcher. It is tricky. It is a matter of organising your time and having good co-workers. I do my morning clinic. I do the ward rounds because I am the chair of the department, and then in the afternoon I invest time in teaching and in research.

"You have to work in order to know what the problems in your working environment are and to avoid losing touch with the scientific reality of your job. I enjoy doing the clinic and seeing patients. I think it grounds you.

"You have to invest time in all aspects of professional life in my opinion. You should not just be a conference traveller and you should not restrict yourself only to the clinical job. You have to see patients; you have to develop clinical trials

and you have to be networked with professional colleagues in Europe and throughout the world."

Pentheroudakis plays basketball, skis, sails and stargazes and is committed to spending quality time with his family and friends to keep his life in balance.

Three of his early years in oncology were spent in Glasgow. "In Scotland people were very friendly and hospitable, I consider it my second country. However, it was very dark. I missed the light so much. I think that I am lucky living in Greece because I feel that the blue sky and the diffused light that is there in our physical universe is a drug that makes you optimistic."

A bright outlook: Pentheroudakis makes time for family life and outdoor activities and says the special quality of light in Greece fuels his optimism

Before he left for Glasgow in 1999, cancer was a taboo topic in Greece. "You were not allowed to say the word, and you got pressure from the family not to reveal the diagnosis to the patient. Now this has changed. People want to know about the nature of the disease, and they want to be informed about the therapeutic plan and the prognosis. But since you ask me about the differences between the Anglo Saxons and the Greeks, let us say that the Greek patient would like to have hope infused into the briefing process. You still have to tell them that they have cancer and be frank and sincere, but you have to find a way to provide some hope. And there is always hope."

"You have to work to know the problems in your working environment and avoid losing touch with the scientific reality"

In his own specialty of gastrointestinal cancer, providing hope has become easier. Patients with metastatic colorectal cancer used to have a life expectancy of six months. With new medicines and surgical techniques, median life expectancy has risen to 30–35 months, and he believes it will become a chronic disease. More than eight out of ten patients with localised gastrointestinal cancers can be cured through surgery.

In areas where treatment is less effective – such as pancreatic and gastric cancers – the research challenge is to find the biomarkers that will predict which patients can benefit from the new therapeutics. Pentheroudakis is a strong supporter of initiatives such as SPECTA, the EORTC's biomarker screening platform for colorectal and other cancers. "The way forward is to create a universal pan-European tissue bank, so everybody who comes through the door of the clinic will have their tumour phenotyped, and the data about molecular characterisation of the tumour will be stored so that it is going to be easier to find the patients you are looking for with a specific molecular tumour make-up."

He hopes that the liquid biopsy lab he is planning for Ioannina will contribute to that process. It is also part of his strategy to attract consultants into the department, since university departments can use soft money to employ an academic fellow, who can also be a specialist consultant. Of course, this gives him another task in writing grant proposals. "This is indeed a problem," says Pentheroudakis, "but what is the mood in this country? It is to survive through the day. So if I have a consultant with a five-year budget I would be fine."

He believes that HeCOG, self-sustained and quality-controlled for more than 15 years, can be seen as a paradigm for restoring progress in Greece. "As a state and society we have to become competitive and rationalise our spending and the way we behave as professionals. Structures such as HeCOG that do a terrific job of clinical and translational research within a spirit of collaboration and self-sustainability can be models for what this country needs."

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Systematic reviews – your key to evidence-based medicine

Evidence-based medicine is the cornerstone of medical practice, and yet clinicians are rarely offered training in the tricky business of finding, evaluating and making sense of the evidence they need. **Anna Rouillard** reports on an ESO-Cochrane Masterclass which seeks to fill that gap.

With the abundance of scientific literature on cancer treatments available, choosing the right one should be a simple matter of consulting the evidence and identifying which best answers the needs and priorities of your patients.

That is easier said than done, however, as around one million papers from clinical trials have been published to date – much of it presenting conflicting results, sometimes derived from poor-quality research methodology, and often addressing questions of marginal interest to patients and practitioners.

The ability to find and evaluate all the relevant studies, and draw robust conclusions from the totality of the

Collaborating to improve decision making

The Cochrane Collaboration was founded in 1993 under the leadership of Iain Chalmers, then director of the UK's Cochrane Centre, with a mission to "prepare and maintain systematic reviews of relevant research to help improve decision making in healthcare". Its roots lay in earlier work done at the UK's National Perinatal Epidemiology Unit on the effects of care in pregnancy and childbirth, which was undertaken by Chalmers and others after he discovered that some of the obstetrics practices he had been taught were unsupported by reliable evidence. Chalmers' mentor, Archie Cochrane, said that obstetrics was "the least scientifically based specialism in medicine", and challenged him to carry out a systematic review of the available evidence.

The results were published in a two-volume book, with a shorter paperback version for women. They were also published in a digital format, for ease of updating. The Cochrane Pregnancy and Childcare database formed the start of the Cochrane library. The Cochrane Collaboration was established a few years later.

Today it is a huge network comprising more than 40,000 contributors across 130 countries, working in 52 review groups, most of whom do their work on a voluntary basis, using an agreed systematic and transparent methodology.

If you are interested in conducting a systematic review to find and evaluate the evidence on a particular topic, you can contact Cochrane to find out how to get involved. http://community.cochrane.org/

evidence, takes skill and practice, but it is not generally taught in medical school. So when the European School of Oncology started teaming up with the Cochrane research collaboration to offer a week-long Masterclass on how to use, evaluate and conduct systematic reviews, there was no shortage of applicants.

Carlos Cargaleiro, a critical care cancer nurse from Portugal, currently working in the Royal Marsden Hospital in London, explains why he was so pleased to get a place on last year's course, which was held as usual at Queen's University, Belfast.

"For me, giving patients the best possible available care is very important. But this means being constantly up to date on the latest evidence, which is a huge challenge when thousands of new articles are being published every single month," he says. "As a nurse, I work as a member of a team which uses a specialised protocol. If I am suggesting changing practice based on evidence from a systematic review, I need to be able to present strong evidence to senior nursing staff. For this reason, I need to be confident of the quality of the articles included in the review, and that the review itself was done based on reliable methodology."

The methodology for appraising and synthesising evidence taught at the Masterclass has its roots in an innovation introduced 40 years ago, when the statistician and researcher Gene Glass presented research findings in psychotherapy in the form of 'an analysis of analyses' (*Educ Res* 1976, 10:3–8). The advantage of this type of 'meta-analysis' was that it made use of all the available evidence by combining and averaging the results of several studies.

It wasn't until the Cochrane Collaboration was set up in 1993, however, that the methodology of systematic reviews began to be developed across all areas of healthcare, covering how to define research questions, identify relevant studies, assess the quality of the studies, summarise the evidence (which may include meta-analysis), and interpret the results. Now known simply as Cochrane, today it involves a network of 40,000 researchers across 130 countries, working in 52 review groups, and the systematic review has become accepted as a cornerstone of evidence-based medicine.

Systematic reviews in cancer

Mike Clarke, Director of the Northern Ireland Hub for Trials Methodology Research, who co-chairs the ESO–Cochrane Masterclass, has been heavily involved in systematic

reviews for the past 25 years, and says they have played a crucial role in developing our knowledge about the comparative risks and benefits of different cancer treatments.

"In the seventies and eighties, the early years of systematic reviews, this methodology enabled us to identify some cancer therapies that weren't working, such as old-style immunotherapy. Some of the big successes of systematic reviews have been in breast cancer, where we've shown that drugs like tamoxifen are beneficial, that chemotherapy is beneficial, and that ovarian ablation or suppression in the absence of chemotherapy is beneficial."

Some, such as the breast cancer reviews, are substantial research projects, with a large amount of funding, while others may be done in researchers' or practitioners' spare time over several years.

"Twenty years ago, there were hundreds of reviews available," says Clarke. "Now there are tens of thousands done, with eight or nine thousand appearing every year." Their proliferation, he adds, shows that they are increasingly considered good pieces of scientific research that practitioners and researchers want to contribute to.

Fergus Macbeth, joint coordinating editor of Cochrane's Lung Cancer group, says that in some countries, systematic reviews have had a significant impact on clinical practice. "In the UK, every time NICE (National Institute for Health and Care Excellence) develops a guideline, a systematic review is routinely conducted." This is not the case in every country, he adds. "In some countries hospitals rely on national or local guidelines of varying quality, or simply follow the practice set by the most senior person in the department."

Macbeth is an ardent believer in the power of Cochrane reviews to deliver strong evidence for decision making. Over the years, his own lung cancer group has completed 45 reviews, 39 of them on treatments, including multimodality therapy and even holistic therapy, in different types and stages of lung cancer, as well as a few on prevention, diagnosis and early detection. He points out, however, that because Cochrane reviews generally only consider evidence from randomised controlled trials, there are whole areas of oncology that are not well covered. "Clearly some very important questions in oncology are related to the best ways of managing the patient in non-pharmacological ways, and there is too little high-quality research done in these areas. This may be because of the research infrastructure and the way research is funded, which currently prioritises studies on new drugs and genomic medicine. So evidence is sorely lacking in these other areas."

As Clarke explains, systematic reviews are useful when a body of research evidence has built up on a topic, but people are struggling to interpret it, and where bringing all the evidence together and analysing it will bring clarity to the problem. A large amount of evidence is not needed for this exercise to be of value, he stresses. "Reviews that resolve uncertainty and give guidance to decision makers are perhaps the most important, but reviews also need to be undertaken in areas where research is sparse, since they can serve to highlight the fact that there is insufficient evidence available on a particular topic and that the existing research cannot answer the question reliably."

A critical approach

The quality of available research may be as much of a problem as the quantity, as John Ioannidis pointed out in his recent paper 'Why most clinical research is not useful' (*PLoS Medicine* 2016, doi:10.1371/journal.pmed.1002049). He highlights frequent problems with transparency, with reports lacking key information on data, methods and analysis that could give readers the opportunity to evaluate for themselves the credibility of the reported results. Highly selective study populations may limit the applicability of findings to real life patient populations. The questions asked, or the endpoints measured, may relate only peripherally to the issues doctors and patients need answers to. And he points out that doing a meta-analysis of flawed studies doesn't address the flaws, and may in fact compound them.

This, says Clarke, is why systematic reviews are so important, because they don't just aggregate data, they take a critical look at the quality of the available research evidence. "The review can draw attention to how flawed the existing research is, which enables decision makers to realise that what they thought was proven, may not actually be proven."

Non-publication of trial results as well as outright fraud may also jeopardise the reliability of the available evidence, he adds, which is why systematic reviews commonly use funnel plots to identify inconsistent data, which may point to publication bias.

Poor quality trials cannot be improved by systematic reviews, he argues, and inadequate and inappropriate review methodologies can lead to unreliable findings, even if the trials are good quality. "It might be called a systematic review", he explains, "but this doesn't mean it actually is a systematic review." That is why it is so important that practitioners learn how to evaluate the quality of a systematic review. "They need to be able to assess how well studies have been sought, and whether the answers actually make sense."

What we learnt

Twenty-four participants from 13 countries and from a range of cancer disciplines – surgical oncology, radiation oncology, medical oncology, urology, nursing and pharmacy – attended the 2016 ESO-Cochrane Masterclass. This is a flavour of what they took away:

"It helped me a lot to have the collaboration of the other participants."

"I refined my question and that helped me to define with more quality the inclusion and exclusion criteria."

"Formulation of the question: it emphasises the importance of getting it right from the beginning."

"I had never received such information before, because it is not taught in my country. Now I can tackle all parts of systematic reviews and know how to do it in the most straightforward and correct way."

"The practical sessions gave invaluable insights about systematic reviews and allowed me to construct a critical reflection about my own work."

"The interactive group sessions were probably the best part."

"It is very helpful to know that there are different kinds of biases and that there are tools to predict the degree of heterogeneity among included studies."

"I frankly and honestly believe that Mike Clarke is the teacher that all of us should have at least once in a lifetime."

"My project Is still a work in progress but I hope that with the support of my mentors and colleagues I will conclude it soon."

ESO hopes to run a third ESO-Cochrane Masterclass on Systematic Reviews in Summer 2018.

Skills for clinicians

Cargaleiro feels his five days at the Masterclass have left him far better equipped for this task. "My ability to analyse and evaluate systematic reviews has improved considerably," he says, and he lists some key lessons he has learnt about how to conduct these sorts of reviews himself. "You need real teamwork to do systematic reviews," he says. "Having a broad spectrum of experts at the table is essential to enable you to come up with a good research question. And once you've defined your research question, you need to know how to search for studies."

When selecting search terms, he adds, it's important to be imaginative, as the studies thrown up by a search will depend on the chosen spelling or terminology. 'Caesarean', for example, will yield 17,000 results on PubMed, whereas 'cesarean' brings up 53,000 results, and 'c-section' 48,000 results.

Language barriers are another problem. "Not all research is translated into English, and such findings will not be published on sites such as PubMed. If you are doing a review of evidence in English, you need to make sure the results will be applicable to the population it is intended for."

But the Masterclass is not just about the theory. Participants get the chance to put some of the theory into practice, in sessions where they present their own ideas for systematic reviews to one another. "When you have different people listening to your ideas and providing feedback, your project idea can only improve," says Cargaleiro. "They will help you see that maybe your idea is too broad, and you need to focus on a narrower theme, or that in fact you are trying to answer two questions when you should only be focusing on one."

Clark believes these sorts of skills should be taught far more widely to reduce waste in medical research and ensure that clinically important gaps in knowledge are identified and researched. He argues that no new research should be done until a review is made of what already exists, to avoid duplication and identify gaps – which may seem like common sense, but very often doesn't happen.

He also points out that systematic reviews are, usually, fairly economical to carry out. "They are scientific projects that require resources, but much of the resource use has already been spent by doing the studies. The research studies may have cost hundreds of millions of dollars, and the review is bringing all that evidence together, and, statistically, has potentially much greater power than any individual study."

Cargaleiro agrees, and says that cancer practitioners should look for opportunities to feed into research prioritisation so the right questions are answered, and they should be aware of the available evidence, and how to assess it, or it will go to waste. "It's important that research is not done just by researchers. They have a key role, but it is also imperative that clinical staff are involved. The worst possible scenario is that research is done that people in the field do not use."

