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n° 70 January / February 2016

Tipping the balance

Risk–benefit equation on trial

Introducing
ELUXA 1

ACTIVE TRIAL
Now recruiting

A multicentre, single-arm, open-label Phase II trial designed to investigate the efficacy, safety, and pharmacokinetics of oral BI 1482694 (HM61713) in patients with non–small cell lung cancer (NSCLC) who have developed T790M resistance mutation following treatment with epidermal growth factor receptor-tyrosine kinase receptor (EGFR-TKI)

Patients with NSCLC harbouring T790M resistance mutation following prior treatment with EGFR-TKI

↓

BI 1482694 (HM61713) 800 mg (2 x 400 mg) QD orally

↓

Primary Endpoint: Objective response rate, by independent assessment

Study countries:

ELUXA 1 is currently being conducted in Australia, Canada, Germany, Italy, Korea, Malaysia, the Philippines, Spain, Taiwan, and the United States. Coordinating Investigators: Prof. K. Park and Prof. Jänne

Primary endpoint:

Objective response rate, by independent assessment

Secondary endpoints:

Disease control rate, duration of overall tumour response, progression-free survival (PFS), overall survival, pharmacokinetics, patient-reported outcomes, and safety

Main eligibility criteria:

- Locally advanced or metastatic NSCLC that is not amenable to curative surgery or radiotherapy
- Documented, activating EGFR mutations known to be sensitizing to EGFR-TKI
- Patients with disease progression after EGFR-TKI with/without additional lines of treatment whose tumours harbour centrally confirmed T790M mutation
- ≥1 measurable lesion according to RECIST 1.1 and ECOG PS of 0 to 1
- No prior T790M-targeting treatment

For more information about the ELUXA 1 (HM-EMSI-202) trial, please visit www.clinicaltrials.gov (NCT02485652) or contact your local Boehringer Ingelheim Medical Representative.

BI 1482694 (HM61713) is an investigational compound and is not approved. BI 1482694 (HM61713) efficacy and safety have to be fully established.

ECOG = Eastern Cooperative Oncology Group; PS = performance status; RECIST = Response Evaluation Criteria in Solid Tumors.

Reference: ELUXA 1: Phase II trial of HM61713 (BI 1482694) for the treatment of ≥2nd line T790M mutation positive adenocarcinoma of the lung (NSCLC). https://clinicaltrials.gov/ct2/show/NCT02485652?term=NCT02485652&rank=1. Accessed December 7, 2015.

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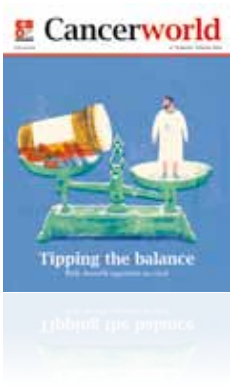

Contents

Printed by
Grafiche Ambert, Verolengo (TO)

Cover by
Lorenzo Gritti

Illustrations by
Maddalena Carrai
Elisa Macellari

Published by
European School of Oncology
www.eso.net

Direttore responsabile
Alberto Costa

Registrazione Tribunale di Roma
Decreto n. 436 del 8.11.2004

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Recommended by:
OECI

Scan this QR code with your smartphone to access our website.

Cancer World is published six times a year by the European School of Oncology.
It is distributed at major conferences, mailed to subscribers and to European opinion leaders, and is available online at www.cancerworld.org

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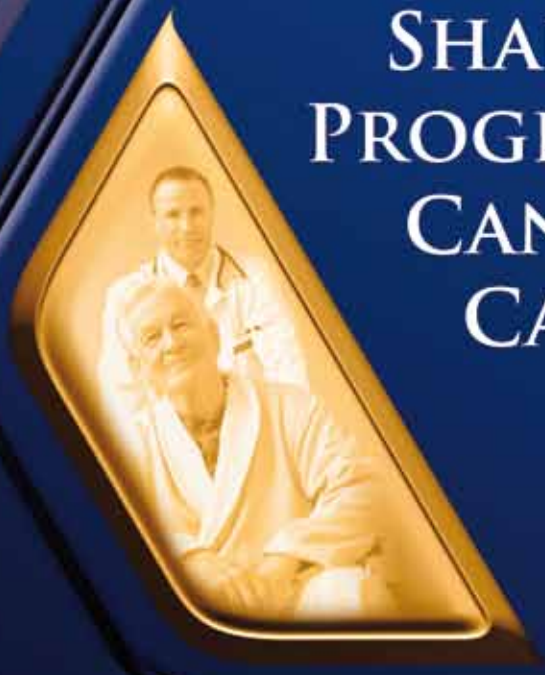
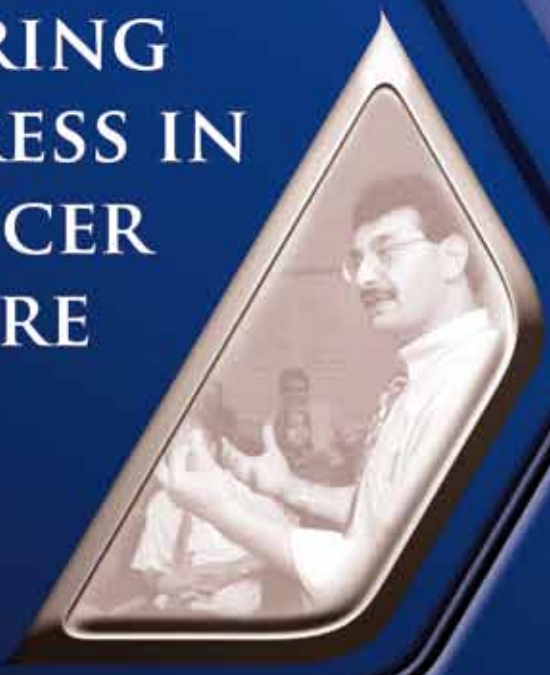
Learning to care

Sharing Progress in Cancer Care





Sharing Progress in Cancer Care (SPCC) is a pioneering partnership between ESO and some of the world's leading pharmaceutical companies. Unrestricted grants from SPCC partners support a spectrum of innovative projects implemented by ESO such as CancerWorld magazine and the Masterclass in Clinical Oncology. The SPCC partners confirmed as of January 2016 are acknowledged on this page.

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Turning more than one page

Alberto Costa MD, Editor

Would you like to receive a regular free copy of *Cancer World*? To receive a printed copy, please complete our online form *http://bit.ly/CW-print*. If you prefer to read it online, please sign up to receive weekly email alerts of new articles at *http://bit.ly/CW-online*. The full version can also be viewed at www.cancerworld.org.

Readers of our printed edition will have noticed that a new chapter has begun in the life of our magazine. We are dedicating our cover stories to exploring the big topics in oncology that define our era, starting in this issue with a look at the under-reporting of toxicities associated with new drugs.

A group of talented young illustrators has been tasked with capturing the essence of each story, and their artwork will appear on the cover of every issue.

Our commitment to passing on the insights and experiences of the women and men who are leading change across the world of cancer – which used to feature as cover stories – remains as strong as ever. The focus will shift, however, to the new generation of emerging leaders, whose stories will be told in a new Profile section, starting with Fedro Peccatori, who has just taken over as Scientific Director of the European School of Oncology.

We will continue to cover clinical and scientific issues in our popular e-Grandround and Cutting Edge features, as well as stepping up our coverage of cancer policy and organisation, giving a voice to people living with cancer, airing debates on contentious issues, and addressing issues in global cancer care.

We will also be broadening our base of journalists to include contributors from a wider range of European countries, and tripling our print run to 16,000 copies, to be distributed by post, through libraries of the major European cancer institutes, and at congresses and conferences.

If you are a longtime reader of *Cancer World*, we hope you will appreciate these changes, which we feel are in step with the changing world of oncology as well as the maturing of our own magazine.

If this is your first time reading *Cancer World,* we welcome you. Published by the European School of Oncology (www.eso.net), under the strapline "Shaping the Future of Cancer Care", the magazine provides a platform for information and inclusive discussions about how to improve support and care for people with cancer.

It is an important extension of the educational work that has been the core mission of ESO since it was established in Milan, in 1982, by the Italian surgeon Umberto Veronesi, with a few close collaborators from across Europe and across disciplines – Franco Cavalli, Louis Denis, Michael Peckham, Bob Pinedo.

As Veronesi's young (at the time) assistant, I had the priviledge of directing the School for 33 years, stepping down at the end of last year to take up my new role as Editor of *Cancer World*.

Most of ESO's funding comes from an endowment set up with a legacy from a family of wealthy Italian industrialists. Some of our activities, including this magazine, are supported by a group of sustaining partners who take part in the Sharing Progress in Cancer Care programme (see opposite).

We at ESO are turning important pages in the history of our service to the European cancer community. We now invite you to turn the pages of *Cancer World*, which we hope you will find both an informative and enjoyable read.

Peter McIntyre

Tipping the balance

Almost four in ten serious adverse drug reactions now listed in the labels of 12 targeted cancer therapies were not mentioned in the studies that led to their approval. Half the serious reactions that were missed are potentially fatal. How can we improve the way we investigate and report the side effects of new drugs?

Questions are being raised about the accuracy and integrity of reports from pivotal clinical trials that provide the evidence for licensing cancer drugs. There is increasing concern that reports overstate the effectiveness of innovative drugs in a real world setting, because patients on trials are healthier and fitter than most of the people it will be used in, and understate side effects. This distorts the information used by clinicians to define the recommended dose, by regulators to assess the risk–benefit profile, and by patients to choose between treatment options.

Researchers and patient groups are calling for changes in the way that trials are designed and reported, with fewer exclusions and a much more rigorous approach to reporting side effects.