Philip Poortmans

ECCO President-elect

As ECCO's new President-elect, Philip Poortmans is the first person to have a full democratic mandate from across all ECCO's 24 member societies which, between them, represent the full range of healthcare professionals involved in delivering specialist cancer care. *Cancer World* Editor, **Alberto Costa**, asked him how he intends to use that mandate.

Alberto Costa: *You'll be taking over as President-elect after the ECCO2017 congress, which is itself an innovation, as the first of the new style of ECCO conference. What will your priorities be?*

Philip Poortmans: My first priority will be to emphasise the critical importance of a truly multidisciplinary partnership, based on equality, mutual understanding, trust and – why not – friendship. This is vital because only by working closely together can we offer patients the best possible personalised treatment and care. For this we need a continuous dialogue between all partners and stakeholders who are active in the cancer community.

We are also facing new challenges, including a growth in the number of cancer patients, an ever-increasing speed at which new developments are being introduced, and an impending shortage of the cancer workforce. Against the background of limited resources, we should all together, in close partnership with the patients, design the best possible oncological landscape and convince the policy makers of investing in this in the best possible way.

My second priority will be to further expand the active involvement of our patients, as they are our most valuable partners. We need their input into defining the goals to

achieve that we should be working on together. This will mean integrating patient advocates in the discussions and processes that will determine how our scientific and professional societies evolve.

It is our shared commitment to design the required changes in the way we conduct our own scientific and educational activities, and to participate in managing change in the way healthcare is organised and delivered. This calls for a partnership with patients, so that we can work together to make a difference by jointly shaping policy, education, health service research and so on.

My third priority is to ensure that we continue to proactively adapt our strategy and ways of working in line with changes in the world around us. We need an open structure and an ability to lead collaboratively, in a very constructive way, to incorporate required changes quickly. The ECCO Board should therefore reflect, on a regular basis, on the extent to which our strategy is up to date and, whenever doubt arises, it should critically review the way in which our vision is translated into a strategic approach. The keywords of 'patient involvement' and 'multidisciplinary collaboration' will apply to whatever adaptation might be required!

AC: *ECCO claims to be 'the unified voice of cancer professionals' in Europe. How can you fulfil this role going forward?*

PP: It is impossible to overstate the importance of engaging with politicians and policy makers, based on a single vision and mission, if we are to achieve the significant changes we need in healthcare policies, in line with our patients' rights and hopes. ECCO will play this role, in close partnership with our patients' representatives, as we represent all European oncology disciplines, united behind our shared mission to "uphold the right of all European cancer patients to have access to the best possible treatment and care".

While inwardly – in the world of oncology – this shared mission serves as a unifying factor, outwardly it is an invaluable asset in our efforts to convince politicians and policy makers to focus much more on efforts to alleviate the burden of cancer in the interests of the future health of mankind.

Patient advocacy groups also have a central role in these political advocacy activities, partnering with the oncology caregivers and researchers we represent. They carry particular weight with policy makers, as they speak for the people who are directly affected, representing a growing electoral constituency with an increasingly influential public voice.

AC: *You were recently elected by means of the first secret ballot to be used in electing a future ECCO President. Is there more democracy to come?*

PP: Yes, certainly! I am a democrat, always searching for consensus-based decisions. But this should not be allowed to paralyse the organisation. Some complex decisions may therefore have to be taken by simple majority voting, using the President's vote as the decisive one if necessary.

Of importance is also the position and the role of the representative of the Patient Advisory Committee (PAC), as member of the ECCO Board and as co-chair of the ECCO congress, which emphasises the importance we attach to actively engaging the patients into the activities of ECCO.

I think the way we set up the ECCO17 congress offers a nice example of democracy in action, with all partners involved as much as possible. But we need to recognise that it's not going to be possible to always satisfy everybody.

AC: *Traditionally we have seen a marked imbalance between the role of the main member societies (the researchers, oncology nurses, medical oncologists, cancer surgeons, radiation oncologists and paediatric oncologists) and the 'minor' ones. How do you intend to generate more involvement and participation among all 24 member societies?*

PP: After the adoption of the new statutes in 2015, all member societies became fully equal. As a first tangible effect, the separate meetings of the so-called Founding Members ended. After more than 30 years of ECCO's existence, the path to equality is not something that will be fully realised and translated into the minds of the members immediately – but who knows, it might be a good objective to translate this into real practice by the end of my presidency!

Philip Poortmans is Head of the Department of Radiation Oncology at Radboud university medical center in Nijmegen, The Netherlands. In Spring 2017 he will move to Institut Curie in Paris. His main topics of interest are the multidisciplinary management of breast cancer, quality assurance in clinical trials, malignant lymphoma and rare tumours. He is Past-President of the European Society for RadioTherapy and Oncology (ESTRO), he has represented radiation oncology on the Multidisciplinary Oncology Committee of the European Society for Medical Oncology (ESMO) and he currently chairs the Oncopolicy Committee of ECCO.
He will serve as ECCO's President-elect in 2017 and take over as President in 2018.

Bridging the gaps in cancer care

ECCO, the European CanCer Organisation, through its 24 member societies represents over 80,000 professionals. It is the only multidisciplinary organisation that connects and responds to all stakeholders in oncology Europe-wide. ECCO is engaged in ensuring that the oncology value chain is optimised for all cancer patients by finding synergies between different members' expertise and knowledge, focusing on patients and their needs and interests, and addressing disparities and inequalities in cancer outcomes across Europe. In 2017, the work of ECCO will result in four new papers: an ECCO position paper on access to innovation in cancer care, two papers defining the ECCO essential requirements for quality cancer care (ERQCC) – for colorectal cancer and for soft tissue and bone sarcomas – and an ECCO position paper on integrated primary and secondary care.

Based on ECCO's new strategic plan, and developed with input from member societies, the ECCO position paper on access to innovation in cancer care offers a truly multidisciplinary perspective on how to encourage access, responsibly and sustainably, while improving on existing practice and decreasing waste and inefficiencies for all patients. This paper is intended to provide the basis for future actions to be taken by all health professionals in oncology. The new ECCO2017 European Cancer Congress in Amsterdam on 27-30 January 2017 will further define these actions.

ECCO's work defining essential requirements for quality cancer care (ERQCC) focused last year on colorectal cancer and bone sarcoma and soft tissue sarcoma in adults. With a focus on the European context, ERQCC manuscripts are produced to give oncology teams, patients, policy makers and managers an overview of the elements needed in any healthcare system to provide a high quality of care throughout the patient journey.

The ECCO expert groups are aware that it is not possible to propose a 'one size fits all' system for all countries, but urge that access to multidisciplinary units or centres must be guaranteed for all patients with colorectal cancer or sarcoma.

The innovative ECCO2017 congress will include a full day of sessions discussing the potential for developing new models of cancer control with greater primary care involvement throughout the cancer care continuum. A multidisciplinary approach of integrated primary and secondary care will be developed with the involvement of a wide range of primary care professions.

Based on the discussions at the congress, the position paper will clearly identify ECCO as the key player willing to engage with all relevant European health organisations in the field of primary care in order to define optimal models of integration for all cancer patients.

Join us at the ECCO2017 congress in Amsterdam on 27-30 January to learn more about these exciting papers and discuss with experts in the field.

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

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- Implementing genomics into clinical practice

KEY DEADLINES

JAN 20 — Abstract submission
20 January 2017

FEB 13 — Registration
13 February 2017

Bursary application
20 January 2017

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Visit the conference website:
www.eacr.org/conference/precisionmedicine2017

No time! How staff shortages are hitting patient care

The European Commission has issued a warning about a 1 million projected shortfall in Europe's clinical workforce by 2020 – with nursing shortages accounting for more than half the total. **Marc Beishon** reports on the severe strains already apparent across our health systems, and looks at some policies that could help address the problem.

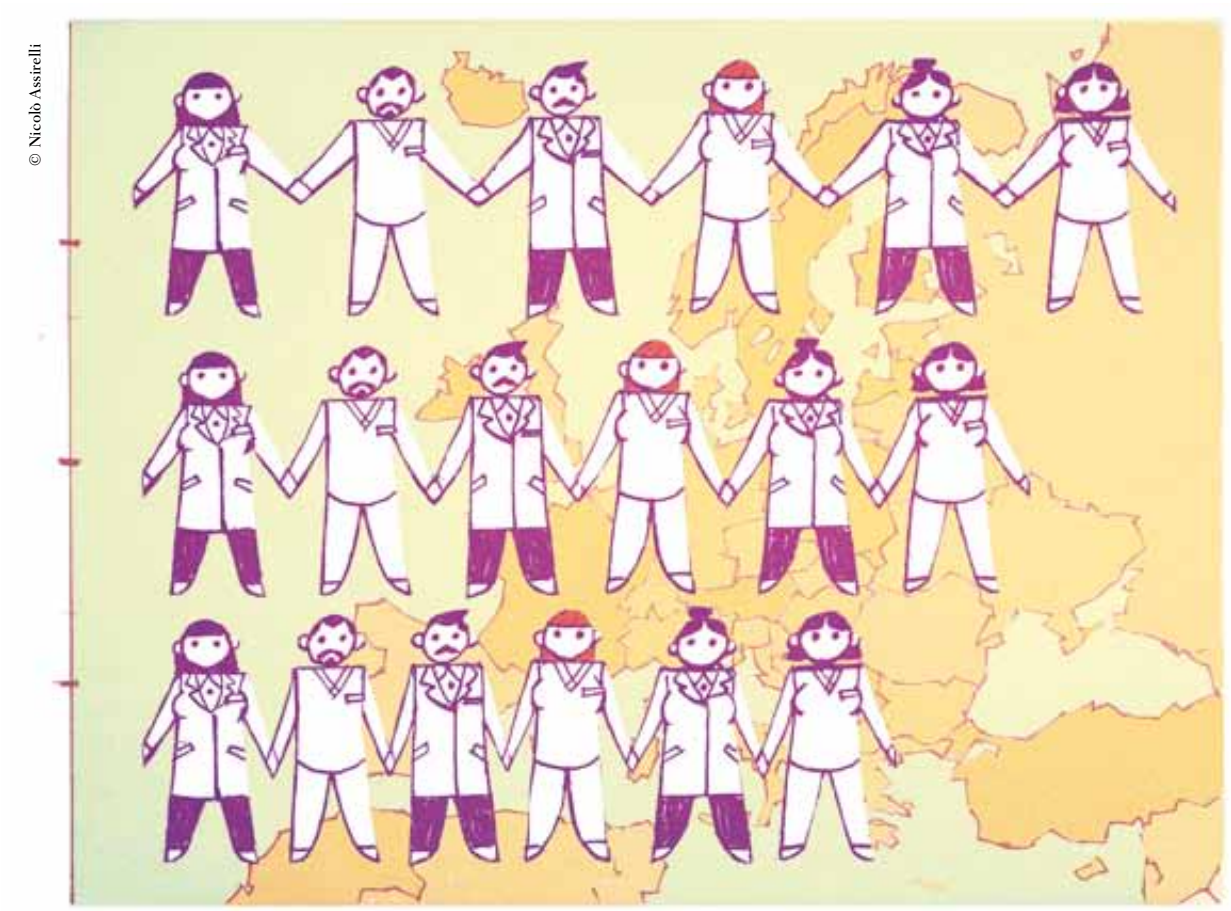
"We just aren't able to spend much time with patients – we can often only talk while we put in an IV line. This has an impact on care but also on us: sometimes we don't have time to go the toilet, our phone is always ringing, and it's very stressful just trying to manage our daily agenda, let alone any extras. And we know that our patients need better: more time for them, more support, more activities. We have no psychological support, and patients only get it from nurses or doctors. Sometimes they just need a five-minute talk and we can't give that to them. It is very depressing for us to know that."

So speaks Sara Torcato Parreira, a specialist oncology nurse at Fernando Fonseca hospital, in Amadora, Portugal, a country that has been one of the worst sufferers from the Great Recession that hit Europe after the 2008 financial crash. But this snapshot is also typical of many oncology departments around Europe, where cancer services are having to cope with ever-increasing patient loads due to ageing populations and longer survival times, while health budgets are failing to keep up, or in some cases are being cut.

A report by the European Observatory on Health Systems and Policies – *'Economic crisis, health systems and health in Europe: impact and implications for policy'* – noted that the crisis radically changed the focus from "worrying about how to pay for healthcare in 30 years' time to how to pay for it in the next three months". Not all European countries have been badly affected, but the report notes that in Croatia, Greece, Ireland, Latvia and Portugal, public spending on health was actually lower in 2012 than in 2007.

Nurses are particularly feeling the strain. In the EU as a whole, their numbers have been increasing at around half the rate of doctors' for the best part of 15 years. In central and eastern European countries, the nursing workforce has barely increased at all over the last 25 years. As the frontline workforce vital to all aspects of care throughout the patient journey, it is easy to understand why many of them feel they are reaching breaking point, and worry that patient care is suffering.

Lemme-Liis Aruvali, a young nurse at the Haematology-Oncology Clinic in Tartu, Estonia, says: "Our patients don't get enough time with the doctors or nurses to ask questions and discuss



problems. Doctors are overworking and nurses who work with outpatients or inpatients are often also too busy. Patients may not get as much time and attention as they need, so they may be more confused, scared and unaware."

And in Slovenia, Katarina Lokar, formerly head nurse at Ljubljana's Institute of Oncology, who now works in epidemiology and cancer registration, reports similar concerns over the capacity shortage in Slovenia. "We are having to deal with a shortage of nurses and doctors, as well as of other professional and supporting staff. We have had a very hard time in the last four years due to the economic crisis and budgetary restrictions. There are big problems with long waiting times for some treatments, including in oncology. This means full waiting rooms, and a lot of people with bad immune systems in closed spaces, and the risk of transfer of hospital infections, as well as less time for holistic care. Psychosocial care is often viewed as less important than getting the treatment on time."

The shortages of staff and pressures on the remaining workforce are not confined to smaller, less well-off countries. In the UK, a country that is still playing 'catch-up' with better performing peers in Europe, and where waiting times for suspected cancer and first treatment have worsened in the past few years, an independent report identifies problems in the numbers and configuration of the cancer workforce as critical issues in delivering better care.

A report carried out by an independent cancer taskforce, *'Achieving world-class outcomes: a strategy for England 2015–2020'*, notes "significant workforce deficits, particularly in diagnostic services, oncology, and in specialist nursing support," which it claims "result in severe bottlenecks in the diagnostic process, suboptimal care in certain parts of the country, and

"This means full waiting rooms, and a lot of people with bad immune systems in closed spaces, as well as less time for holistic care"

an inability to deliver newer, evidence-based and cost-effective treatments."