A team at the Princess Margaret Hospital in Toronto has turned a spotlight on this issue in a series of papers which highlights the gap between adverse events reported from 'pivotal' trials (which form the basis for marketing approval) and the warnings eventually added to drug labels – often years later.

The first of these, published in 2011, showed that 39% of serious adverse drug reactions – half of them potentially fatal – were not described in any of the randomised clinical trial (RCT) reports associated with 12 targeted anti-cancer agents (*JCO* 2011, 29:174–185) They had to be added to drug labels at a later date.

The same team analysed anti-cancer drugs approved by the US Food and Drug Administration (FDA) between 2000 and 2010 and found that most were associated with increased odds of toxic death, treatment discontinuation or severe adverse events (*JCO* 2012, 30: 3012–19).

In 2014 the team demonstrated that adverse effects also led to increased costs of treatment (*JCO* 2014, 32: 3634–43)

Saroj Niraula, lead author on the 2012 and 2014 papers and now a medical oncologist at Cancer Care Manitoba, in Winnipeg, Canada, stresses that new therapies have saved tens of thousands of lives and that criticism of trial reports should be seen in that context. "My point is to do what we can to improve the reporting of the trials so we can make the best judgement about efficacy and toxicity, rather than pointing out flaws in reporting research."

However, he says that RCTs are focused on demonstrating clinical efficacy rather than testing toxicity. "Frequently when we read pivotal RCT published papers we see statements like 'no differences in toxicities', but most trials are not powered to support such statements."

"Pivotal RCT papers often contain statements like 'no differences in toxicities', but there is no real data to support that"

His 2012 paper noted that treatment-related mortality associated with bevacizumab (Avastin), the cardiovascular effects of aromatase inhibitors, and the increased risk of cardiopulmonary arrest with cetuximab (Erbitux) all went unreported in the original trials.

Bevacizumab was approved in the EU for treating metastatic breast cancer in 2007 and in the US in 2008, on the basis of trial reports that showed tumour shrinkage and an increase in progression-free survival. Further evidence on both safety and efficacy that emerged in the two years following the trial, however, prompted the FDA to withdraw that approval, on the grounds that patients would "risk potentially life-threatening side effects without proof that the use of Avastin will provide a benefit, in terms of delay in tumour growth, that would justify those risks." (The European regulators, the EMA made a different judgement call after deciding that the benefits of tumour shrinkage did outweigh the risks.)

The aromatase inhibitor Arimidex was approved by the FDA in 2002 as an adjuvant treatment for early breast cancer in postmenopausal women, on the basis of the ATAC trial, which showed improved disease-free survival compared to tamoxifen and a lower incidence of certain side effects associated with tamoxifen.

A secondary analysis of the ATAC data by the FDA later led to a warning being added to the drug label to indicate that "anastrozole may be linked to an increased risk for ischemic cardiovascular events in women with pre-existing ischemic heart disease."

Yet the report of a ten-year update on the trial, published in 2011, made no reference to the new evidence, or the additional warning.

The 2006 trial comparing cetuximab and radiotherapy with radiotherapy alone for people with squamous carcinoma of the head and neck reported 'similar' incidence rates of severe reactions for the two treatment arms. The 2% of patients who died on the cetuximab arm as a result of cardiopulmonary arrest went unreported because the trial only reported acute adverse events that affected at least 10% of patients.

Lapatinib (Tykerb), is another striking example, which was flagged up by Bostjan Seruga, one of the collaborators in the 'Toronto papers', at a presentation he made at the European Cancer

Congress in Vienna in September 2015. He pointed out that Tykerb's drug label has been revised 12 times since it was approved in 2007 to treat women with metastatic HER2-positive breast cancer. Added warnings include notice of potential damage to lungs, severe skin reactions, and a 'boxed' warning on hepatotoxicity – the strongest warning that the FDA can mandate.

Seruga, who is based at the Institute of Oncology in Ljubljana, Slovenia, pointed out that new evidence from post-marketing surveillance can significantly change the risk–benefit balance, but it is the early impression about lack of harm that sticks. "Patients do not know what symptoms to expect based on prior experience, drug developers may have a false impression as to how a drug is tolerated, regulators may not have confidence in the fidelity of information about balancing risks and benefits and payers cannot accurately predict the utilisation of health care services."

"New evidence can significantly change the risk–benefit balance, but it is the early impression about lack of harm that sticks"

A distorted picture

There are a number of ways in which trial reports paint a distorted picture: patient selection for trials, a failure to detect or report side effects, and the way data are presented are all implicated.

Patient selection

Patients who are fit enough to join clinical trials are not representative of the substantial proportion of patients with the condition in the wider public. Trials usually exclude those with heart or kidney disease or a previous history of cancer. It has been half-seriously suggested that to enter a clinical trial you need to be "a marathon runner who happens to have cancer".

This means that when drugs are used in clinical practice, results very often don't live up to expectations. Niraula says, "Drug companies put a lot of investment into clinical trials, and mostly with good intentions want the drug to work for the benefit of the patient and understandably, want a return on their investment. When it enters the real population, the result is a higher likelihood of toxicities and a lower likelihood of benefits."

A study at the Princess Margaret Hospital in Toronto provides some confirmatory evidence. It compared outcomes for patients with metastatic castration-resistant prostate cancer, treated at the same hospital, to identical standards of care, according to whether or not they were on a trial. They found that the trial patients were younger, had less comorbidity and better performance status. Patients treated in routine practice had shorter survival and experienced more toxicity, notably fever and infection (*Ann Oncol* 2013, 24:2972–77). This difference between outcomes inside and outside clinical trials even has its own label: "the efficacy–effectiveness gap".

The likelihood is that differences in outcomes will be even greater for patients treated away from major centres, since patients are likely to have poorer access to supportive care to address side effects. As quality of life worsens, patients may suspend treatment or reduce the recommended dose.

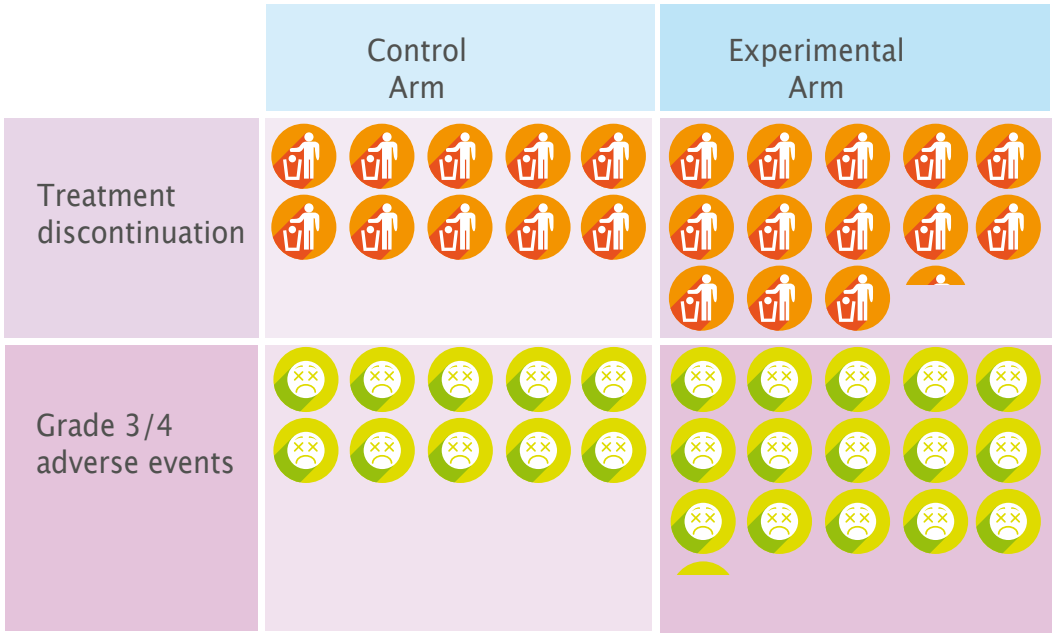
Age discrepancy is widespread within clinical trials, as a by-product of excluding patients with comorbidities. The CML Advocates Network found that the average age of CML patients on phase III trials was 47, while the average age of real world patients in Europe is nearer 65, meaning that side effects in the older population with comorbidities are not discovered in trials.

There is, however, evidence that exclusions do not necessarily invalidate trial results. In a study with some similarities to that conducted in Toronto, Joseph Unger and a team at the Fred Hutchinson Memorial Hospital in Seattle studied 21 RCTs supported by the National Cancer Institute. By comparing the survival of patients on the control arm – who were receiving standard care – to similar patients treated outside trials, they were able to gain insight into differences relevant to being in a trial (*JNCI* 2014, 106:dju002 doi:10.1093/jnci/dju002).

Unger and his colleagues found that, while being on a trial was associated with better survival, the difference lasted for only one year after diagnosis. They believe the difference is simply due to patients in the trial being younger and fitter with fewer comorbidities.

Survival curves for standard treatment patients in trials and non-trial patients were very similar in the longer term. Of course, looking at control arm patients does not say anything about the efficacy of treatments, but Unger says it suggests that any benefits found for new treatments should translate to a real-world setting. "The fact that over the long term patients had very similar outcomes suggests that trials are not picking off qualitatively different cancer patients, they are just excluding those with comorbid conditions that affect survival in the short term." However, this conclusion would not be valid, he says, if

The price we pay for progress



A 2012 study of 12 widely used targeted cancer drugs approved since 2000 (*JCO* 30: 3012–19) showed that most are associated with higher rates of toxic death (odds ratio1.4), treatment discontinuation (OR 1.33) or severe adverse events (OR 1.52)

the treatments have too much toxicity or poor compliance.

Unger is also concerned that some of the exclusions of patients due to concern over safety are outdated, and that it is increasingly unrealistic to exclude patients from trials simply because they have had a previous cancer.