The report also highlights the needs of a growing number of people with chronic cancer conditions who need to be cared for in the community by a combination of health and social services, and says the system lacks the capacity, and has the wrong workforce configuration to support patients beyond their initial treatment.

Common problems

Healthcare systems are hard to compare, but all countries are facing increasing numbers of people, especially older people, living with cancer; new, costly and complex treatments such as immunotherapies; and difficulties in attracting young health professionals to take up positions such as primary care practitioners, amid an overall trend for doctors to be older with not enough people in training or being recruited in some countries.

There are several policy responses that countries are using to try to stabilise their health systems and help protect those hardest hit, such as vulnerable and unemployed people, including raising taxes, introducing user charges for some, and restructuring purchasing systems to cut the price of buying drugs and other products and services. But several countries are also increasing funding for primary care, aiming to shift care out of hospitals to the community, as there is evidence that health systems with strong primary care perform better.

So the economic crisis may have stimulated much needed changes, and as many as 15 countries are reported to have taken steps to shift care out of hospitals. There also appears to have been a speeding up of closures and mergers of hospitals in the acute sector. In turn, though, this is raising questions about the availability of staff with the appropriate skills to work in expanded community settings, such as GPs and nurses with specialist knowledge in chronic conditions such as cancer. This has been a particular problem in countries where the numbers and pay of health professionals have been cut, which includes many of the countries subject to the 'economic adjustment programmes' determined by the European Union and International Monetary Fund, such as Greece, Ireland and Portugal.

Several countries are also increasing funding for primary care, aiming to shift care out of hospitals to the community

Europe-wide data are not easy to come by, at least in terms of staffing shortages. Such research as has been done seems to indicate that the staffing situation is much less of a problem for doctors than nurses, at least in oncology. In medical oncology, a paper titled 'The landscape of medical oncology in Europe by 2020' (*Ann Oncol* 2014, 25: 525–8) found that the availability of oncologists will probably meet the projected need in most of the 12 countries analysed, provided that current increases in doctor numbers continues (the mean increase was a healthy 5% a year), and that there are no unforeseen changes in cancer incidence. The authors do note, though, that little information was available from eastern European countries.

In Romania, Laura Mazilu, head of oncology at Constanta Emergency Hospital, says there are shortages of oncologists and nurses in her country, although her own department has loyal staff. "We don't currently have a recruitment problem, but we are only a small 25-bed oncology department," she says. "We are though overloaded with patients."

Funding is a big problem in Romania, which has been spending only about 5% of its GDP on healthcare, and salaries and conditions for staff are currently not sufficient to stem a substantial brain drain to other countries, and also to the private sector in clinics in the capital, Bucharest.

Mazilu says that while her team in Constanta – the country's fifth largest city – is able to provide a good standard of medical oncology care, according to international guidelines, the hospital currently lacks a radiotherapy unit. "The 'bunker' is there but not the staff or machinery, so patients have to travel to other centres," she says, adding that they also lack specialist palliative and psychosocial care professionals.

Salaries and conditions for staff are currently not sufficient to stem a substantial brain drain

The staffing situation is far worse in rural areas (Feraru, *Global J Med Res Interdisc* 2013, 13(5)). As reported on thecancerblog.net, the county hospital in Vaslui, along Romania's eastern border, caters for a population of 375,000, but has no oncologist at all; in the west of the country, one oncologist based in Resita has responsibility for

over 8,000 patients recorded in the cancer registry.

EU recognition of medical oncology as a medical specialism in 2011 – a longstanding demand of the European Society for Medical Oncology (ESMO) – will have helped encourage young doctors into the field, but may also have added to the challenges poorer countries like Romania face in retaining their trained specialists. ESMO has set up a 'women for oncology' committee to look at leadership and work–life balance issues – many countries still suffer from male-dominated hierarchies.

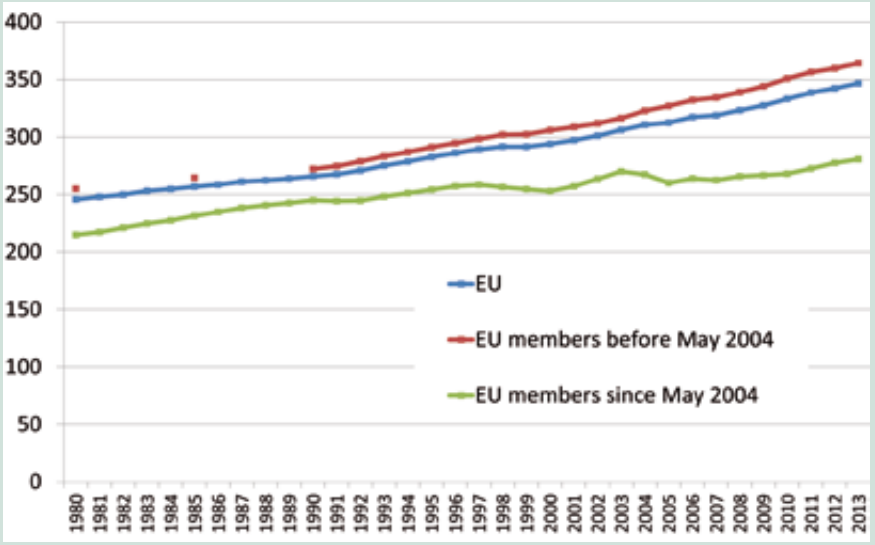
The European Society of Surgical Oncology is now looking to promote a similar harmonisation of minimum training and competencies required for all surgeons who treat cancer patients, with its recently published Global Curriculum for Surgical Oncology, which has, as its principal aim, raising standards in cancer surgery. And ESTRO, the society of radiotherapists, has recently published the latest paper in its Health Economics in Radiation Oncology (HERO) project, in which it predicts a 16% increase in the number of radiation treatment courses will be needed from 2012 to 2025, varying from 5% to 30% across Europe, which will require some increases in staffing capacity among radiotherapists and the many other specialities required to plan and deliver the treatment.

Clearly, the workforce is also only one part of establishing high-quality cancer care – quality systems, research and technology are all critical, and the drive for quality can also have a big impact on the location and size of cancer centres. There is plenty to investigate in how multidisciplinary teams and information technology, including telemedicine, can best be configured for various tumour types and patient pathways.

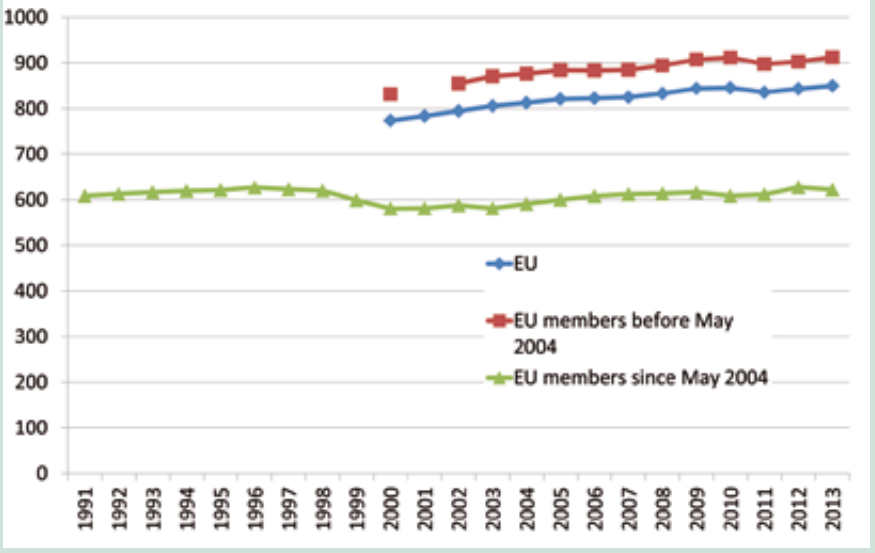
There are also gaps in technical positions, such as in nuclear medicine

Growth trends in the EU healthcare workforce

Physicians/100,000 population



Nurses/100,000 population



The number of doctors per head of population rose by almost 20% between 2000 and 2013 – though more slowly in central and eastern European countries. The number of nurses rose at less than half that rate over the same period, remaining static in most of central and eastern Europe. The proportion of Europe's population aged over 65 years has more than doubled over the same period.

Sources: Improving the Skills Mix for Chronic Care in Europe: Presentation by Matthias Wismar, European Observatory on Health Systems and Policies http://ec.europa.eu/health/workforce/docs/ev_20151116_co06_en.pdf (accessed 14 November 2016); Eurostat

and radiotherapy, and a need to invest more in diagnostic services. The NHS in the UK, for example, is aiming to have sufficient numbers of sonographers, radiographers and radiologists in the cancer workforce, and will train 200 more 'non-medical' endoscopists by 2018 for gastrointestinal investigations – non-medical meaning 'not doctors', but nurses and other professionals. Currently, one in ten consultant posts in breast radiology and 15% of radiographer jobs are unfilled in the NHS.

Pressure on the frontline

The cancer nursing workforce has probably attracted the most attention, as it has a big impact on patients. ECCO, the European Cancer Organisation, last year made nursing one of its top 'oncopolicy' issues, and has kicked off a nursing project, which has greatly pleased Daniel Kelly, president of the European Oncology Nursing Society (EONS).

Of all the jobs involved with cancer, nursing has greatest variation across Europe, says Kelly, who is a professor of nursing research at Cardiff University in Wales. "Some countries are open to innovative ideas on how nurses can take on much more than they traditionally did, but others still have an old-fashioned picture and restrict the roles of nurses," he says.

Countries such as the UK, Sweden and Ireland have had advanced and specialist cancer nursing roles in place for some time, he notes – but sustaining and developing such roles needs support. Helena Ullgren, who coordinates 'contact' nurses from the Karolinska University Hospital in Stockholm, says all patients are entitled to have a contact nurse who specialises in one or two cancers (her own interest is head and neck cancer).

Safety concerns. When time is short, communication can suffer, for instance at handover time, leading to potentially serious mistakes

"But we have a shortage of nurses, more so than doctors, and in particular these specialist nurses. We don't offer high enough salaries, there are heavy workloads and, especially, we don't offer good career paths – so we have a high nurse turnover," she says. "Nurses want to know they can train to be a specialist or take a Masters course, and the university has places for them, but employers are reluctant to let them attend owing to staff shortages."

To make things worse, says Ullgren, some hospitals are now placing generalist nurses in specialist cancer or surgical care roles, without recognition of the specialist status of these posts, and the Swedish National Board of Health and Welfare no longer issues licences for such positions. "This undermines the system for everyone – we have gone backwards in Sweden," says Ullgren.

Cancer outcomes are currently good though, and patients are mostly satisfied with their care, she adds. But there is concern about workloads and staff working in 'silos': "We feel that patient safety is getting worse, which can happen without timely handovers of patients between departments, for example. When you have limited time you tend to work in silos, and many of us feel we cannot influence our daily working conditions, as decision-making is too hierarchical. Hospitals need to empower their staff much more."

The risk posed to patients by using nurses to take on roles they are neither adequately trained nor recognised for is something that also concerns Katarina Lokar in Slovenia. "At the Institute of Oncology, nurses in the outpatient unit also prepare cytotoxic drugs – the pharmacy covers only hospital wards – and this is more than half of all drugs, and the standards are lower than in the pharmacy. This brings a number of safety issues and additional workload."

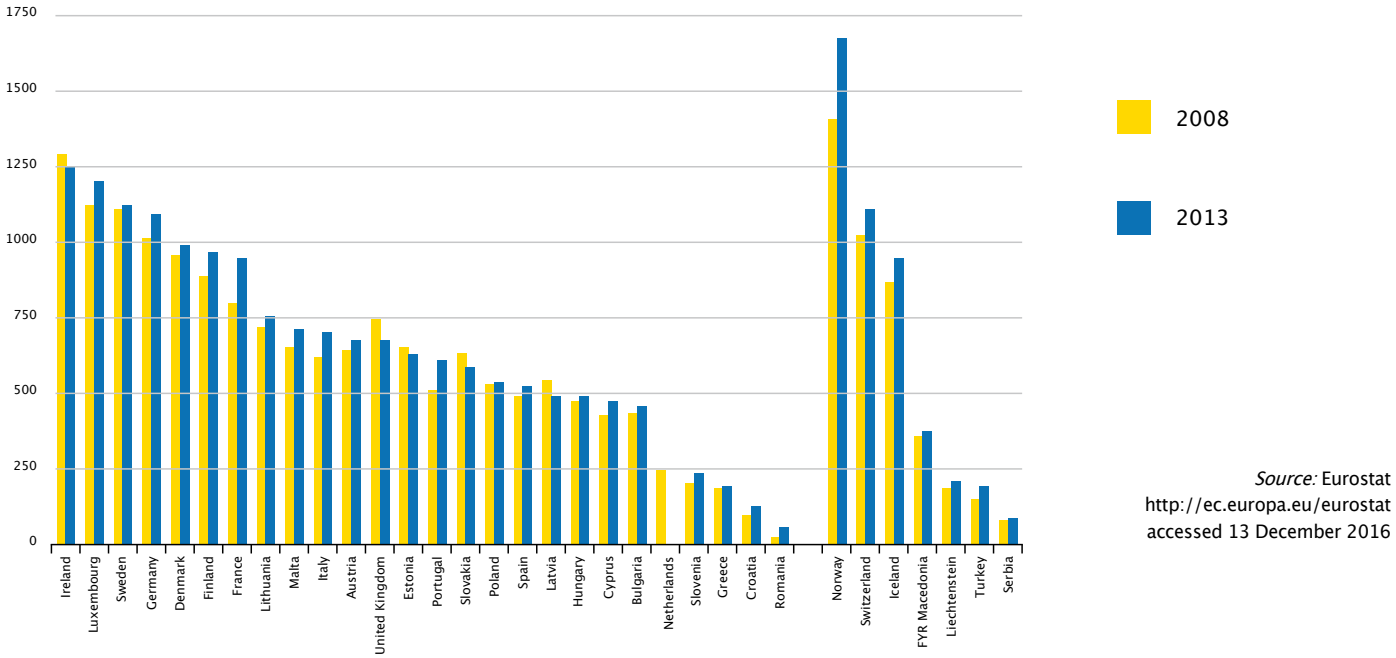
"We have a shortage of nurses more than doctors, especially specialist nurses"

She adds that they lack staff, funding, specialised knowledge, facilities and equipment, and says that patients should expect better. "Mostly we have understanding patients who are willing to wait, because they see how much work is done and how many patients there are. In my opinion they are too good with us – I think they should be more demanding. The truth is that we [nurses and doctors and other professionals and management] are not heard by the politicians unless something bad happens."

Parreira in Portugal says there is a freeze on hiring more health professionals. In her department, which has eight nurses, she is the only cancer nurse specialist, and someone who wants more qualifications has to use their own time and money to do so.

Practising nursing professionals per 100,000 population, 2008–2013

Staffing shortages are more acute in some European countries than others, with EU regulations making it easy for health professionals to travel to where job opportunities, pay and career prospects are most attractive



Source: Eurostat
http://ec.europa.eu/eurostat
accessed 13 December 2016

"The primary care system suffers from a similar lack of resources – there are plans to have a network of community nurses, in particular for palliative care, though." One barrier comes not from the authorities but from doctors – despite being short staffed, they have been against nurse specialists taking on initial assessments in emergency departments, she says.

Offering better training and recognition for specialist cancer nurses may prove key to solving some countries' healthcare staffing problems, according to researchers behind the EU-funded project which studied breast cancer roles in Scotland. The MUNROS study into the *'Impact on practice, outcomes and cost of new roles for health professionals'*, found that career progression is a primary motivating factor for nurses, which echoes the point made by Ullgren in Stockholm.

Some countries currently do not have any oncology nursing programmes. Lemme-Liis Aruvali says her country, Estonia, is one of them. "In Estonia we don't have a special educational programme for oncology nurses. All nurses who work in our department are registered nurses, or students who are becoming one. We learn everything from older colleagues.

> **"The truth is we are not heard by politicians until something bad happens"**

We definitely need a programme for cancer nurses," she says. The situation is similar in Slovenia. Lokar mentions attempts to introduce a national cancer nurse specialisation programme, but says it lacks financial backing for implementation, and as it is not pitched at a Master's level, it does not meet the criteria set by European Specialist Nurses Organisations (ESNO).

Some larger, more affluent, countries are also lagging. In Germany, nursing roles mostly remain at diploma level: just 5% of the nursing workforce have university degrees, and there are fewer specialist cancer nurses than in other countries, says Patrick Jahn, an oncology nurse and head of nursing research at Halle University Hospital, near Leipzig. Only about 20% of nurses in cancer centres have *post-hoc* basic training in procedures such as administering chemotherapy, he says, and generally at federal level the role of nursing in Germany's national cancer plan has not been given enough emphasis. The regional government structure does not help, he adds. Things may be set to

change, though: Jahn is currently sitting on an expert commission that is charged with spending over €800 million to improve the nursing situation and address a general shortage of nurses across the country.

An increased role for primary care

Where Germany does have a potential head-start is in local outpatient clinics, which Jahn explains are separate from day clinics at hospitals, and where some doctors specialised in cancer collaborate with GPs. This does make the health system more complicated, but can create stronger networks of care, he says. "But what is missing are advanced practice nurses – most of the other workers at these clinics are doctors' assistants. We need nurses to help patients adhere to drugs and manage side effects, such as new ones we are seeing with oral targeted therapies, and provide supportive care."

His own research is addressing the nursing role in supportive cancer care, and he further points to a trial currently underway in Hamburg, where nurses are helping patients with the side effects of oral cancer drugs to see if it improves their quality of life.

The general direction of travel, albeit a slow one at present, is for more community-based specialists and 'blended' roles, with people having two or more main tasks. As Kelly says, cancer hospitals need to restrict their role to care of the acutely ill, including those who present as emergency cancer cases, and those who pose particular challenges for the oncology workforce. Most cancer care should take place at home or at a day clinic, he argues.

Rebalancing care for survivors away from oncology centres and towards community/primary care is seen as a particular priority, given the rapid increase in people who are either surviving with no detectable cancer, or simply living longer with chronic disease. Recently, Macmillan reported a study showing that 7,000 colorectal cancer survivors in the UK are struggling with side effects and distress years after their diagnosis.

"Cancer hospitals need to restrict their role to care of the acutely ill"

Pilot studies run by the UK National Survivorship Initiative have shown that many survivors – particularly those with a good prognosis – are amenable to having responsibility for their care shifted to a primary care setting, and to taking a more active role in self-managing ongoing health problems.

But the same research also showed that cancer survivors will be more likely to self-manage if they are better supported with information and specialist support after their anti-cancer treatment – which is typically a role for specialist cancer nurses.

In France a project in the Auvergne region has nurses coordinating care after hospital discharge, and a greater role for GPs in caring for survivors. Getting lines of communication right between GPs and oncology specialists will be important to making this work. In Israel, the Israel Cancer Association supports GPs with annual seminars focused on topics they request. It also publishes a journal for GPs. In Stockholm, meanwhile, Ullgren says there is a new cancer rehabilitation centre that caters for long-term effects, but already an emerging issue is lack of communication with other professionals, such as palliative care nurses.

Ultimately, however, the critical shortfall in health professional staff is unlikely to be resolved by shifting roles and responsibilities between different elements of the workforce.

Other professions, such as social care, are expected to become increasingly involved in new models of cancer care, raising further issues of training, competencies and coordination. For a model of holistic support at European level, the European Commission Expert Group on Rare Diseases has recently adopted recommendations on how social services can help support people with rare diseases, such as certain cancers – see the INNOVCare project on the EURODIS rare disease group's website.

Other professions, such as social care, are expected to become increasingly involved in new models of cancer care

Given the importance of care at home and in the community, there is another part of the cancer workforce that is widely neglected but which saves countries millions of euros a year – namely carers of people with cancer. Better social and financial support – and also training, given that carers often help with clinical work – for this large number of people is long overdue.

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The role of immunotherapy in treating solid cancers

Engaging the body's own immune system in controlling cancer has long been an aspiration for cancer researchers and clinicians. This overview looks at progress towards that goal, and how it is changing the paradigm of cancer treatment.

This grandround was first presented by Aleksandra Filipovic, from the Department of Surgery and Cancer, division of cancer, Imperial College, London, as a live webcast for the European School of Oncology. It is edited by Susan Mayor. The webcast of this and other educational sessions can be accessed at e-eso.net.

Death rates due to cancer fell by only 8% between 1950 and 2012. Other diseases saw death rates fall markedly over the same period: by 67% in the case of heart disease, 77% for cerebrovascular diseases and 66% for pneumonia and influenza.

Why was the reduction in cancer death rates so much lower than in other diseases? Recent developments suggest that our understanding of cancer was oversimplified. However, understanding of tumour immunology has increased dramatically over recent years, which has led to the development of immuno-oncology agents that have created a paradigm shift, addressing areas not covered by previous treatment options.

The immune system and cancer

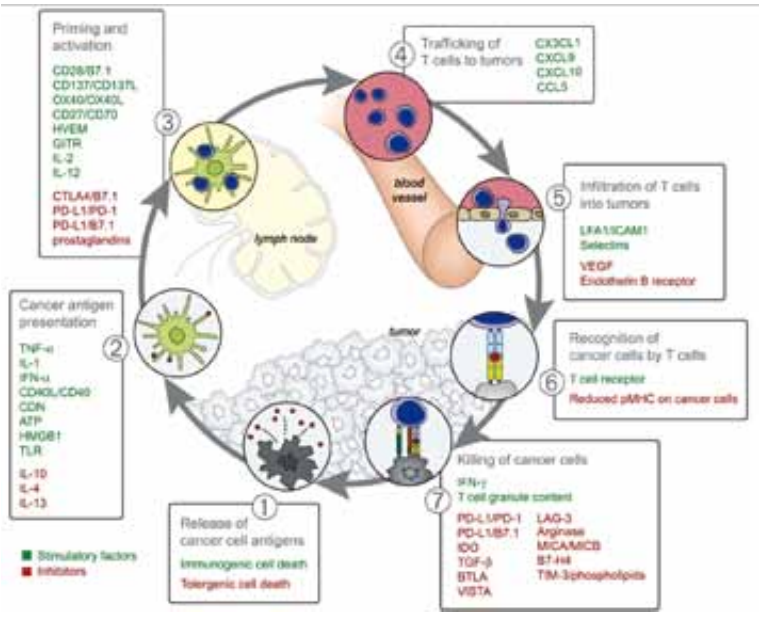
At a simplified level, a tumour can be considered as a mass of tissue growing in an organ where it is not supposed to be. Tumours contain cancer cells, blood vessels that supply nutrients to the cancer, cells involved in the inflammatory response, and connective tissue cells, in addition to cells from the immune system. Tumour cells initially grow in a primary organ before spreading through lymph nodes or blood vessels, or both, to distant sites. This is a complex process requiring cancer cells to leave the primary tumour, enter the lymphatic system or blood vessels, and travel around the body before exiting and establishing themselves in a secondary site. Each step of this metastatic process involves a significant contribution from cells of the immune system, particularly T cells.

Immuno-oncology agents

The first immuno-oncology agent to be approved for treating solid tumours was the anti-CTLA-4 antibody ipilimumab, followed by anti-PD-1 antibodies, including nivolumab and pembrolizumab. They have very distinct mechanisms of action, blocking the inhibition that cancer cells impose on the immune system.

Oncologists and researchers have

Cancer immunity cycle

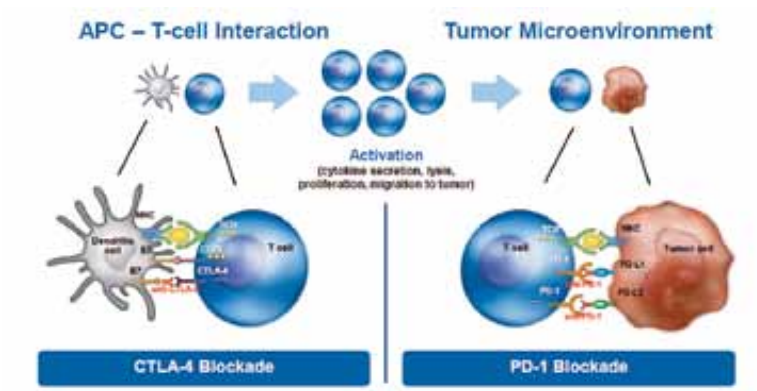


The cancer immunity cycle provides the framework for how we can manipulate the immune system to attack and destroy tumour cells.
Source: DS Chen and I Mellman (2013) Oncology Meets Immunology: The Cancer-Immunity Cycle. *Immunity* 39:1–10. Republished with permission from Elsevier

been trying for decades to activate or boost the immune system in targeting cancer. Until recently we failed, because we did not understand the mechanism underlying the intricate interaction between tumour cells and cells of the immune system. We now understand that a cancer cell interacts with a T cell by direct contact through receptors such as CTLA-4, PD-1 or PD-L1, causing inhibition of the immune system.

These new immuno-oncology drugs block the interaction between cancer cells and cells from the immune system, effectively creating a firewall that prevents inhibition from occurring. These drugs do not activate the immune system but, instead, they inhibit the inhibition that cancer cells impose on immune cells.

Mechanism of action of immuno-oncology agents



What does immuno-oncology add to treatment outcomes?

Chemotherapy prolongs survival to a certain extent, and the new generation of targeted agents contribute to further prolongation of survival. However, most cancer patients inevitably die of their disease. Immunotherapy lifts the survival curve, with anywhere between 5% and 30% of patients under the curve who survive and continue to live with their disease, even if immunotherapy is introduced late in their disease, at an advanced or metastatic stage.

Pivotal clinical trials with immunotherapy agents

Ipilimumab was approved on the basis of a phase III trial that showed important survival gains for patients with metastatic malignant melanoma, with 24% alive at two years compared to only 14% with the peptide vaccine gp100 (*NEJM* 2010, 363: 711–23).

The CheckMate 057 Trial, which led to the approval of nivolumab in metastatic lung cancer, was stopped early, with an interim analysis showing that nivolumab prolonged overall survival by three months (*NEJM* 2015, 373:1627–39).

A trial leading to the approval of pembrolizumab in lung cancer showed overall survival was significantly longer than with docetaxel (median 14.9 vs 8.2 months) (*Lancet* 2016, 387:1540–50).

The CheckMate 025 study of nivolumab in renal cell carcinoma showed prolongation of overall sur-

vival to 25 months compared to 19.6 months with everolimus (*NEJM* 2015, 373:1803–13). Immune checkpoint inhibitors are now approved for melanoma, lung cancer, renal cell carcinoma, and squamous cell head and neck cancer, and are being used worldwide.

Unique features of immunotherapy

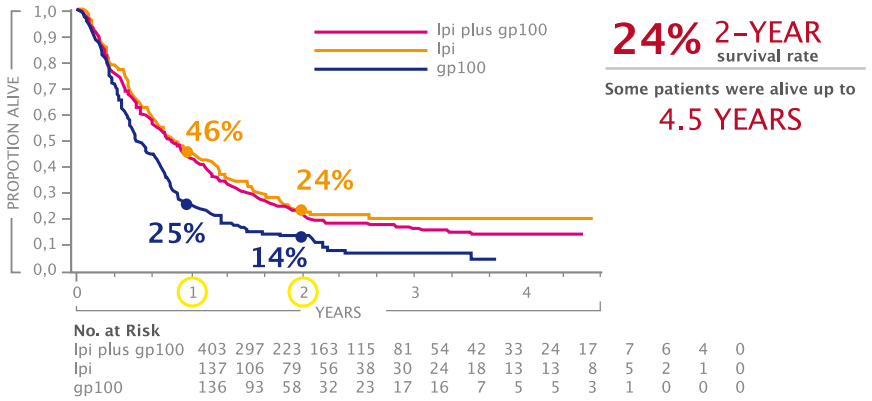
Side effects

Immunotherapy delivers survival benefits for patients with many types of solid tumours, but it is important to consider the side effects of these agents. Fatigue is one of the commonest side effects, affecting around one-quarter of patients treated with immunotherapy. Grade 3–4 adverse events are uncommon, typically affecting fewer than one in ten patients.