However, the tendency to exclude patients appears to be increasing. A study of 86 practice-changing RCTs showed that the proportion of patients excluded from trials had doubled to 18% after 2010, compared with the 9% before 2000 (*Cancer Treat Rev* 2016, 43:67–73). There were increases in exclusions of patients with cerebrovascular events, gastrointestinal bleeding or cardiac conditions. There was also a decrease in the average upper age limit.

Trials in denial

Deciding on which side effects to look for can influence what is found. Ian Tannock, a leading member of the Toronto group, believes the ATAC trial led to a distorted view of the relative safety of Arimidex to tamoxifen, because it was left to the doctors involved in the trial to make a judgement on which events could be connected with the treatment. In a letter to *The Lancet* (March 2011), he argues that this created a bias "because side-effects due to tamoxifen were recognised better at the start of the ATAC trial than were those due to anastrozole," and he suggests it would be better to have a prespecified checklist.

Patients, however, point out that prespecified checklists can also lead to under/non-reporting of important side effects that have been omitted from the list. This is a particular problem for side effects such as exhaustion and diarrhoea, which are not life-threatening but can make life almost unbearable.

Gilly Spurrier-Bernard, president administrator of MelanomaFrance, describes how difficult it was for her husband to record side effects on a trial of vemurafenib (Zelboraf), despite being under the care of the Gustave Roussy Institute, one of Europe's best cancer centres.

"Clinicians only want to report the effects that the trial pharmaceutical companies have identified as a high risk. My husband had a number of skin reactions which we knew were to do with the drugs, because he had never had them before, and they look down the list and say, that is nothing to do with the trial.

"We were treated at a very good centre but it used to drive me up the wall that what you were reporting as potential side effects did not even get recorded."

Several studies show that clinicians under-report adverse events that are very significant for patients.

In 2015 a study from the Italian National Cancer Institute in Milan found extensive under-reporting by doctors of six symptoms that blight the lives of

patients in three randomised trials, including nausea, diarrhoea and anorexia (*JCO* 2015, 33:910–915). Six years previously, in 2009, a survey by Myeloma Patients Europe had shown fundamental differences in perceptions between patients, nurses and doctors in assessing the impact on quality of life of various side effects, including hair loss, fatigue, reduced body function, neuropathy and thrombotic events.

Eric Low, chief executive of Myeloma UK and the chief author of that report, says it shows why patients must have more of an input into reporting side effects to ensure that trial reports paint an accurate picture. He points out, however, that it is only when drugs come into everyday use that clinicians learn how to deal with side effects. He gives the example of bortezomib (Velcade), the first significant proteasome inhibitor, which was given accelerated approval in 2003 as a treatment for relapsing myeloma.

"Initially bortezomib had many side effects, particularly neuropathy, but over time we got a subcutaneous version and doctors moved to giving it once a week and that made a dramatic difference. Now peripheral neuropathy is quite rare.

"Almost half of patients who suffered severe side effects had their first episode after the treatment cycle used to define dosage"

"The real benefit of a new drug comes as clinical experience accrues and patient management and patient selection improves. At the point where a new drug is approved we don't have in depth data, and with a move towards accelerated approval we are going to have even less."

Data from general clinical practice is, however, only used to update clinical trial reports in a small minority of cases. Bostjan Seruga reported that his team had looked at 311 RCTs of prostate, breast and lung cases published over a 30 year period and found that only one in five had published updated reports. Where publications were updated they predominantly showed a smaller magnitude of effect and a greater number of side effects, than the original reports.

There is increasing support, by EMA in Europe and the NCI and the FDA in the US, for moving towards patient-reported outcomes to mitigate the inaccurate reporting of side effects. The EMA completed a public consultation on this issue in 2015 and is expected to report back early this year.

The issue is complicated by the fact that, in the context of certain clinical trials, patients themselves may feel they have an incentive to downplay the seriousness of side effects. Gilly Spurrier-Bernard knows this from her own family experience, when her husband was on a trial for ipilimumab, and in her advocacy role hosting online forums for melanoma patients.

"I spent four years filling in patient questionnaires and as far as I am concerned they are totally useless. Patients lie through their teeth because they know that patients get kicked off the trial if they show any slightly scary signs of side effects. With the ipilimumab trial the slightest sign of colitis or diarrhoea of significant amount you were pretty much kicked off. This is all discussed on patient forums."

She fears for what will happen when the trial treatments come into general use. "People with brain mets, or comorbidities or lupus are excluded from most of these trials. How will side effects affect people who already have autoimmune problems? None of this has been recorded properly. They need to get it sorted."

Misreporting data

Whether by accident or by design, the process of writing up clinical trials offers further opportunities to downplay the negatives and talk up the positives.

In 2004 An-Wen Chan and colleagues reported on 122 journal articles from 102 clinical trials and found that 50% of efficacy outcomes and 65% of harm outcomes were incompletely reported (*JAMA* 2004, 291:2457–65). In 62% of trials, at least one primary outcome from the trial protocol was changed or omitted. The authors concluded that "reporting of trial outcomes is not only frequently incomplete but also biased," and that "published articles may overestimate the benefits of an intervention."

Another of the landmark studies from the Princess Margaret Hospital, Toronto, found that a third of clinical trials for women with breast cancer showed "bias in reporting" in primary endpoints, and two thirds showed bias in reporting toxicity (*Ann Oncol* 2013, 24:1238–44). Positive trials were particularly associated with under-reporting toxicity.

Peter Jüni, Founding Director of the Clinical Trials Unit of Bern University Hospital, outlined at the 2015 European Cancer Congress how the reported results of clinical trials are often distorted. Common practices include 'fishing' through data for spurious positive outcomes, swapping primary and secondary outcomes because the primary outcomes are not very good, and excluding outliers to make results statistically significant.

Perhaps the most pernicious practice

Incomplete information

Laws governing the marketing of medicinal products in European Union member states require that all medicinal products must "be accompanied by labelling and package leaflet which provide a set of comprehensible information enabling the use of the medicinal product safely and appropriately".

But research into the reporting of side effects for some of the most widely used targeted anti-cancer drugs shows the majority are not reported in the pivotal trial and are added to the label, sometimes many years later.

The TKI HER2-blocker lapatinib (Tykerb) has had 12 amendments to its label since it received marketing approval in March 2007, even though safety had already been evaluated in clinical trials in more than 3,500 patients with advanced or metastatic breast cancer. The most common adverse reactions (i.e. in more than 20% of patients) initially recorded for Tykerb plus capecitabine were diarrhoea, hand-foot syndrome, nausea, rash, vomiting, and fatigue.

Warnings given on the label included:

- Reports of decreases in left ventricular ejection fraction
- Foetal harm if administered during pregnancy
- Dose reduction to be considered for patients with severe hepatic impairment.
- Prolonged QT interval in the heart's electrical cycle in some patients.

In **August 2007** further warnings were added about:

- Interstitial lung disease and
- Pneumonitis

In **2008** a boxed warning (highest grade of warning) was added about:

- Reports of severe and sometimes fatal hepatotoxicity – "If changes in liver function are severe, therapy … should be discontinued"

Various notices were added about drug-drug and drug-food interactions in the intervening period.

In **June 2013** the label was amended to warn about:

- Grade 3/4 diarrhoea. "The diarrhea may be severe, and deaths have been reported," says the label. (Most cases of diarrhoea are less severe, occur early in treatment and last 4 to 5 days.)

is selectively omitting inconvenient results, such as the 2% of patients on the cetuximab arm who died as a result of cardiopulmonary arrest. A bigger problem may be the non-publication of entire trials that generate inconvenient results. It is such practices that sparked the launch of the AllTrials campaign in January 2013, which calls for "all trials past and present [to be] registered, and the full methods and the results reported" (alltrials.net).

Wrong dosage, worse effects

While many of the biases listed above may be nothing new, it seems that reporting of side effects from targeted drugs may be a particular problem. One reason is that cytotoxics are prescribed for fixed protocols, whereas targeted drugs are often continued until resistance develops, and adverse effects that are not immediately apparent often occur later.

The big problem here is not just that, as Seruga remarked, it is the early impression about lack of clinical harm that sticks, but that early toxicity results set the basis for defining dosing, and as a result recommended dosage levels may be set too high.

Research led by Sophie Postel-Vinay from the Gustave Roussy Institute found that more than half of the most serious toxicities in phase I trials occurred after the end of the 'dose-limiting-toxicity' period used to determine tolerability (*JCO*

2011, 29:1728–35). Although the severity of toxicities decreased during the trials, the proportion of unresolved toxicities increased, more medication had to be prescribed to deal with side effects, and dose reduction became more frequent, suggesting that "benign late toxicities may not be bearable over time and might require specific management."

This was confirmed in a much larger study led by Postel-Vinay and coordinated by the EORTC, which gained unprecedented access to raw patient data from institutions and pharmaceutical companies covering more than 2,000 patients in 54 phase I trials (*EJC* 2014, 50:2040–49). Almost half of patients who suffered severe side effects (grade 3 or worse) had their first episode after the cycle of treatment that was used to define dosage. One in 11 patients experienced dose-limiting side effects (i.e. the medication had to be paused or reduced), of which the most common were fatigue, nausea, vomiting, gastro-intestinal disorders and hypertension.

The way forward

Most experts agree on a number of steps to improve reporting on data from clinical trials and assess the value of new drugs.

Saroj Niraula, in Winnipeg, says that good-quality population-based studies are required from real-world use after a drug receives full approval, along with stricter regulations about reporting. "We as physicians should be able to provide our patients with the most comprehensive information possible on efficacy and toxicity before they come to a decision about the amount of toxicity that is acceptable to them for a given benefit.