Immunotherapy agents have a specific set of immune-related side effects (see table). Gastrointestinal side effects such as colitis can occur, and, in rare cases, patients have gastrointestinal perforation. Liver-related side effects include hepatitis, while pulmonary adverse events include pneumonitis. Skin, neurologic and endocrine side effects can also occur. Side effects should be graded and treated with corticosteroids until they reduce to grade 1, or resolve, when immunotherapy can be restarted.

Liver side effects can be detected by an increase in liver enzymes, and skin side effects by clinical examination. It is also important to monitor thyroid function and adrenal function, and to be aware of clinical symptoms such as cough, which may occur in pneumonitis, or diarrhoea in colitis.

The survival curves that led to approval of ipilimumab



Ipilimumab, the first immune checkpoint inhibitor to receive approval, showed a significant improvement in survival for patients with malignant melanoma, with the characteristic tail showing a proportion of patients derive long term benefit

Source: Adapted from FS Hodi et al. (2010) Improved Survival with Ipilimumab in Patients with Metastatic Melanoma, *NEJM* 363:711–723. © 2010 Massachusetts Medical Society. Reprinted with permission

Pseudoprogression

Pseudoprogression is a unique phenomenon that occurs in 7–10% of patients treated with checkpoint inhibitors, and which stems from their mechanism of action. The figure overleaf shows this in scans for two lung cancer patients treated with PD-1 inhibitors. Two months after starting treatment, lesions increased in size compared to the pre-treatment scan, but at four months there was complete response.

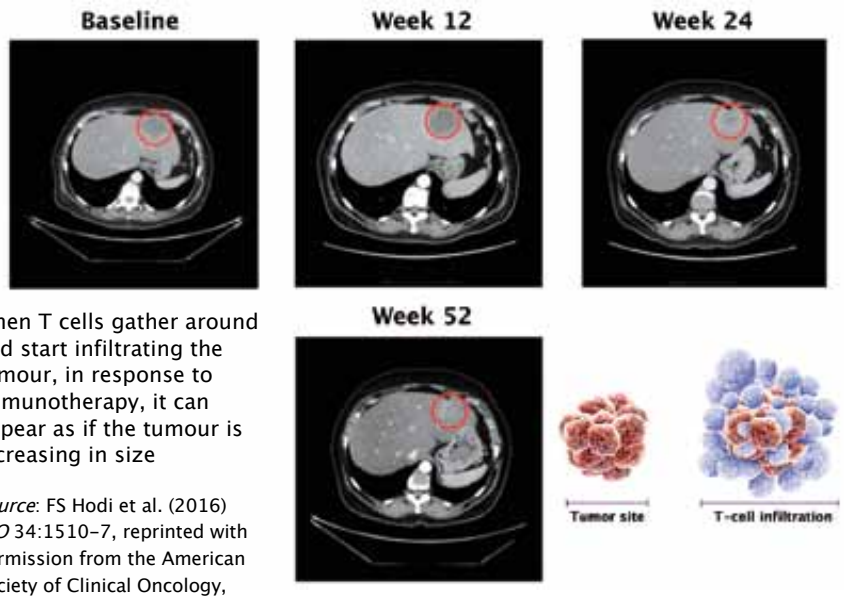
If a patient is treated with chemotherapy, it hits the cancer cell head on, and very shortly after starting treatment we would expect to see tumour shrinkage or complete response.

Treatment-related adverse events

Fatigue is the most common adverse event (24%)
Grade 3–4 adverse events are uncommon (6–12%)

System	Immune Related Adverse Events
Gastrointestinal	Colitis (diarrhea, perforation)
Renal	Acute interstitial nephritis (increased serum creatinine)
Pulmonary	Pneumonitis (dyspnea, cough)
Dermatologic	Dermatitis (lichenoid/spongiotic dermatitis, rash), vitaligo
Hepatic	Hepatitis (elevated LFTs)
Neurologic	Central and peripheral (aseptic meningitis, Guillan–Barre Syndrome, myasthenia gravis)
Endocrine	Hypophysitis, thyroiditis, adrenal insufficiency
Ocular	Uveitis, iritis

Pseudoprogression



When T cells gather around and start infiltrating the tumour, in response to immunotherapy, it can appear as if the tumour is increasing in size

Source: FS Hodi et al. (2016) *JCO* 34:1510–7, reprinted with permission from the American Society of Clinical Oncology, ©ASCO. All Rights Reserved

However, the whole concept with immunotherapy is to engage the T cells, which gather around tumour cells and elicit cell killing. When T cells reach tumour cells they secrete cytotoxic mediators, which then act to kill the tumour cells.

Question: Are there any other imaging methods that could better detect pseudoprogression?

Answer: At the moment we don't have any particular imaging methodology that can conclusively identify pseudoprogression. However, these imaging modalities are being developed using a specific type of contrast to detect T cells expressing PD-1 or PD-L1 that have infiltrated a tumour.

Current scanning techniques show only the boundary of the tumour mass, and cannot distinguish where the tumour ends and T cells begin, but we hope to have better techniques within the next few years.

For now, radiologists are starting to better understand what pseudoprogression looks like with current scanning modalities, and it is obviously important for them to be aware that a patient is being treated with immunotherapy.

The timeline is also important: pseudoprogression occurs shortly after starting treatment, but an increase in tumour size at six months, for example, is more likely to be disease progression, so using common clinical sense in these circumstances is very important too.

Question: What proportion of patients experience pseudoprogression?

Answer: Up to 10% of patients experience pseudoprogression, but I think figures in the future will show that the proportion is actually lower than this – that's why we say "up to 10% max".

Identifying predictors of response

An important aspect of using immunotherapy agents is selecting the right patients in whom to use them. These are costly drugs, and they are not without side effects – although these are less frequent than with chemotherapy or targeted agents – so we should be choosing the right population to treat.

One of the main indicators being investigated as a biomarker for PD-1 and PD-L1 inhibitors is expression of PD-L1 by tumour cells and also by immune cells infiltrating a tumour. The degree of expression varies considerably across different types of solid tumour (as shown in the table opposite).

Checkpoint inhibitors in development

Many types of checkpoint inhibitor are in development for a wide range of cancers.

CTLA-4 inhibitors: Ipilimumab is approved for metastatic melanoma, and is being trialled for both non-small-cell lung cancer (NSCLC) and small-cell lung cancer; tremelimumab is in development for NSCLC.

PD-1 inhibitors: Nivolumab is approved for NSCLC in Europe and the USA, while pembrolizumab is approved for PD-L1-positive NSCLC in the USA.

PD-L1 inhibitors: Several agents are in pipeline development, including atezolizumab, durvalumab and avelumab.

These agents and other comparators are in clinical development for a large number of other solid tumours.

Anti-PD-1 and anti-PD-L1 agents have different antibody isotypes, either IgG1 or IgG4. This has an impact on how these agents work – whether they engage only cells from the immune system or also elicit involvement of complement- or antibody-dependent cytotoxic cell killing.

Sequencing of immunotherapy

There is a lot of discussion as to whether there is an optimal sequence for using immunotherapy agents. Do we give chemotherapy and then immunotherapy, and can we then go back to chemotherapy? The answer to the latter question is 'yes', with several large clinical trials showing that anywhere from one-third (*NEJM* 2015, 373:123–35) to one-half of patients (*NEJM* 2015, 373:1627–39) can safely go back to receiving standard of care chemotherapy after immunotherapy.

The anti-CTLA-4 and anti-PD-1 agents that have been approved so far have found their place in the treatment of advanced and metastatic disease, and have gained approval after being tested in second- or third-line treatment. The first-line treatment for metastatic disease is typically standard of care – most likely chemotherapy – and immunotherapy is used when that fails.

Now that we have seen such impressive efficacy with immunotherapy in later lines of treatment, there is a lot of interest to see how effective and safe these agents are when used first line or combined with chemotherapy from the start.

The CheckMate 012 study is investigating this question in advanced NSCLC, combining nivolumab with different regimens of chemotherapy (gemcitabine, cisplatin, paclitaxel, carboplatin) (CMSTO 2014, Abstract #3). Initial results suggest that the best response rates are seen with a combination of nivolumab (5 mg/kg) with paclitaxel/carboplatin.

There is a wide range of ongoing clinical phase III trials, including trials of pembrolizumab (Keynote 042) and nivolumab (CheckMate 026) versus chemotherapy of investigator's choice, as first-line treatment for patients with advanced NSCLC. The AstraZeneca MYSTIC trial is investigating durvalumab (anti-PD-L1) in combination with tremilimumab (anti-CTLA-4) versus durvalumab alone versus chemotherapy in first-line NSCLC.

In addition, there is interest in combining two immunotherapy agents as first-line treatment, for example an anti-PD-L1 agent with an anti-CTLA-4 agent. The MYSTIC trial is combining the anti-PD-L1 agent durvalumab with an anti-CTLA-4 agent tremelimumab (both from AstraZeneca) in first-line treatment of lung cancer, and will report later this year. This may be the first combination of two checkpoint inhibitors in first-line lung cancer treatment.

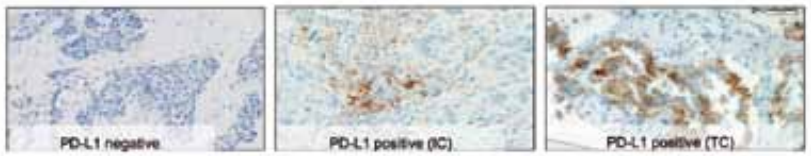
A similar combination – nivolumab plus ipilimumab (both Bristol-Myers Squibb) – is in a phase I trial (CheckMate 012). Dosing is important because combining two agents is likely to increase toxicity.

Other trials are investigating the relationship between biomarkers and outcome, such as the KEYNOTE-010 trial investigating levels of PD-L1 expression and outcome with pembrolizumab versus docetaxel in patients with previously treated PD-L1-positive NSCLC.

Following on from the success of checkpoint inhibitors in cancers such as melanoma and NSCLC – both squamous and adenocarcinoma – these agents are now showing signs of efficacy in very difficult-to-treat cancers, such as small-cell lung cancer (SCLC), which represents an important area of unmet medical need.

CheckMate 032, a phase I/II multicentre, multi-arm, open-label trial presented at the 2016 congress

Identifying predictors of response

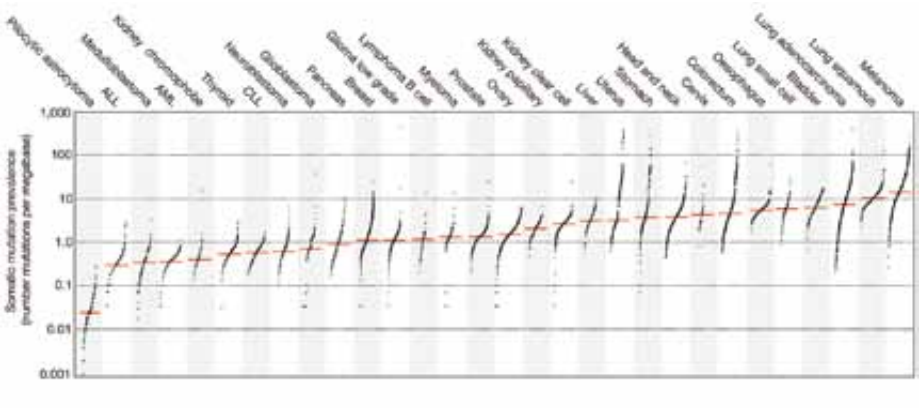


PD-L1 IHC Expression By Various Assays

Tumor	GNE	DAKO 28-8	Merck CC23	5H1
Melanoma	40%	45%	71%	42%
NSCLC	45-50%	49%	45% (25% if ≥50% Staining)	
Renal	20%			24%
Bladder		21%		28%
Head And Neck		31%		46%
Glioblastoma		25%		100%

Expression of PD-L1 is being investigated as a potential predictive biomarker of response to PD1 and PD-L1 inhibitors. A variety of immunohistochemistry assays are used to measure expression levels, with a variety of cut-off points to indicate positivity
IC – tumour-infiltrating immune cells, TC – tumour cells
Source: Adapted from C Grigg and NA Rizvi (2016) *J Immunother Cancer* 4:48, reprinted under creative commons licence http://creativecommons.org/licenses/by/4.0/

Treatment-related adverse events



Tumours with high mutational loads seem to respond particularly well to immunotherapy, and tend to be highly resistant to traditional treatments
Source: LB Alexandrov et al. (2013) Signatures of mutational processes in human cancer. *Nature* 2013; 500:415. Reprinted with permission from Macmillan Publishers Ltd

of the American Society of Clinical Oncology (ASCO), showed objective response rates in up to 23% of patients with recurrent SCLC, with the anti-PD-L1 agent nivolumab plus the anti-CTLA-4 agent ipilimumab (*Lancet Oncol* 2016, 17: 883–95), and the combination is being investigated in further trials.

These agents are also being tested in other solid tumours that are not easy to treat and have shown important responses.

A study with nivolumab achieved a response rate of 65% in patients with relapsed or progressing Hodgkin lymphoma (www.fda.gov), and a multicentre, non-randomised phase Ib trial in heavily pretreated triple-negative breast cancer showed an 18.5% response rate to pembrolizumab, which is not seen in this setting with chemotherapy (*JCO* 2016, 34:2460–67).

In previously treated advanced pleural mesothelioma, pembrolizumab showed a disease control rate of 76% in a phase IB trial of 25 people (AACR 2015, abstract #CT103). Excellent response rates have also been seen in gastric cancer and colorectal cancer.

Assessing tumour suitability for immunotherapy

How do we select tumours that may be suitable for treatment with immunotherapy? Mutational rate varies across different types of cancer, with a higher mutational burden in SCLC, NSCLC and melanoma (see figure). Tumours with the highest mutational load have historically been the most difficult to treat, and had the poorest response to standard of care treatments, but are showing good response to immunotherapy agents. Tumours with a lot of mutations are thought to produce more neoantigens. Once the immune system is engaged by the use of checkpoint inhibitors, a tumour producing more neoantigens will be more readily detected as foreign tissue to be destroyed.

A variety of tests can be used to assess mutational burden in tumours in the clinic. These include sequencing, but a simpler test that measures mismatch repair deficiency – a DNA repair process in tumour cells – can also be used. Colorectal cancer tumours harbouring mismatch repair deficiency have shown impressive response rates (62%) to immunotherapy, and high rates of disease control (92%), while mismatch repair proficient colorectal cancers show much lower disease control rates (16%) (*JCO* 2015, 33 Suppl: Abstract #LBA100). These tests are now being used in other tumours, including pancreatic, gastric and other gastrointestinal cancers.

The scope and rate of approval of immune checkpoint inhibitors in different types of cancer, including melanoma, lung cancer, renal cell carcinoma and Hodgkin lymphoma, and the wealth of clinical trials underway – not only in metastatic and advanced disease but also in the adjuvant setting – suggest there may be a significant increase in their use over the next 10 years. Trials are also being carried out with combinations of immunotherapy agents plus chemotherapy, radiation therapy, targeted agents or with other immunotherapy agents.

I think we are looking at a scenario where immunotherapy could become the backbone of cancer treatment, and other treatment options will be used in a dynamic way around this. Instead of waiting until a patient has metastatic disease, in the future we may be using immunotherapy as first-line treatment and perhaps even in the adjuvant setting.

In summary

Immunotherapy has delivered a paradigm shift in the treatment of cancers so that in the future many patients will live with their disease rather than dying from it. We need to learn how best to use these agents, including defining the best combinations, the patient populations in which to use them and the optimal treatment duration. As these drugs are not cheap, we must also consider how to fund these treatments as they become standard of care.

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If accessing relevant evidence is the question, are medical journals still the answer?

With social media platforms, search algorithms and online research tools designed to let people upload, share, find and comment on information in real time, **Sophie Fessl** asks: why are we still reliant on a 350-year-old model for disseminating medical research?

> *It is astonishing with how little reading a doctor can practice medicine, but is not astonishing how badly he may do it.* – William Osler

Getting new evidence from clinical trial to the practising doctor requires two pieces to click: researchers need to publish their findings, and the doctor has to read them. Since the 17th century, the journal has been the means for this communication. Some processes, such as peer review, evolved to be crucial parts of journal publishing. With the internet revolutionising how we communicate, these 'print-native' processes are set to be overhauled by their 'web-native' counterparts – or have been already. "[…] the Web has irrevocably changed our information environment – it is no longer the habitat the journal evolved in," publishing futurist Jason Priem argues in his opinion piece published in *Nature* (2013, 495:437–40). Whether or not the journal as we know it now survives in the digital age, the way a clinician seeks information from the literature may change dramatically in the future.

A 350-year history

In 1665, Henry Oldenburg founded the first English-language scientific journal, *Philosophical Transactions of the Royal Society of London,* to improve the dissemination of scientific knowledge. Before then, scholars shared their findings by sending letters to their networks of contacts. With the invention of the printing press, print materials could be mass produced and scientific knowledge spread widely. The first journals presaged some of the print-native elements of scientific journals: *Philosophical Transactions* were judged by Royal Society members, setting the framework for peer review, while Thomas Basset, editor of the first English medical journal *Medicina Curiosa*, saw his editorial responsibilities as guiding his readers to new information.

Medical journals unarguably proved a success; more than 25,000 biomedical journals are currently published worldwide. And yet, all is not well in the world of medical publishing. Peer review may have evolved since the 17th century, as a way to control the scientific quality of

published papers, but in recent years it has increasingly come under fire. Richard Smith, former editor of the *British Medical Journal*, who spent some time studying the peer review system, reached the conclusion that it is "slow, expensive, ineffective, something of a lottery, prone to bias and abuse, and hopeless at spotting errors and fraud." The benefits of peer review, he argued, have been much harder to establish (*J R Soc Med* 2006, 99:115–119).

Similar criticism has been levelled against the "impact factor", a statistic that represents the mean number of citations to articles published in a given journal in the preceding two years. This metric was intended to function as an indication of the importance of a journal in its field, though interestingly it has also been found to predict for rate of article retractions due to fraud (*PNAS* 2012, 109:17028–33). A related problem is the way it has been widely (mis)used as an indicator of the quality of work of academics who publish in them, including by research funders and appointment committees, which provides people with an incentive to fabricate or twist results to get published in the 'best' journals.

A few years ago the Wellcome Trust– the world's largest medical research charity – announced it would no longer take into account journal impact factors when assessing the quality of research done by a grant applicant. Speaking to *Cancer World*, Robert Kiley, Head of Digital Services at the Wellcome Trust, said: "We need to move away from using the impact factor as a proxy for research assessment. It is a flawed metric... It is the intrinsic merit of the work, and not the title of the journal or the publisher with which an author's work is published, that should be considered in making funding decisions."

Philosophical Transactions, first published in 1665, established a format for disseminating scientific knowledge that continues to this day (*left*, the first issue, *below*, the 19 December 2016 issue)

Focusing on readers' needs

The greatest challenge for medical journals is how to present new findings in a way that doctors can best integrate them into their everyday practice. Twenty-five thousand biomedical journals is an impressive number, but with most doctors spending, by different measures, between one and three hours a week on professional reading, filtering what is most relevant has become a daunting task.

Marije Hamaker, a geriatric oncologist at the Diakonessenhuis in Utrecht, the Netherlands, who has helped develop an educational webcast on her speciality (e-eso.net, 30 June 2016), says "I still believe that publishing in a journal has value in itself, as a means of spreading a particular message. But with so many journals around, I wonder how well read these journals really are and therefore how much that message is actually being received."

Questions are being asked about whether the business model of journal publishing serves the interests of publishers better than those of academia, based as it is on authors freely contributing reports of research – frequently funded by charities or the taxpayer – which publishers then distribute back to the academic community at considerable profit to themselves.

While the internet and social media are unlikely to be a cure-all for the ills of academic publishing, they are already changing the shape of medical publishing: nearly 10% of

journals are estimated to use social media, such as blogs, Twitter or Facebook pages, to allow commenting on articles. Lisa Hutchinson, Chief Editor of *Nature Reviews Clinical Oncology*, sees an opportunity in social media: "I think social media and the internet will greatly affect how doctors acquire information and gather evidence. To some extent, I don't think this will negatively affect the 'traditional' formats in terms of how this guides daily practice. There are benefits and limitations to all aspects of medical publishing (whatever format), so this creates a more competitive environment, that will challenge business models currently and in the future."

"I would define post-publication review as the process whereby scientists and others decide whether a piece of work matters or not"

For some publishing futurists, the internet can and should do more than just tinker with the existing journal model. It could revolutionise the way medical evidence spreads when print-native elements that make up a journal become disentangled. As Jason Priem argues, "the journal and article are being superseded by algorithms that filter, rate and disseminate scholarship as it happens," (*Nature* 2013, 495:437–40). Rather than having more than 25,000 journals that each archive, rate and disseminate scholarship, a variety of interoperable, modular services could offer these traditional journal functions. These include certifications of peer review, web-based marketing, archiving, aggregated commentary and broad dissemination. Authors would be able to choose the services best suited for each purpose, adding certifications of peer review, significance, statistical review, altmetrics aggregators and more.

Opening access

While such a complete dissolution of the academic journal into a pick-and-choose self-publication model seems a long way off, the internet is already picking away at the subscription-only business model of publishing. Many journals have introduced delayed free access, but true open access publishing, with articles freely available upon publication, is changing the publishing landscape. Since 2013, the number of open access journals in the Directory of Open Access Journals has risen from 300 to 9,175. Last year, the Competitiveness Council – a gathering of EU ministers of science, innovation, trade and industry – called for all scientific papers to be freely available by 2020.

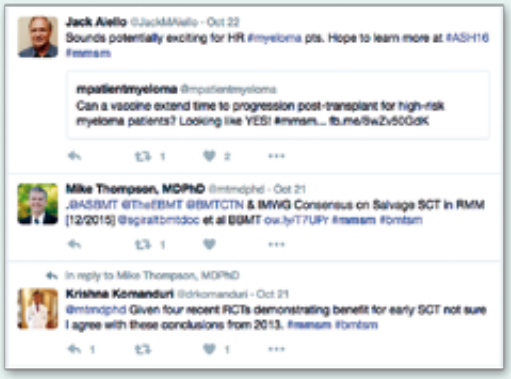
Open repositories, such as *F1000Research*, take the direction of open access journals a step further. They use the resources of the internet to make freely available the underlying data, analyses, and other publication formats such as posters. Last autumn, the Wellcome Trust launched *Wellcome Open Research*, a publishing initiative contracted out to *F1000Research* that, as Robert Kiley describes, "provides a platform in which our researchers can publish any research they think is worth sharing." This platform, he adds, makes use of post-publication peer review, "and encourages the publication of *all* research outputs – case studies, datasets, protocols, null/negative studies as well as research articles."

Kiley believes that by ensuring all research is available – and not hidden behind paywalls – and encouraging researchers to make available the data that underlie the research, open publishing may help doctors take evidence-based decisions.

Speeding up access

F1000Research and *Wellcome Open Research* are moving the point of peer review until after publication, so readers can access articles more quickly. Whether doctors should act on recently published information before reviews have come in will be left to their own judgement. A larger concern relates to the rigour and objectivity of the post-publication peer review, given that both systems leave it up to authors to invite people to review their papers. And while the system is intended to facilitate dynamic discussion of evidence, this is not always easy to achieve. PubMed Commons was launched in 2013, allowing users to comment on any of the 26 million research articles on PubMed. As of October 2016, only 4,523 have been commented on.

Former *British Medical Journal* editor Richard Smith argues that post-publication peer review is more about how a study is received: "I would define post-publication review as the process whereby scientists and others decide whether a piece of work matters or not… beginning to act on its conclusions, throwing it in the bin, and taking a thousand other actions that constitute the 'market of ideas'." (*BMJ* 2010, 341:c3803)



Social media platforms like Twitter are ideal for sharing and commenting on research in real time. In the example shown here (*left*), the hashtag #mmsm (for multiple myeloma social media) is used to flag up the messages to anyone 'following' that hashtag. The emergency medicine community has taken this one step further with a website that curates and archives the best in a weekly round-up – the *Life in the Fast Lane Review* (*right*) http://lifeinthefastlane.com/litfl-review/

Flagging up and filtering

Web-native processes are also likely to change how research impact is measured, adding new ways to find articles that others in a subfield deem noteworthy. New metrics of scholarly influence, 'altmetrics', track conversations generated by an article and include saves in reference managers, inclusion in public policy documents, or mentions on Twitter. These might also influence funding and hiring decisions, as researchers can begin to showcase their work's diverse impacts in real time.

When trying to find the evidence most relevant to them, publishing futurists foresee that doctors will come to rely on 'personalised recommendation engines', which provide a curated stream of the most important things to read. Moving from narrow, personally defined subfields to a wide subject area, the presented contents become increasingly filtered, with articles and other scholarly products, such as blog posts or videos that have been read/viewed, discussed, shared or cited by others in a field. With every interaction, such recommendation schemes become increasingly refined, like Google Search.

FOAM – The critical care model

Everyone can publish, market and share information on the internet. While journal articles and conferences were once the main conduit to presenting new research, the internet allows everyone to broadcast their ideas. In the field of emergency medicine and critical care, this gave rise to FOAM, Free Open Access Med(ical Ed)ucation. Michael Cadogan, who coined this term in 2012, describes the FOAM movement on his blog *Life in the Fast Lane* as "Medical education for anyone, anywhere, anytime", and describes the material posted in the blog's weekly review as "sophisticated, cutting edge learning resources that enable clinicians and students to update their knowledge and improve their understanding in a fun, motivating and time-efficient way."

FOAM is a dynamic collection of resources and tools that include blog posts, tweets, podcasts, videos, Google hangouts and more

FOAM is a dynamic collection of resources and tools that include blog posts, tweets, podcasts, videos, Google hangouts and more. Social media are used to share and disseminate FOAM resources. On Twitter, for example, this is done by including a link to the resource and using the hashtag #FOAMed. A timeline of all tweets using that hashtag can be accessed by anyone, by using the search term '#FOAMed on Twitter'. Tweetdeck or similar apps

also allow Twitter users to 'follow' hashtags, ensuring every post appears in their home Twitter timeline.

Some FOAM blogs, podcasts and websites directly provide educational resources, some compile conference talks, others highlight or review the literature. Rather than replacing journals, Michael Cadogan sees FOAM as "more akin to the editorials and commentary articles that appear in medical journals," (*Emerg Med Australas* 2014, 26:76–83).

New hashtags have now emerged relating to different fields, eg #FOAMtox (toxicology), #FOAMped (paediatrics), and #FOAMim (internal medicine), whose subject matter sometimes extends beyond the emergency setting.

While there is as yet no #FOAMonc, several cancer 'hashtag communities' drive conversations between oncologists, researchers, and anyone affected by cancer. These communities centre around the different cancer types, which makes sense, and is probably an indication of the way these sorts of online cancer communities are likely to develop. The first community, #BCSM (breast cancer social media) started on July 4, 2011, with its first tweet chat. It has since been followed by others, such as for multiple myeloma (#MMSM), lung cancer (#LCSM), and neuroendocrine cancer (#neuroendocrinecancer).

While FOAM and #FOAMed conversations focus on promoting educational resources, the tweets tagged with the hashtags of cancer social media communities are conversations that touch on a range of topics, including advocacy and awareness, but also medical news and updates around relevant conferences. In tweetchats, participants usually discuss pre-set questions for which the patient perspective has a particular relevance, and tweets are archived and published on a website. Discussions of new evidence tends to peak when presented at major meetings, but new findings are regularly flagged up in tweets. While for FOAM, teaching tools and new evidence are collected in several websites, such as *Life in the Fast Lane*, such projects do not yet exist for resources in any field of oncology.

Professional and educational organisations have certainly been making increasing use of social media to disseminate their own materials for many years. Andres Cervantes, who chairs the Education Committee of the European Society for Medical Oncology, cites the example of ESMO's internet portal, OncologyPRO, a resource for members, "which not only focuses on educational material but also provides videos of ESMO congresses, symposia and educational meetings." As congress attendance is decreasing, he adds, improving access to these resources is seen as a priority.

It has certainly proved invaluable as a way of disseminating ESMO's clinical guidelines. "Every year, these guidelines are downloaded more than 1 million times, as all types of doctors need updates and the most recent data," he says.

The European School of Oncology is also embracing the opportunities the internet offers for reaching more people at greater distances, by broadcasting publicly accessible fortnightly educational sessions as webcasts, in which participants anywhere in the world are able to pose questions and get responses in real time. These are archived at e-eso.net.