"Journals have to be more stringent. There should be academic incentives to report toxicities well. We want honest and exhaustive information from pivotal drug trials."

Joseph Unger at the Fred Hutchinson in Seattle believes that trials should have fewer exclusions. "From a patient perspective access to trials is a huge issue. But also from a researcher's perspective we want to be able to do these trials as quickly as possible. If we are excluding patients for reasons that are unnecessary, that is hindering our efforts."

"The key recommendations are that everything about late toxicities is reported, which is not the case at the moment"

At the Gustave Roussy, Sophie Postel-Vinay is calling for data on adverse effects to be collected more comprehensively and for longer periods. "The key recommendations are that everything about late toxicities is reported, which is not the case at the moment, and that the recommended phase II dosage is based on everything that is seen over the whole trial."

These recommendations are already being adopted in protocols or written into guidelines for some phase I trials, although there is as yet no settled methodology for deciding on the dose limiting toxicity definition and duration, or the phase II dose recommendation.

Gilly Spurrier-Bernard from MelanomaFrance is campaigning for a patient-driven reporting system filled in on laptops or phones whenever there is a significant event, as some patients already do with pain diaries. "Patient issues change over time and according to how healthy you are feeling. Researchers need to be asking how it impacts on daily life. Then you need some clever algorithms for data mining."

Bettina Ryll, who founded Melanoma Patient Network Europe after her husband Peter developed malignant melanoma, agrees. "We see more and more selected trial populations and it automatically becomes less representative of the entire patient population," she says. "RCTs are the wrong way to tackle safety. We need a much better pharmacovigilance system where we capture data much more systematically and then act upon it.

"We need new drugs, as every patient with a life-threatening condition will tell you. We also need a way to study them meaningfully and in a way that does not prevent access for patients, does not drive up cost and captures reality."

Melanoma Patient Network Europe is preparing a project with the Uppsala Monitoring Centre to harvest direct patient reports of symptoms and side effects. The Centre runs the WHO international drug monitoring programme, which was set up after the thalidomide disaster, and has the world's largest dataset of adverse events, publishing data from 120 national health authorities worldwide on an open website at vigiaccess.com.

Bostjan Seruga from Ljubljana would like to see the American NCI initiative on patient-reported adverse events (PRO-CTCAE) fully incorporated into clinical trials, along with updated reports to capture data not originally reported by RCTs, and specific trials to address the needs of patients who were ineligible.

"Oncologists, journal editors and societies like ESMO and ASCO need to introduce measures to ensure complete reporting of toxicity to serve our patients better."

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Anna Wagstaff

A strategic moment

New knowledge favours promoting peace over waging war

The world spends billions on trench warfare with cancer and makes slow progress with heavy collateral damage. New knowledge about the process of carcinogenesis and tumour growth is now fuelling calls for a change of strategy to focus on containing potential trouble and keeping the peace.

Prevention is better than cure, and nowhere is that more true than for cancer, where cures are not always attainable, treatment not always affordable, and the short- and long-term side effects can be severe.

In light of what we now know about cancer's extraordinary ability to mutate in all directions and to outwit every therapy we come up with, strategies aimed at intervening as early as possible in processes that lead to tumour formation make perfect sense.

Yet research into preventing cancer has traditionally been relegated to the lowest priority, both in terms of public health initiatives and the sort of medical prevention strategies that have been successful in cutting heart disease.

Research into all aspects of cancer prevention typically receives only between 2% and 9% of the total cancer research spend (*Molecular Oncol* 2008, 2:20–32). The number of people involved in the medical prevention effort is tiny – almost non-existent in Europe – and has barely increased since pioneers like Michael Sporn, Professor of Pharmacology and Medicine at Dartmouth Medical School, in New Hampshire, began investigating chemoprevention back in the early 1970s.

Two profound developments, however, may now be coming together to give prevention its big moment. The first of these is the growing recognition, in the words of the World Oncology Forum (worldoncologyforum.org), that current strategies for controlling cancer are demonstrably not working.

New treatments – the fruits of multibillion dollar research efforts – are hugely complex, have limited efficacy and come at a cost that renders them unsustainable even in richer countries. Middle- and low-income countries trying to get to grips with the disastrous rise in cancer among their citizens are focusing hard on prevention. It is no surprise that China leads the world in population-based prevention studies; with more than three million new cancer cases every year, focusing resources on treatment rather than prevention simply isn't an option.

The second development is the emergence of a more holistic, systemic understanding of the nature of cancer,

where the focus is less on the mutated cancer cell itself and more on the role played by the body's own physiological processes in turning normal cells into cancer cells and enabling those cancer cells to thrive and spread.

Explorations of the role of the tumour "micro-environment" in tumour formation and growth are expanding into a new and fascinating field that is examining the role played by our microbiota – the trillions of microbes, bacteria and fungi that live inside us.

Our immune response, inflammatory response, and angiogenic response (building new blood vessels) are all under the spotlight, together with a range of hormones that are related to nutrition.

Step by step, researchers are starting to reveal the mechanisms behind associations that have long been documented at an epidemiological level, linking cancer risk with diet, exercise, and obesity. In doing so, they are strengthening the evidence-base for strategies aimed at intervening to prevent, suppress or reverse the carcinogenic process.

"They are strengthening the evidence base for strategies that aim to prevent, suppress or reverse the carcinogenic process"

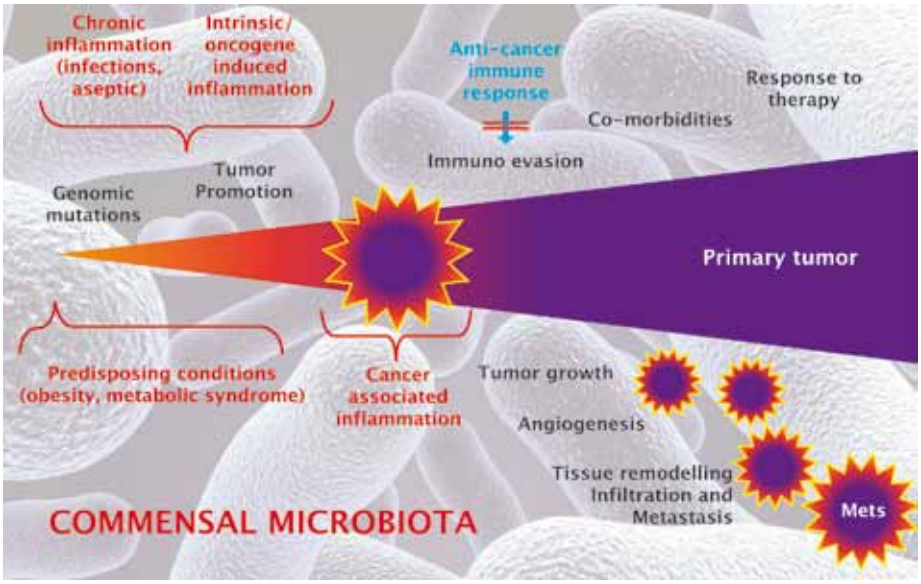
Prevent the preventable

This exciting time of joining dots and fitting together puzzle pieces formed the context of the third meeting of the World Oncology Forum, which took place in Milan in October 2015, under the title Prevent the Preventable.

For the European School of Oncology, who convene the Forum, it was a return to their philosophical roots.

ESO's founder, the surgeon Umberto Veronesi, best known for pioneering breast conserving surgery and adjuvant chemotherapy, was an early

The microbiota: a potential target for prevention?



Trillions of bacteria that line the surfaces of our body are involved in promoting or suppressing the carcinogenic process through their role in regulating inflammation and our innate adaptive immune response
Image courtesy of Giorgio Trinchieri

advocate of developing preventive therapies to avoid the aggressive treatments that are needed for established cancers.

ESO has long been supportive of the efforts of people like Sporn in the US and Andrea DeCensi, a self-styled 'heretical oncologist' in Genova, Italy, who has pioneered a methodology for trialling "repurposed" drugs in a preventive setting.

It was satisfying for ESO, therefore, to host a Forum that positioned this traditionally marginal field of preventive therapies at the centre of a discussion involving leaders in the field of cancer epidemiology on the one hand and biology on the other.

As with the previous World Oncology Forums, this was not an academic exercise. It was about coming up with recommendations on the role prevention, including medical prevention, should play within wider policies and strategies for tackling the rising tide of cancer.

What's new?

Giorgio Trinchieri, head of the US National Cancer Institute's Cancer and Inflammation Program, presented what could come to be seen as an "ah-ha!" moment in expanding our understanding of the link between diet, lifestyle, environment and cancer risk.

Meet the commensal microbiota. These are the bacteria, fungi and viruses that live in our body all the time and don't do damage, Trinchieri explains. They are on all the surfaces of our body that communicate with the outside environment: the skin, respiratory tract, gastrointestinal tract, urogenital tract. They are most abundant in the gastrointestinal tract, particularly the colon.

These vast colonies comprise up to five times more micro-organisms than we have cells in our bodies, and include 1000–2000 different species. They can be highly responsive to changes in diet, environment and other lifestyle factors, and it turns out that they play a very important role in regulating or modulating numerous physiological functions.

Some of these functions, notably the inflammatory and innate adaptive immune response, play a key role in determining whether or not a cancerous mutation will go on to proliferate, thrive and metastasise. The really big surprise is that this regulatory role is not confined to the locations where these micro-organisms live: "If you have an inflammatory viral infection in your lung, the immunity in the lung will not be effective unless you have the presence of gut microbiota," says Trinchieri.

The extent of the role of the microbiota in cancer has been convincingly demonstrated in a number of ways. With the first tumour oncogene, the rous sarcoma virus, it was shown that if you inject a virus into an adult bird you will get a tumour at the site of the infection or other parts of the body where it induces inflammation. But if you inject it into a germ-free embryo, you don't get any tumour. Even if the cells where it was injected show a transformed phenotype, they won't grow in the embryo without the right microenvironment, Trinchieri says.

"It could be the microbiota [acting directly] or it could also be that you need inflammation damage for the virus to induce a tumour, and the microbiota clearly plays a role in that. If it is sterile nothing happens. The virus puts the oncogenes in the cells but the cells don't grow."

Inducing a highly aggressive tumour into germ-free mice, by injecting muta-

ted KRAS cells and knocking out their p53 tumour suppressor gene shows a similar result, he adds – virtually no tumour growth.

This is not to say that the mutated cell itself is irrelevant, Trinchieri stresses, but it does show the importance of the microenvironment, and the potential for intervening in the processes that regulate it.

"There's no doubt a tumour is a genetic alteration of normal cells and a lot of money has been spent understanding the oncogene, the tumour suppressor gene, genotyping of tumours to find the different mutations. But a mutated cell would never be able to grow and metastasise if the seed doesn't find the right soil, the right tissue, and right micro-environment, particularly the right level of inflammation and innate adaptive immune response in the microenvironment that would allow this mutated cell to grow and form a tumour."

Piecing the picture together

Inflammation and immune response

What we are learning about the role of the microbiota throws new light on an existing body of knowledge about the role inflammation and the adaptive immune system play in carcinogenesis and tumour development, some of which dates back to the earliest days of medicine.

As Trinchieri points out, similarities between cancer and inflammation were noted by the Greek physician, Claudius Galenus, almost 2000 years ago. Virchow, the "father of modern pathology", suggested in 1863 that cancers may grow at the sites of chronic inflammation. And twenty years ago Harold Dvorak, now Professor of Pathology at Harvard, observed that inflammation and cancer share some basic developmental mechanisms (angiogenesis) and cells (lymphocytes, macrophages, and mast cells), and that tumours act like "wounds that do not heal".

The key here is the word "chronic". One of the lessons learnt in the painful and rocky road to developing the first effective immunotherapies is that there are two types of inflammatory responses.

Acute inflammation induces a strong active immune response, which can be harnessed to fight cancer. Chronic inflammation, by contrast, induces a different response, which actually promotes tumour growth, suppresses the immune response and favours metastasis.

> **"It suggests a likely involvement of the microbiota, which in turn opens up possible new strategies for prevention"**

This explains the reduction in many types of cancer seen in people who have taken low-dose aspirin, which acts in part as an anti-inflammatory, over a period of many years.

It also suggests a likely involvement of the microbiota, and its role regulating inflammatory and immune responses, in the mechanisms linking certain diets, environments and lifestyles with a raised risk of cancer. This in turn opens up possible new strategies for prevention.

We can alter some of these factors with diet and lifestyle changes or become more sophisticated in directly altering and affecting certain microbiota species, says Trinchieri.

The cancer detectives of Linxian

The first strong evidence that nutritional interventions can not only significantly reduce the risk of developing and dying of cancer, but can actually reverse precancerous lesions, was generated by the Nutritional Intervention Trial. This was a Chinese population-based study, initiated in 1985, which looked at the impact of a range of vitamin and mineral supplements on rates of oesophageal and other upper gastrointestinal cancers, which are a particular problem in China.

You-Lin Qiao, head of the Department of Cancer Epidemiology at China's National Cancer Centre, presented some of the key findings, which included a 23% reversal rate of atypical oesophageal dysplasia, and a reduction in oesophageal and gastric cancers of 13% and 21% respectively. He also talked about the evidence being generated by numerous subsequent and ongoing population-based trials, where China continues to lead the world.

Many findings are not directly transferable to other parts of the world – evidence from countries where a full range of fresh food is always available suggests that it is a healthy balanced diet rather than dietary supplements that make the difference.

But some is of relevance, such as the importance of getting the diet right at a young age. The Chinese data will contribute to a broader picture in the context of findings generated in populations with different environments, lifestyles and genetics.

More important, perhaps, has been the proof of principle of this approach to cancer prevention. The meticulous epidemiological research that provided the scientific rationale for the Nutritional Intervention Trial started back in 1959, when China was among the

Preventive cancer medicine in action. A doctor talks to villagers about their participation in a trial for preventive interventions that have shown impressive results in reducing high rates of oesophageal and other cancers in some areas of China

poorest countries in the world. Immortalised in the 1972 BBC documentary, 'The Cancer Detectives of Linxian', this low-tech approach, which drew on traditional Chinese medicine and focused on changing behaviours, is to this day held up as a template for cancer control, by the WHO among others.

'Meet-in-the-middle' studies

Relying on population-based epidemiology to inform preventive strategies does, however, have its limits, as Paolo Vineis, Chair of Environmental Epidemiology at Imperial College, London, pointed out.

Vineis plays a leading role in the 500,000 strong European Prospective Investigation into Cancer and Nutrition (EPIC) study, which over the past decade has generated data indicating, for instance, that fibre and fish in the diet are protective against cancer risk, while red and processed meat significantly raise the risk.

He came to the Prevention Forum directly from participating in the expert meeting of the International Agency for Research on Cancer that evaluated processed red meat as carcinogenic to humans (Group 1), and unprocessed red meat as "probably" carcinogenic (Group 2A).

Vineis says that the problem with observational epidemiology is the difficulty in singling out different risk factors, which occur in patterns. "Disentangling single risk factors from others is not always straightforward."

Vineis and his group at Imperial College are trying to pinpoint mechanisms that could give biological plausibility to the epidemiological findings and provide markers that could be used in prevention trials.

They call this "meet in the middle" studies, because they are looking for biological markers that are associated with both the disease and with particular dietary exposure.

"We did a small study using metabolomics. We looked at breast cancer and colon cancer in EPIC Italy, and we found eight metabolomic signals, or 'features', associated with colon cancer. Out of those signals associated with colon cancer, four were associated with dietary fibre. These were statistically significant after correction for multiple comparisons.

"One of these indicates a possible link with gut microbial fermentation of plant phenolics in the colon, so there is some biological plausibility there."

This points the finger at the composition of the colonic microbiota, which would fit in with other evidence on colon cancer, including studies showing that two families of bacteria commonly found in the colon – bacteroides and clostridium – increase the incidence and growth rate of colonic tumours induced in animals.

This opens possibilities for preventive

"We found eight metabolomic 'features' associated with colon cancer; four of these were also associated with dietary fibre"

strategies that intervene directly, rather than through diet, to modify the microbiota, as Trichieri is suggesting.

A surprising role for nutritionally related hormones

Rising obesity rates are one of the big drivers of the escalating rate of cancer. Understanding the "bit in the middle" that links weight with cancer, with a view to learning how to lower the risk, is a challenge that Michael Pollak, Director of the Division of Cancer Prevention at McGill University, in Montreal, has made his own.

Speaking at the prevention forum, he talked about a surprising picture that is emerging, which implicates nutritionally related hormones – insulin, insulin-like growth factors, and many more – as the link.

"The more food you eat the bigger your insulin secretion, and cells are informed that it's OK to use energy for proliferation and growth or storage," Pollak explains.

He makes a link back to Thomas Beatson, the pioneering British doctor who made the connection between the ovaries and breast cancer, at the end of the nineteenth century. "The dietary energy supply influences some tumours by influencing the hormonal environment rather than the energy available to the tumour. The effect of macronutrient intake on cancer biology is just another context of hormonal dependency of neoplastic cells," he says.

This has important implications for prevention, because it means that, essential though it is to eat moderately and exercise, this may not always be enough, and there may be other ways to intervene directly on this group of hormones, using diabetes as a model.

Experiments on mice show that prostate cancer grows faster when they are fed on a 'junk food' diet. However, if you then induce type 1 diabetes, the growth rates slows. "The glucose is very high, but insulin is low. It's not the glucose they need. It's the insulin," says Pollak.

He is interested in the antidiabetic drug metformin as a potential preventive agent for people at high risk of insulin-related cancers. The safety and side-effect profile of metformin is well known, and use of the drug has been linked with a very significant reduction in cancer incidence in a major observational cohort study (*Diabetes Care* 2009, 32:1620–25).

Pollak accepts the study may be flawed and needs confirmation; however, he argues that there is a strong rationale for such a preventive effect. "Metformin acts on mitochondria to inhibit energy production. It gets to the liver and the liver cells feel energy stressed and keep the glucose for themselves. Glucose levels fall, so insulin levels fall, and insulin dependent cancers could then be hit, provided the magnitude of decline is sufficiently large."

Change the strategy

The principle of preventive therapies is now widely accepted – and approved by the FDA – specifically for hormonal therapies in people at high-risk of breast cancer. The strong consensus at the forum was that extending this principle to other agents and other cancers is now a strategic imperative.

The evidence for the impact of aspirin, for instance, in reducing the risk of colon cancer through its anti-inflammatory effect, is undeniable (*Ann Oncol* 2015, 26:47–57), and demands urgent research to define who will benefit and the optimum dose and duration of treatment.

More generally, there is now a compelling case for paying more attention

More than 1 in every 20 cancers diagnosed in women in 2012 were attributable to being obese or overweight. Promoting healthier lifestyles is essential, but can we also find a 'statin' equivalent to protect those most at risk?

The World Oncology Forum

The Prevent the Preventable forum was the third gathering of the World Oncology Forum (worldoncologyforum.org), which is convened by the European School of Oncology, in conjunction with *The Lancet*.