Several cancer 'hashtag communities' drive conversations between oncologists, researchers, and anyone affected by cancer

Moving towards a model where oncology professionals and the wider community see themselves less as recipients of education and more as participants in the process of flagging up, sharing and commenting on relevant material in real time is still rare in oncology communities. However, we can probably expect to see more hashtag communities emerge around different cancer types, and some of these may see the #FOAMed – Free Open Access Meducation – model as one to emulate.

Whether people are ready to dispense with the established pre-publication peer review process altogether, however, remains an open question. Geriatric oncology specialist Marije Hamaker has yet to be convinced. "I am not sure there is a good alternative [to academic journals], as I do believe that a process of peer review etc. is needed. The internet is full of information that has no scientific base, but is just someone's opinion. I don't know how else this process would work with sufficient quality control."

FOAM pioneer Michael Cadogan, counters that "FOAM opinions and arguments live or die by being hammered on 'the anvil of Truth' that is free and open debate and discussion," (*Emerg Med Australas*, 26:76–83). But it is the models being pioneered by the likes of *F1000 Research* and *Wellcome Open Research* that may point the way to the future for academic communications, based on open access, and immediate sharing of evidence with transparent review by peers, to "Enable(s) others to build upon new ideas right away, wherever and whoever they are."

Time will tell whether their use of the internet will be as disruptive as Gutenberg's printing press proved to be.

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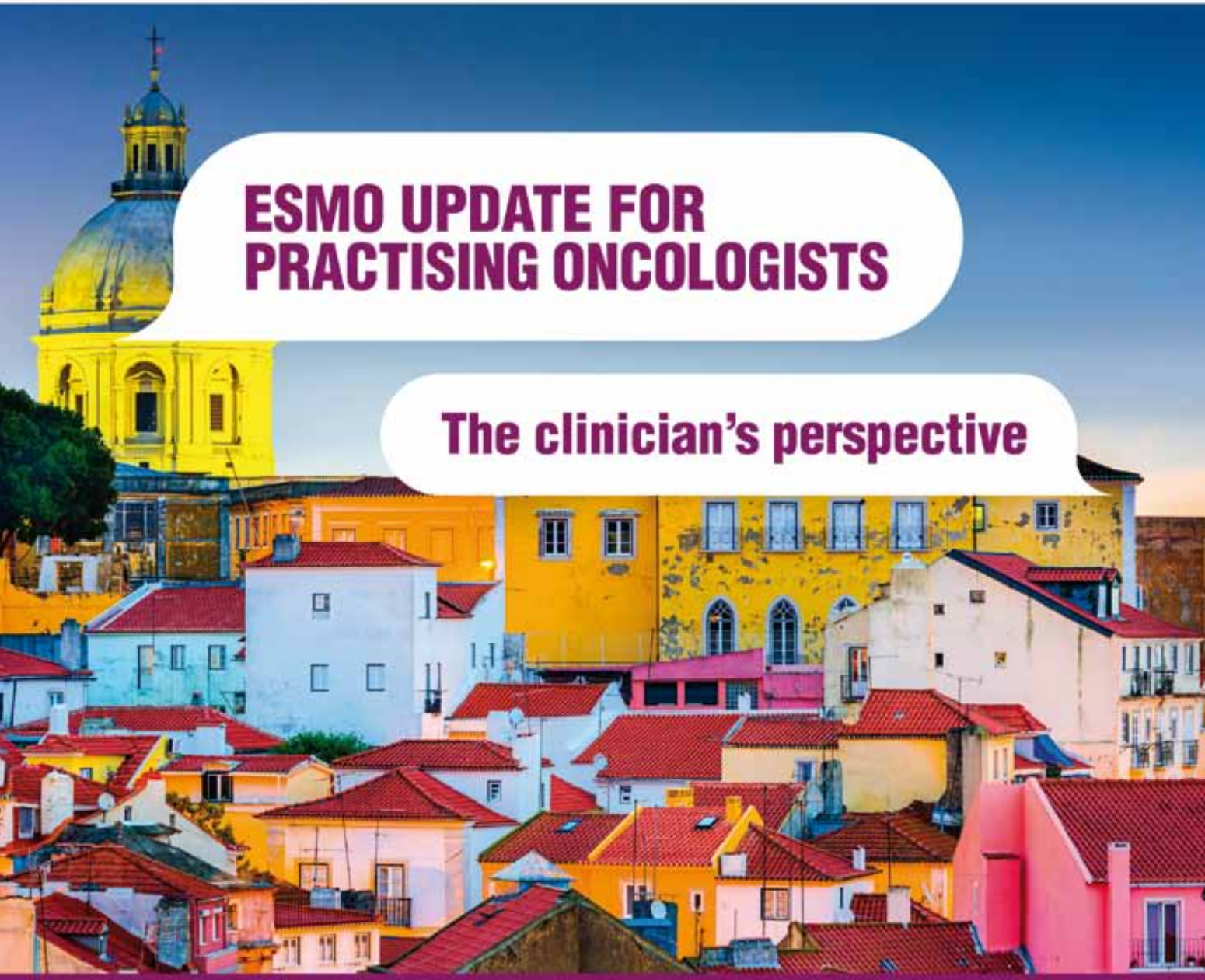

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HPV-FASTER: broadening the scope for prevention of HPV-related cancer

Combining the complementary approaches of HPV vaccination and screening could accelerate declines in the burden of cervical cancer argue **Xavier Bosch** and colleagues. They are proposing the HPV–FASTER protocol as a way to achieve it.

This is an abridged version of FX Bosch et al (2016) HPV-FASTER: broadening the scope for prevention of HPV-related cancer. ***Nat Rev Clin Oncol*** *13:119–132. It was edited by Janet Fricker and is published with permission* © *2016 Nature Publishing group. doi:10.1038/nrclinonc.2015.146*

nature REVIEWS CLINICAL ONCOLOGY

Cervical cancer is the third most common cancer in women worldwide. The burden varies widely between countries, which is largely attributed to variations in cancer prevention efforts and healthcare resources. Countries with a well-organised screening programme and high levels of participation in screening have observed a substantial decrease in cervical cancer incidence. Social inequity and access to evidence-based preventive services are major issues in cervical cancer control.

Current strategies for preventing cervical cancer include primary prevention via HPV (human papillomavirus) vaccination and secondary prevention using cytology tests or HPV detection methods to screen for cervical cancer precursors.

Cervical screening

Cytology-based screening programmes have achieved large reductions in cervical cancer incidence and mortality, particularly in countries where coverage of the target population has been at a consistently high level for more than a decade.

One limitation of cytology-based screening is its relatively low sensitivity for detecting precursor cervical cancer lesions (CIN2+) compared with HPV testing, necessitating repeated screening and complex infrastructures. These limitations are factors behind the failure to successfully implement cervical cytology screening in most developing countries, where screening tends to be unorganised and selective for individuals from high socioeconomic classes in urban areas

(*Vaccine* 2012, 30 Suppl 5: F183–191).

Clinical trials have shown that HPV testing provides a 30–40% gain in sensitivity for detecting precursor lesions of cervical cancer (CIN2+ and CIN3+) compared to cytology, at the cost of a 3–5% loss in specificity. HPV testing also shows less variability across populations (*Int J Cancer* 2014, 134:1835–43).

Likewise, previous HPV-negative tests predict a lower incidence of subsequent detection of CIN3+, as compared to a previous normal cytology screening result, thereby allowing safe extension of the intervals between screening episodes.

Reviews have concluded that HPV-based technologies could be used for primary screening (*Ann Oncol* 2014, 25:927–35), with several guidelines currently recommending HPV testing for primary screening.

However, since an increase in overdiagnosis of naturally regressive CIN is observed in women below the age of 30, the World Health Organization mainly recommends HPV-based screening in women over 30 years old (over 25 years in some protocols).

In order to be effective at population levels, screening initiatives need the infrastructure of publicly funded, coordinated and centralised programmes, with networks of specialised colposcopy clinics to ensure proper management of positive screens.

Desired features include 'call and recall' procedures, regular staff training, and systematic audits of invasive cancer cases occurring within screened populations.

The logistics and technology needed for successful deployment remain barriers to the introduction and sustainability of cervical screening in low-income countries.

HPV vaccines

At present three prophylactic HPV vaccines are licensed – the tetravalent vaccine Gardasil, based on virus-like particle (VLP) antigens for HPV types 6, 11, 16, and 18; the bivalent vaccine Cervarix, based on VLP antigens for HPV types 16 and 18; and a nonavalent vaccine Gardasil9, based on VLP antigens for HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58.

HPV vaccination programmes mainly target single cohorts of adolescent girls (aged 9–14 years), with some countries extending the coverage up to age 18 or 26. However, women above the age of 25 are also vulnerable to new infections. Recent results of phase III HPV vaccination trials have documented that the vaccine is highly effective at preventing HPV-specific persistent infection and CIN1+ in adult women testing DNA-negative for HPV (some 85–95% of women in screening age groups), with efficacy estimates above 80%.

The vaccination scenario is rapidly changing with the arrival of the 9vHPV vaccine, which is expected to protect against 95–100% of HPV infections included in the vaccine, which account for some 80% of CIN2+ lesions and 90% of invasive cervical cancers worldwide.

Further, in countries that have implemented HPV vaccination programmes, a significant reduction of prevalent infections, precancerous lesions and genital warts has been observed in the vaccinated cohorts, and also in their sexual partners, demonstrating the effectiveness of HPV vaccination, including a herd-protection effect (*Clin Ther* 2014: 17:23).

The cervical cancer prevention field is now expanding in three ways. The age group for vaccination is expanding, by reducing the vaccination age towards paediatric populations (age 9+), and increasing the upper limit to include young women (e.g. up to age 26 in Australia and Denmark). Boys are being included in routine vaccination programmes (e.g. up to age 18 in Australia and Finland). And HPV DNA testing is being used for primary screening.

The HPV-FASTER protocol

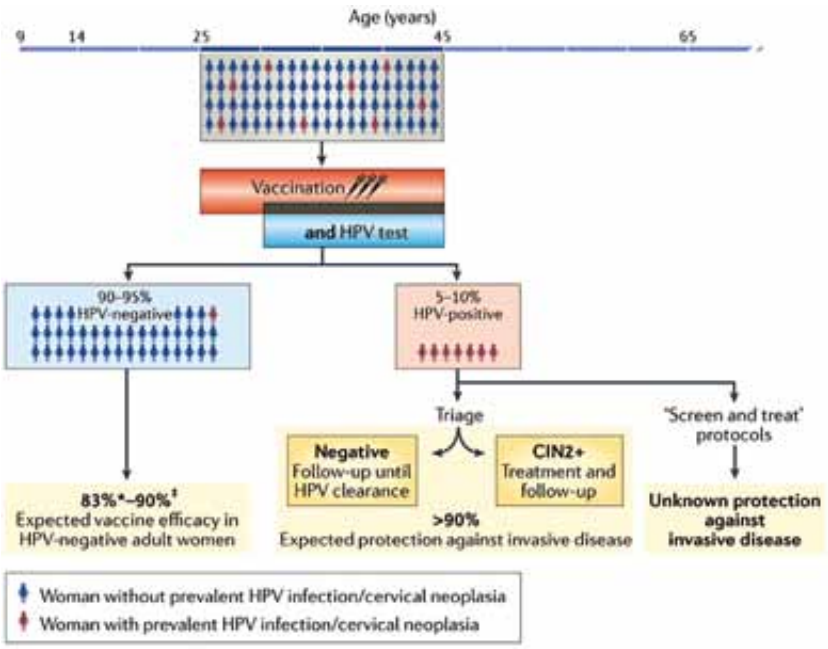
The HPV-FASTER protocol has been developed to address disconnects between HPV screening and vaccination, through combining both strategies with the aim of accelerating reductions in cervical cancer incidence and mortality.

The concept proposes a generalised HPV vaccination campaign aimed at females aged from 9 up to 30–45 years, paired with at least one HPV-screening test at any age above 30 years, and triage/diagnostic assessments of women who screen HPV positive (see figure opposite).

One controversial element of the HPV-FASTER strategy is whether to vaccinate women irrespective of their HPV status, or restrict vaccination to women who test HPV-DNA negative. Current HPV vaccines lack therapeutic effects against development of cervical lesions in women who are HPV-DNA positive (*JAMA* 2007, 298:743–53).

Evidence indicates that vaccination of women who are HPV-positive or CIN2+ does not interfere with treatment or follow-up of CIN2+. Compliance with three-dose vaccination regimens, it is felt, would be facilitated if first doses were delivered in combination with the HPV test in women aged over 30 years. One HPV-based screen after vaccination would identify most of the CIN2+ cases and HPV positive women requiring more frequent follow-up.

The HPV-FASTER core concept



The HPV-FASTER strategy proposes to offer HPV vaccination to women aged 25–45 years, with concomitant HPV-DNA screening in women aged 30 years and above. Additional research will have to determine the required number of HPV-screening events in the vaccinated individuals and the optimal sensitivity of the HPV tests adopted, in order to maximise cervical cancer prevention. Updated results on HPV-vaccine studies, notably on efficacy, duration of protection, and spectrum of HPV genotypes covered, are expected to significantly reshape the quantitative predictions for prevention of the future HPV-FASTER protocols.

CIN2+ – cervical intraepithelial neoplasia grade 2 or higher; HPV – human papillomavirus.

An alternative HPV-FASTER protocol could be to vaccinate females aged 9 to 45 years, and offer HPV screening at any age above 30 years, but starting at one to five years after vaccination, rather than at the time of the first dose. For effectiveness, it is of great importance for HPV-FASTER to ensure all women are HPV tested at least once after vaccination, as no protection is available against current infections.

Finally, the most conservative HPV-FASTER approach, based on women who are HPV-positive being at low risk of invasive disease if triaged, offers vaccination only to women testing HPV-negative up to 45 years.

Implementation and research

With HPV-FASTER, cervical cancer prevention models would evolve from traditional 'repeated screening rounds' to a simplified 'screen and vaccine' strategy, followed by campaigns of generalised HPV vaccination of girls aged 9–14. The approach would allow screening to remain more intensive for pockets of non-vaccinated adult women, marginal social subgroups and immigrant populations who might have missed routine vaccination.

The HPV-FASTER trials will address several important questions such as:

- Which is the best lifetime combination of screening and vaccination for women in all age groups?
- Which combination will offer a more favourable cost–benefit balance without compromising security under limited budgetary resources?
- How can we bridge the inequality gaps displayed in the incidence and mortality rates across countries?
- How can we coordinate the screening and the vaccination programmes in any given country, which are typically separated in national budgets, composition of their advisory boards, and logistics in daily practice?

Optimal combinations of vaccination and screening would be different in countries where minimal screening activities are in place compared with those where screening is established.

Uncertainties regarding HPV-FASTER

Uncertainties for HPV-FASTER include whether HPV infections that occur after 30 years are an important

Take home message from the author

Xavier Bosch is a senior consultant at the Cancer Epidemiology Research Programme, at the Catalan Institute of Oncology, L'Hospitalet de Llobregat, in Barcelona.

"Since the introduction of HPV vaccines in 2006 significant advances have been made, notably showing very high protection and safety among adult women, provided they are HPV-negative at the time of vaccination (i.e. no therapeutic effect). Likewise, more than 20 clinical trials have shown very good sensitivity to detecting HPV-positive cases in the context of screening programmes. Yet the field of cervical cancer prevention is still based on the limited use of HPV vaccines and repeated screening tests (cytology in most countries and HPV tests in some). Most international regulations and guidelines (including the EU's) recommend HPV tests as the single test for primary screening at longer intervals (i.e. 5+ years), and starting not before age 30. Only a few countries, such as Australia, support vaccination programmes that extend recommendations for vaccination to age 26 years.

Open questions

The two alternatives for HPV-screened women are to undergo repeat HPV tests every five years, or to receive a broad spectrum vaccine and then perhaps one or two lifetime additional tests. The number of lifetime additional tests will need to be determined by trials, but in reality the number of tests undertaken in developing countries is likely to be very small. Middle-aged women who are HPV-positive will need to be triaged and treated if necessary.

HPV-FASTER

The HPV-FASTER alternative calls for generalised vaccination of girls and young women (i.e. from age 9 to 45), paired with at least one episode of HPV screening from ages 25/30 to 65. HPV vaccination of young women would be offered at enrolment irrespective of their HPV status. The HPV-FASTER alternative is anticipated to be a cost-effective option in developed countries with generalised social access to quality-monitored screening services. More important, the HPV-FASTER alternative is proposed as a game changer for countries with historically high cervical cancer incidence rates, limited screening deployment, but good vaccination expertise, such as the Latin American region and Eastern Europe.

Further studies

We are organising formal trials comparing HPV screening and vaccination against HPV screening alone. In countries with limited resources (where there is one screening episode at around age 30), projects will need to be put in place to monitor vaccination coverage, quality of treatment of women who test HPV positive, and long-term incidence of cervical cancer."

cause of cervical cancer, and whether women who have cleared HPV infections and test HPV-DNA negative are susceptible to new infections with the same or other types of HPV.

There are also questions about the level of continuing participation in reduced follow-up (e.g. five screening events over a lifetime), if programmes create a false sense of complete protection.

Finally, in developing countries, HPV screening and associated triage/ treatment need to be sustainable in local settings. Where vaccination campaigns and one round of HPV screening/ treatment might be too costly, decisions will need to be made regarding which preventive measure should be introduced first.

Modelling cost-effectiveness

Natural history models of HPV and cervical cancer will be used to estimate the cost-effectiveness of different strategies and variants of the HPV-FASTER design. In terms of effectiveness, several model-based studies have predicted that catch-up vaccination campaigns of older girls and young women would advance by several years the impact of HPV vaccination on cancer reduction compared to vaccinating only adolescent girls (*Int J Public Health* 2011, 56:153–62).

In terms of cost-effectiveness, all

studies show the same decreasing pattern with advanced age at first vaccination, but they are not consistent regarding the age at which vaccination becomes unattractive.

The price of the vaccine has a major impact on the cost-effectiveness balance in the models. As an example, when the vaccine price is reduced from €105 to €45 per dose, the age limit for cost-effectiveness (under US parameters) changes from 12-year-old girls to 30-year-old women (*J Infect Dis* 2011, 204:377–84).

These results suggest that systematic HPV vaccination of women up to the age of 30 years – and possibly up to the ages of 40–45 years – at a sustainable price, paired with a limited number of lifetime HPV screening visits, could be clinically effective and cost-effective in many settings.

Ongoing studies

In Europe, the European Commission funded CoheaHr, a feasibility project across 11 countries, to address social and logistic uncertainties regarding HPV-FASTER.

If the initial evaluation proves successful, the aim is to organise a full-scale trial randomly assigning women aged 25–45 years to HPV screening or HPV screening plus HPV vaccination, with endpoints including incidence rates of HPV infections and cervical pre-neoplastic lesions.

In Mexico, the FRIDA trial is offering HPV testing and HPV16/18 genotyping to large numbers of women aged 25 to 75 years who have limited access to screening. To examine gains from HPV vaccination, the FRIDA-2 trial will compare repeated HPV screening with repeated screening and vaccination, with the trial powered to examine protection gains in the 25–55-year age group. Other researchers are exploring opportunities to implement the HPV-FASTER concept in settings with no or minimal screening activities in place, such as Latin America, in under-screened aboriginal populations in Australia, and in other isolated populations.

Conclusions

The successful combinations of HPV screening / treatment and HPV vaccination has the potential to move the preventive paradigm from our current 'cancer control' objective to a cervical 'cancer elimination' goal in selected populations – an essential step to envision cancer eradication in the future.

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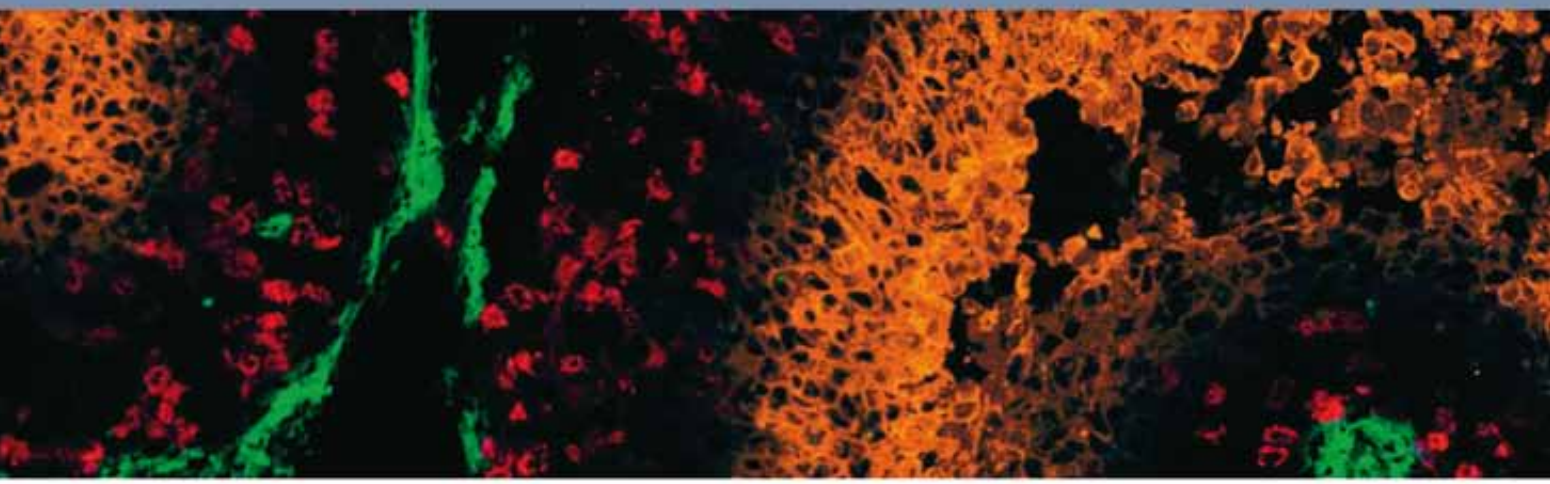

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ECCO

EVENTS DIRECTORY
2016 – 2017

ECCO - the European CanCer Organisation manages multidisciplinary meetings of excellence on behalf of its Members:

EVENTS	SAVE THE DATE
EORTC NCI AACR 2016	**29 November – 2 December 2016** ***Munich, Germany*** ENA2016 28th EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics
ECCO 2017	**27 – 30 January 2017** ***Amsterdam, The Netherlands*** ECCO2017 European Cancer Congress From Evidence to Practice in Multidisciplinary Cancer Care
MCCR WORKSHOP	**17 – 23 June 2017** ***Zeist, The Netherlands*** MCCRWorkshop ECCO-AACR-EORTC-ESMO Workshop on Methods in Clinical Cancer Research
2nd Special Conference EACR AACR SIC	**24 – 27 June 2017** ***Florence, Italy*** EAS2017 2nd EACR-AACR-SIC Special Conference onThe Challenges of Optimising Immuno and Targeted Therapies

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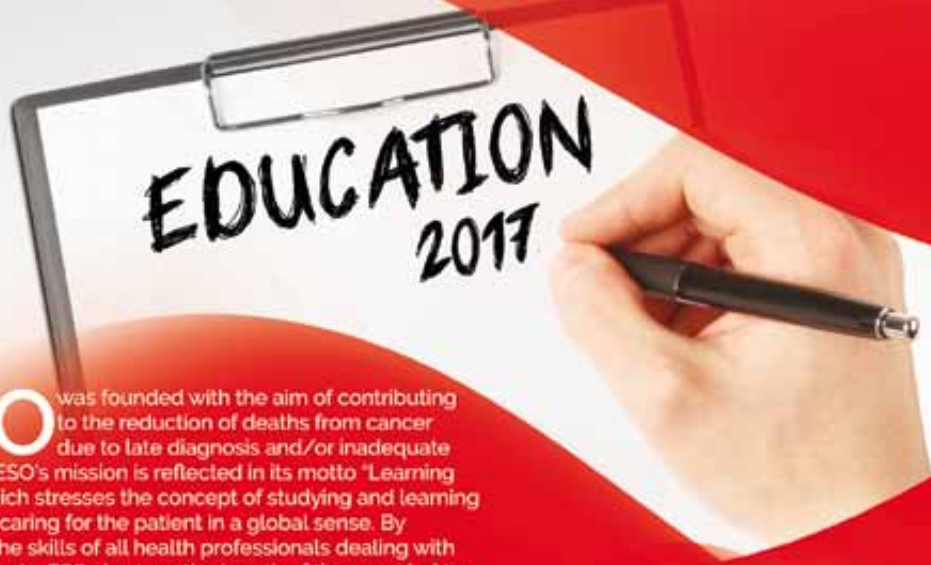

35 years

ESO European School of Oncology
learning to care

ESO was founded with the aim of contributing to the reduction of deaths from cancer due to late diagnosis and/or inadequate treatment. ESO's mission is reflected in its motto "Learning to Care", which stresses the concept of studying and learning and also of caring for the patient in a global sense. By improving the skills of all health professionals dealing with cancer patients, ESO shortens the length of time needed to transfer knowledge from research centres to daily practice, combining advanced technology with humanism in care.

Eso's events are:
- clinically oriented
- interdisciplinary
- multiprofessional
- open to advocacy

Further information available at:
www.eso.net
www.e-eso.net
www.cancerworld.net
www.breastcentresnetwork.org
www.prostatecancerunits.org

MASTERCLASSES

3-6 March 2017 | Nijmegen, Netherlands
Masterclass in Endoscopy in Gastrointestinal Oncology

25-30 March 2017 | Berlin area, Germany
16th ESO-ESMO Masterclass in Clinical Oncology

25-30 March 2017 | Berlin area, Germany
10th ESO-EONS Masterclass in Oncology Nursing

22-26 May 2017 | Lisbon, Portugal
3rd ESOP-ESO Advanced Masterclass in Oncology Pharmacy

21-23 June 2017 | Cambridge, UK
Masterclass in Oncology Basics for Beginners

COURSES AND SEMINARS

27-28 January 2017 | Leipzig, Germany
Workshop of the European Laryngeal Society: Early Cancer of the Larynx

1-3 March 2017 | Tel Aviv, Israel
Innovation in Radio-Oncology

April 2017 | Krakow, Poland
9th Clinical Oncology Update - Onkologia 2017

10-13 June 2017 | Ascona, Switzerland
Leukaemia and Lymphoma

13-18 July 2017 | Valencia, Spain
ESMO-ESO Course on Medical Oncology for Medical Students

28 August - 8 September 2017 | Antwerp, Belgium
ESO-ESSO-ESTRO Multidisciplinary Course in Oncology for Medical Students

27-29 November 2017 | Milan, Italy
ESO-ESMO-RCE Clinical Update on Rare Adult Solid Cancers

INSIDE TRACK CONFERENCES

27 January 2017 | Amsterdam, The Netherlands
ESO Society Day at ECCO: Breast Cancer Screening and Early Detection

2-4 November 2017 | Lisbon, Portugal
Advanced Breast Cancer Fourth ESO-ESMO International Consensus Conference (ABC4)

24-25 November 2017 | Rome, Italy
Molecular Diagnostics, Genomics and Epigenetics in Clinical Oncology

ARAB COUNTRIES

November 2017 | Location to be announced
6th Arab Countries Masterclassin Clinical Oncology

EASTERN EUROPE AND BALKAN REGION PROGRAMME

30 June - 5 July 2017 | Belgrade, Republic of Serbia
3rd ESO-ESMO Eastern Europe and Balkan Region Masterclass in Medical Oncology

6-7 October 2017 | Krakow, Poland
Eastern Europe and Balkan Region Refresher Course on Breast Cancer

EURASIA PROGRAMME

18-19 May 2017 | Moscow, Russian Federation
Eurasia Course on Gastrointestinal Malignancies

18-20 October 2017 | Tbilisi, Georgia
4th Masterclass in Clinical Oncology

LATIN AMERICA PROGRAMME

26-30 April 2017 | San Jose, Costa Rica
3rd ESO-ESMO Latin American Masterclass in Clinical Oncology

WORLD ONCOLOGY FORUM®

19-21 October 2017 | Lugano, Switzerland
Stop Cancer Now! Cancer and Global Health: From Research to Policy

ESO OBSERVATORIES AND SESSIONS

E-ESO ONLINE EDUCATIONAL RESOURCES

e-Sessions (live and recorded on the internet)
ePatCare (clinical cases)

CAREER DEVELOPMENT

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Certificate of Competence in Breast Cancer (Second cohort 2017-2018)
Clinical Training Centres Fellowship Programme
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Cancer World Journalism Award, Media Training and Events, Cancer World Journalist Network and The Cancer Blog

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