The first World Oncology Forum – a gathering of 100 international experts and journalists held in 2012 – was called to evaluate progress in the so-called "War on Cancer". It called for a major change in strategy and launched the 10-point Stop Cancer Now! Appeal, aimed at governments, policy makers and leaders of the cancer community, which was published on World Cancer Day 2013 in *The Lancet* and leading newspapers across the world, inluding *Le Monde, El País,* the *International Herald Tribune*, the *Neue Zürcher Zeitung* and *La Repubblica*.

Tackling cancer is also being flagged up as a key international policy issue by *The Economist*, which has launched a series of conferences on the topic, starting in Boston last September, then London in October, with a third set for March 2016 in Singapore.

to denying precancerous lesions the environment they need to become cancerous and to thrive and spread.

The NCI's Giorgio Trinchieri, put it this way. "When we look at cancer in the organism, it is like an invasive plant that grows in the wood and destroys the wood. We need to decide how to deal with that. The traditional way – the medicine battlefield strategy – is to go out with very strong weapons. We destroy the tumour, the pathogens, but we also destroy the body by doing that."

The ideal, he argues, would be to see medicine more in terms of managing the environment. "We need to look at the habitat, the tumour, the microenvironment, the whole organism, and use prevention if we can, and the very targeted removal of the invasive species, and restore and promote the native species, thus re-establishing the homeostatic ecology of the healthy organism."

> **"The traditional way is the battlefield strategy. The ideal would be to see medicine as managing the environment"**

While public health prevention measures will be essential to managing this environment – promoting healthier lifestyles, reducing exposure to carcinogens, e.g. through vaccination programmes against cancer causing viruses – preventive medical interventions could also play a vital role.

"By itself, a better lifestyle is not sufficient to solve the cancer problem; if the genetic burden is high enough, carcinogenesis results in invasive cancer, despite living an optimal lifestyle," argues Michael Sporn, and he points to the example of BRCA mutation carriers.

"What good is it for a young woman to know that she has a BRCA mutation if all that we can offer her is bilateral prophylactic mastectomy, with the extra bonus of an oophorectomy? What is critically needed right now in the total effort to prevent cancer," he argues, "is the development and eventual clinical testing of new, safe, and effective chemopreventive drugs. Big Pharma is not interested in such an approach, and woefully little is being done in this area."

This is hardly surprising coming from Sporn, who has been arguing this line for most of his career. What has changed is that his views are now finding support among some leading pioneers in cancer genomics, including Bert Vogelstein, Director of the Ludwig Cancer Research Centre at Johns Hopkins, who is equally vocal in calling for a change in strategy.

In a high-profile piece in *Science* magazine (2013, vol 339, pp 1546–58), Vogelstein argues that, "The focus on curing advanced cancers might have been reasonable 50 years ago, when the molecular pathogenesis of cancers was mysterious and when chemotherapeutic agents against advanced cancers were showing promise. But this mindset is no longer acceptable."

The experts gathered at the third World Oncology Forum, agree. They will be launching an appeal calling on policy makers and opinion leaders to provide leadership and resources to promote the development and implementation of new evidence-based strategies aimed at cancer prevention, risk assessment/early detection and early intervention, and tailored to specific communities, cancers and populations.

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... no matter where they live

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- ExPO-r-Net is uniquely positioned to address the current **inequalities in childhood cancer survival and healthcare capabilities** across Europe
- This pilot project is developing innovative modalities for better treatment, care, and expertise-sharing by building a **European Reference Network for Paediatric Haematology-Oncology**
- The project is set to adopt **eHealth solutions** to move information and knowledge rather than patients whenever possible
- **Virtual European Tumour Boards** will enable access to expertise in paediatric oncology institutions where case numbers are low and only few reference sites exist
- The paediatric cancer community is strongly committed to **identify cross-border healthcare needs**
- Supported by the European Commission, ExPO-r-Net has been possible thanks to the **joint efforts of the paediatric haemato-oncology community**

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Co-funded by the Health Programme of the European Union

This publication arises from the project ExPO-r-Net which has received funding from the European Union in the framework of the Health Programme (2008-2013), grant agreement nr. 2013 12 07. The content represents the views of the author and is his sole responsibility and it can in no way be taken to reflect the views of European Union bodies. The European Commission and/or Chafea do not accept responsibility for any use that may be made of the information it contains

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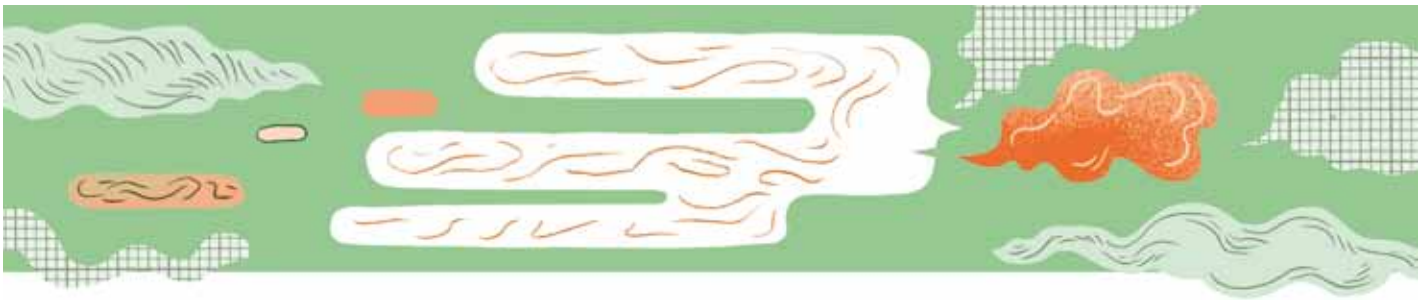
Daniela Ovadia



Fedro Peccatori: teaching the world to care

First he was a pupil, then he joined the faculty. Now Fedro Peccatori has taken charge of ESO's entire educational programme, and he knows exactly where he wants to take it.

"There is no difference between my work at the hospital and my work at the European School of Oncology. In both cases it's about finding the best way to treat patients." This is how Fedro Peccatori, an expert in women's cancers and fertility preservation at Milan's European Institute of Oncology, interprets his new role as ESO's Scientific Director, which he started this January.

His appointment puts him in charge of developing and directing the educational activities of the School, to further its mission of contributing through education to reducing the number of cancer deaths, and ensuring early diagnosis, optimal treatment and holistic patient care.

His mandate is to focus on the unique strengths of ESO's style of teaching and to give special attention to covering topics and reaching young oncologists that hold no interest for other – predominantly commercial – training providers.

For Peccatori it is a welcome new challenge, but it also marks an important generational milestone for the School itself. His only two predecessors – Alberto Costa, and before him Umberto Veronesi – were both founding members of ESO. Peccatori is the product of its schooling.

A unique contribution

He takes charge at a time when ESO is no longer the sole provider of specialist oncology training in Europe, as it was when he was starting out. However, he is clear that there is nothing to rival the unique contribution the School continues to make. ESO is special, he says, because of its vocation, summed up in its motto 'learning to care', which puts patients at the centre. "We are not interested in simply teaching techniques, or in explaining what cancer is and how to treat it."

Caring for patients has been an important driver for Peccatori throughout his career. But it was his love of research that first motivated him to specialise in gynaecological oncology after completing his medical degree at the University of Milan. "I spent my first year at the hospital without getting out of the lab: I barely saw a patient! I was working on the immunology of gynaecological tumours, particularly on ovarian cancer – a research area that is now very current, but was really pioneering at the time."

Pathology held a particular fascination for Peccatori. "In my view, it was the best way to understand the roots of disease. Twenty-five years ago, cancer

– and particularly women's cancers – were in need of basic research."

After one year on the lab benches, he returned to the wards: "I really enjoyed taking care of people and interacting with the patients, but my first interest in research never vanished," he recalls. "I think that a good doctor needs to do both. Now we call it 'translational research', but in the '80s there was no name for it."

Peccatori completed his specialisation at the San Gerardo Hospital in Monza, north of Milan, and it was here that he was given a tip that was to change the course of his career. Costantino Mangioni, the professor he was working with, had strong connections with the Oncology Institute of Southern Switzerland, in Bellinzona, and advised Peccatori to spend a month there learning how to set up and conduct phase I and phase II trials, which were not being conducted anywhere in Italy at that time.

By chance, the Institute's director, Franco Cavalli, was looking for someone to provide temporary cover for one of his assistants, who had been called up for army duty. "I was just married and had no salary from Italy, because the doctors in training weren't paid at the time, so I was really happy to find a job!" he recalls with a smile.

"I was used to implementing decisions taken by my mentor, but here we were all expected to take responsibility"

In the end, he stayed at the Institute for almost two years, taking care of all kinds of cancer patients, in a working environment that was radically different from the one he had grown up with in Italy. "I was used to implementing decisions taken by my mentor, but here we were all expected to take responsibility for the care of the patients," he recalls. "It was a great school, which strongly influenced the way I looked at the practice of medicine."

It also taught him some hard truths about the nature of scientific progress. Invited to give a lecture on ovarian cancer, right at the start of his internship, Peccatori gave an enthusiastic account of the great results being obtained with cisplatin. "I called this therapeutic novelty 'the paradigm of success'," he recalls. Later that day, he was called on to care for a woman who was dying of a drug-resistant ovarian cancer. "I realised that an almost unbridgeable gap separates what we call a 'great achievement' in our peer-reviewed journals from what is a

All photos by © Davide Bal[illegible]ci

Staying in practice. Peccatori is combining his new responsibilities as Scientific Director of the European School of Oncology with continuing to work part time in a clinical and research capacity at the European Institute of Oncology in Milan

small improvement from the point of view of patients."

Gender-specific oncology

On completing his PhD in gynaecological oncology Peccatori moved to Amsterdam's Vrije Universiteit, to pursue his research interests at the Department of Anatomical Pathology. Focusing initially on cervical cancer, and on a model for a vaccine, he later moved on to researching the full spectrum of women's cancers. "This is the root of my interest in what we call today 'gender-specific oncology'."

With the establishment of Milan's European Institute of Oncology in 1994, he grasped the opportunity to return to Italy, and has remained there ever since. In his current role as director of the Fertility and Procreation in Cancer unit, he works with women with all kinds of cancers who want to preserve their chances of having children after treatment.

He also works with women who are diagnosed while pregnant, which, as he says, is a "very traumatic issue" that occurs in around 1 in every 1000 pregnancies. "Until a few years ago, the choice was often between saving the mother or the child. Now we can save both," he says.

Doing the best for these patients requires the sort of expert multidisciplinary team they have at the European Institute, with a deep understanding of the effects of hormones on the tumour and on the development of the foetus, as well as the impact of chemotherapy side-effects. But much of this expertise is delivered remotely, as advice to doctors in hospitals closer to the woman's home.

"We act as consultants for our colleagues working in other hospitals, to help them take the best decision on delicate issues such as the ideal gestational age to induce the delivery so as to be able to start treatments that are still potentially toxic for the foetus, such as trastuzumab or radiation therapy." For the chemotherapy during pregnancy itself, his team decided, after long debate, that a cancer centre is not the best place for either mother or child, "so our patients are referred to outside maternity hospitals."

The right setting

Finding the right setting for delivering care is an issue that preoccupies Peccatori beyond the specific situation of pregnant women. He argues that women's cancers should be treated at specialist centres.

"Breast cancer and gynaecological cancers often have the same molecular basis. Even other kinds of cancer can be responsive to hormones when they occur in women, so you have to look at your patient as a complex and interrelated system," he argues. "On the other hand, every woman with cancer has to face the same, very practical, problems: how to deal with family and work, with children, and with husbands who are not always ready to face such a difficult moment in their life as a couple. That's why I think that women's cancers should be treated all in the same place, with a multidisciplinary team that is able to tackle every aspect of the disease in a specific way."

"I think women's cancers should be treated all in the same place, with a multidisciplinary team that can tackle every aspect of the disease"

A new challenge

Peccatori is leaving none of this behind as he takes up his new role as ESO's Scientific Director. Like his two predecessors, he will continue his clinical practice alongside his work directing the School's educational activities.

It's a lot for one person to take on. But then Peccatori is used to hard work and juggling home and work commitments. His typical day starts at 6.30 am, he bikes to work and returns home again in time to have supper with his wife and five children at 7.30 in the evening. "The lack of time for family life is probably my main regret," he says.

In some ways he sees his appointment as simply an extension of a relationship with ESO that stretches back decades, first in his capacity as a student and later as part of the faculty. "ESO has been part of my professional life since the beginning of my career. I could say that it was part of my personal life too, as I spent my honeymoon in Amsterdam because there was an ESO masterclass in gynaecological oncology."

The arrangement, he adds, worked well for everyone, as the young couple had no money at the time. "I went to the masterclass while my wife visited the city, then we spent some more days together at the end of course. We stayed at a very romantic location fronting onto the canals!"

His early experiences with ESO had both a European and an Italian flavour:

"I remember the courses on breast cancer at Orta San Giulio, a small island in the middle of the Orta Lake, in Northern Italy. They were the best masterclasses for a young oncologist, and a truly new opportunity for attendants. We met people from all over Europe and beyond, and also the most important key opinion leaders in the field, building networks that are really useful for our professional life until now."

Today, the training opportunities for young oncologists are more widespread, and Peccatori will be focusing ESO's activities where they can have the greatest impact, particularly on aspects of oncology that are essential for patient care, but do not interest other education providers.

"There are areas where, without ESO, there would be no continuing education for oncologists. It's not only a matter of income level or of organisation, but also economic interests. We can offer training in how to treat diseases that no pharmaceutical company would be interested in, because there are no drugs involved. I would say that pharmaceutical industries are our only real competitor in the educational programme, but they naturally focus on cancers that can be treated with their products, and in the same way in every country."

ESO masterclasses, by contrast, are carefully tailored to fit the region where they take place. "It's true that there is always a 'best way' to treat a cancer, but not every region has the same healthcare organisation or can afford the same treatments. We have to deal with these issues, which is why half the faculty at our events is always composed of local experts."

It's also why in recent years the School has increasingly taken a lead on the global policy agenda, through initiatives such as the World Oncology Forum, a series of policy conferences involving global experts, which Peccatori is particularly proud of. "We need a global cancer plan to fight the disease, especially now that we have tools like the HPV vaccine, which could really bridge the gap between richer and poorer countries," he says.

"Peccatori will be focusing on aspects of oncology that are essential for patient care but do not interest other education providers"

"Prevention is very important, but we can also treat cancer patients and save lives with highly accessible low-cost drugs," says Peccatori, pointing to studies that indicate that global deaths from breast cancer could be dramatically reduced if every country had access to 80% of the drugs on the WHO's essential medicines list. "The same could be done for some paediatric cancers, like acute lymphoblastic leukaemia, which can be treated with a couple of very old drugs and better organisation of the health system," he adds.

Promoting this low-cost, very international approach to cancer treatment will be an important focus for Peccatori as he takes over as Scientific Director. "We can have a strong impact

"We target the young generation of oncologists. We can shape their views on what cancer is and what are the priorities"

on healthcare systems even if we are not directly involved at a policy level, because we target the young generation of oncologists and even medical students. We can shape their views on what cancer is, how we should deal with it and what are the priorities."

As he points out, this international perspective is nothing new for ESO – he was involved 20 years ago in the School's Latin American programme. What has changed is the potential for delivering training at a global level, so upgrading ESO's capacity to operate in the new virtual environment will be essential, he believes.

The School has made a good start, he says, with its e-grandrounds – the fortnightly webcasts it delivers live, accessible to participants the world over, who can ask questions and interact with the presenter in real time.

"But we need to improve online access to all our courses to allow more people to participate even when they cannot attend the workshop in person," he says, adding that it is now possible to follow an online course on a smart phone "even in the most remote area of Africa." That is the sort of reach ESO should now be seeking to achieve, he argues, "as is fitting in a globalised world."

Meet the staff

Nobody can work alone. Like his predecessors, Fedro Peccatori relies on a team of people who ensure that the European School of Oncology can maintain the quality of its education and expand the involvement of oncologists across Europe and beyond.

"ESO has a very dedicated staff. It would be impossible to achieve the standards we do without their help," he says. "I'm really happy to have them with me. I'm not leaving my job as a doctor and researcher, so I will need their support and professionalism."

From back to front, left to right: **Dolores Knupfer** – Eastern Europe and Balkan Region Programme and Lymphoma Programme and Events, **Laura Richetti** – Events, **Gabriele Maggini** – Communications, **Luis Carvalho** – Latin/American Programme, **Fedro Peccatori** – Scientific Director, **Alberto Costa** – CEO and *Cancer World* Editor.
Marina Fregonese – Rare Cancers programme, **Corinne Hall** – Editorial and Media Office and Clinical Training Centres Fellowship Programme, **Lorena Camarini** – Administration, **Francesca Marangoni** – Breast Cancer Programme, e-ESO, WOF and Events, **Chatrina Melcher** – Chief Operating Officer, **Elena Fiore** – Events, **Alexandra Zampetti** – Certificate of Competence in Breast Cancer and Events.

Not present: **Daniela Mengato** – SPCC, Eurasia Programme, Arab Countries Programme and Events, **Paolo Gatti** – Administration, **Rita De Martini** – Prostate Cancer Programme and Events.

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Reference
1. Sparano J et al. *N Engl J Med* 2015; 373: 2005–2014.

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Simon Crompton

Unleashing the potential of prevention

The revised European Cancer Code, launched last October, gives clear and concise information on what people can do to lower their own cancer risk. But until policy makers – and doctors – take prevention more seriously, millions of lives will continue to be lost unnecessarily.

Knowledge is power. And knowledge about what to do to lower the risk of developing cancer has the power to save lives. According to the International Agency for Research on Cancer, at least half of the world's cancers are preventable on current knowledge alone. And IARC's new European Code Against Cancer (published as a centre insert in this issue of *Cancer World*) takes the evidence about the exposures, agents and behaviours that definitely cause cancer and turns it into advice for the general public. It is a brief guide to what you can do to genuinely reduce your risk of getting cancer.

This 4th edition of the code, first published in 1987, was launched in October 2014 following two years of research analysis by scientists and cancer specialists with backing from the EU Health Programme. Its 12 points of simple advice focus on group 1 carcinogens – influences we know cause cancer – and those that people are most commonly exposed to. So smoking, diet, exercise, alcohol and exposure to sun feature most prominently, alongside advice on breastfeeding, vaccination and screening.

The highly publicised risk from processed meat is significantly not

included: IARC has classed processed meat as a group 1 carcinogen, but the extent of its effect on mortality is still unclear.

"The Code is aimed at the ordinary European citizen wondering what they can do to reduce their cancer risk," says Chris Wild, IARC's Director. "People are faced with all sorts of information about cancer prevention on the internet and we hope the Code will stand out as an authoritative summary, with the science behind it."

If people take the advice, the effect on cancer incidence could be spectacular. Research in 2011, conducted by Max Parkin from the Wolfson Institute of Preventive Medicine in London, found that tobacco, diet, alcohol and body weight together accounted for 34% of cancers in the UK in 2010; and that 45% of cancers in men and 40% of cancers in women could have been prevented if 14 known lifestyle and environmental risk factors had been acted on.

The potential impact of effective prevention strategies on the public purse as well as cancer mortality has also been well documented. In its 2014 report on the economics of cancer prevention and control, the Union for International Cancer Control (UICC) pointed out that implementing appropriate strategies for prevention and early detection and treatment could save between 2.4 and 3.7 million lives a year. Investing just $11.4 billion in core prevention strategies in low and middle income countries could save $100 billion in cancer treatment costs.

But despite regular calls from IARC for prevention to become a priority, it still fails to attract national funding or prominence. Detailed research into cancer research funding by Richard Sullivan from King's Health Partners in London found that just 2–9% of public cancer budgets is spent on prevention in Europe, the USA and Canada. This compares with 25–45% on causes and mechanisms and 20–25% on treatment.

The only serious option

Sullivan has commented that prevention "remains the only serious option for managing the long-term socio-economic impact of cancer," but it is threatened by lack of funding, lack of international co-operation and lack of understanding of human behaviour – the science of prevention.

"It's clear there is an under-financing of research into prevention at the moment," says Chris Wild. "That's presenting us with a problem. We need an integrated approach to cancer control that balances the emphasis on the exciting new personalised treatments with efforts to prevent the disease in the first place – or detect it very early."

"Costs are spiraling because the sophisticated treatments are increasingly expensive. If we can reduce the number of people developing cancer then the money available to treat those who do develop the disease should be greater – it's a simple law really. If we can turn off the tap, or reduce the flow of new cases, that may help us in having sustainable cancer services in the next two or three decades."

"If we can reduce the flow of new cases, that may help in having sustainable cancer services in the next decades"

Last year a paper was published in the *European Journal of Cancer* which indicated how wasteful over-investing in new treatment modalities might be. Belgian epidemiologist Philippe Autier analysed different age cohorts in WHO mortality statistics to provide projections of the future incidence of cutaneous malignant melanoma. He demonstrated that – regardless of what happens in screening or treatment over the coming decades – death from skin cancer in light-skinned populations is likely to become an increasingly rare event. Melanoma, he suggests, will become limited to older age groups, and fade away after 2040.

The reason? In the 1970s, increasing knowledge about the carcinogenic effects of ultraviolet radiation caused parents to start protecting their children from the sun – reducing the likelihood of cancer in adulthood. The preventive effect starting from childhood had not previously been anticipated.

His analysis contrasts with other reports emphasising a current increase in melanoma incidence, which has fuelled the drive to develop new treatments. Immunotherapies such as ipilimumab and pembrolizumab, and BRAF inhibitors like vemurafenib and dabrafenib, have been hitting the headlines, and dominating conversations at cancer conferences for years. But their development has been enormously expensive, and cost–benefit analyses have raised questions about whether they give value for money: a course of ipilimumab costs $150,000, for a median progression-free survival of 2.9 months.

The Autier paper demonstrates the continuing narrative of how, if a longer view is taken, prevention brings dramatic effects.

This story was told most famously by epidemiologists Richard Doll and

Richard Peto, who provided compelling evidence of falling mortality related to smoking cessation. In 2004 they showed how male smokers born between 1910 and 1930 lost on average 10 years of life, but stopping smoking at 40 bought them nine more years of life, and stopping smoking at 30 bought them nearly the full ten.

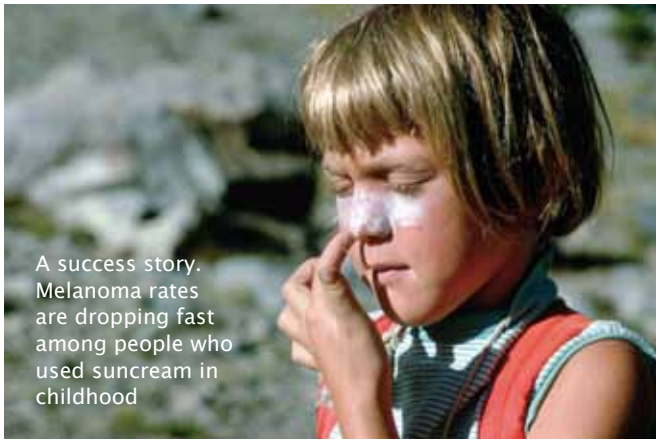
In practical terms, the health experience of Finland has vividly demonstrated the effectiveness of population-based prevention strategies. In the 1970s, the country led the world in heart disease rates, and the sparsely populated region of North Karelia became the testing ground for a massive raft of community-based interventions – blitzing the population with positive incentives to give up smoking, eat more healthily, become more active.

Competitions between communities to produce the most tobacco quitters or healthy eating outlets were complemented by changes to national legislation – banning cigarette advertising, providing incentives to farmers to produce fruit, vegetables and low-fat produce. Between 1972 and 1997 the number of men under 65 from North Karelia dying from heart disease dropped by 73% and from lung cancer by around 70%.

So why aren't such initiatives occurring on a wider scale? According to Chris Wild, the problem is partly that people's personal experience of cancer means cure has an emotional pull that prevention doesn't – and this carries through to charities, funding bodies and governments. However, no-one is suggesting that cure isn't a priority too.

"Of course it's important to treat patients," says Finnish epidemiologist Pekka Puska, now the Director General of the National Institute for Health and Welfare in Finland, and the man who spearheaded the North Karelia project between 1972 and 1977. "But health service costs, overwhelmingly on clinical treatment, are becoming a very difficult issue even for rich country governments.

These expensive treatments deal with consequences and not cause. Based on what we already know, cancer is to a large extent preventable, and there's no doubt that prevention is the most effective way to control the cancer epidemic."



A success story. Melanoma rates are dropping fast among people who used suncream in childhood

Investing in behaviour change

Puska, who was the WHO's director of health promotion between 2001 and 2003, believes that action needs to be taken on two levels to make effective cancer prevention a reality. First, in the face of increasingly confusing media health messages, people need exposure to accessible and reliable information about what action they can take to prevent cancer. That is why he is behind the European Code – he was a member of the scientific committee that helped compile its evidence base.

The second level, he acknowledges, is more tricky: it revolves around converting knowledge about risk factors into behaviour change. "Information alone does not help," he says. "Information initiatives are very important if they are linked to primary healthcare activities in the field, for example, measuring and advising people on their individual risk. This isn't something for doctors alone, but other professions too.

"It's also about making the healthy choice the easy one. That involves looking at social support. If everyone else smokes or serves certain food, that has a big impact, which is why the emphasis has to be on environmental changes, community changes, national policies on alcohol and tobacco and so on."

What if international cancer funding priorities changed, and more money was diverted into prevention? Where would it be best spent? Undoubtedly, some should be spent on research, says Puska.

"Information initiatives are very important if they are linked to primary healthcare activities in the field"

"There are certain cancers where we know too little about cause and further research is needed. We also need more research on the effectiveness of certain intervention methods. But when you examine complex prevention work like comprehensive health promotion activities or legislation, the fact is that

you never get clean proof of effectiveness. The potential impact is great but the strength of evidence is always a bit shaky. So you need studies but you also need to learn simply by doing."

There is already a sufficiently clear and strong evidence base to know what to do, according to Robert West, Professor of Health Psychology at University College London, and a leading researcher on smoking behaviours.

Research recently carried out by his department found that the public thinks that around 10–15% of the cancer spend should go on prevention. The actual UK figure is around 1–3%. West believes that if 10–15% was indeed spent on prevention, then cancer rates would go down at an unprecedented level.

"If I were to quantify that, I would say you would at least double the rate of decline," he says. "When you consider that behaviour accounts for roughly 40% of cancer deaths, then you don't have to make a huge amount of progress on the behavioural front to really eat into that. Obviously there are some quick wins, like smoking cessation and bowel cancer screening."

He has a clear four-point plan for how the extra money could be used.

First, invest in prevention research: "an integrated programme of intervention and evaluation as a virtuous spiral". Second, fund government action on price, availability and marketing of tobacco and other products linked with cancer.

"For example, some countries need funding to help them develop legislation around taxation, smoke-free policies and so on. Unfortunately, that does require resources because the countries don't have the expertise to draft the legislation and they are fighting an industry that has unlimited amounts of money to try and prevent it happening."

Third, fund mass marketing campaigns and advertising to promote healthy choices, smoking cessation services and screening. "It's like Coca Cola or anything else: if you stop promoting it, people stop doing it."

Finally, provide people with support once they've decided to stop smoking or other unhealthy lifestyles: "This might be digital, or using Skype, or a whole range of new technologies, medications and support services. There's plenty of evidence that it works."

IARC too is clear that its European Code Against Cancer is only part of a complex picture. "It needs to go together with the right legislation on exposures such as air pollution which the individual has no control over," says Chris Wild. "Taxation on cigarettes and the legislation around tobacco have illustrated just how important policy is to reducing exposure."

But if the war against cancer is to move into fruitful fields of prevention, it's going to take more than lobbying politicians and funders to achieve. Cancer clinicians too have an important role – a role they may currently be overlooking as they focus on the here and now of saving lives.

The clinical community can help

"The clinical cancer community could do more to put across the synergies between these areas of prevention and treatment – translating basic science about, say, a mutation, into both targeted treatment and understanding of causes to benefit populations," says Chris Wild.

"I would ask leaders of the large comprehensive cancer centres to use their platform to promote prevention"

Large comprehensive cancer centres, which have prevention within their remits, are particularly well positioned to promote an integrated approach, he adds.

"They have a big responsibility to show leadership and influence at policy level,. The leaders of those centres are rightly well respected, and I would ask them to use their platform to promote prevention as part of an integrated approach to cancer control."

European Code Against Cancer

The European Code Against Cancer focuses on actions that individual citizens can take to help prevent cancer. Successful cancer prevention requires these individual actions to be supported by governmental policies and actions.

1 Do not smoke.
Do not use any form of tobacco.

2 Make your home smoke free.
Support smoke-free policies in your workplace.

3 Take action to be a healthy body weight.

European Code Against Cancer

4 Be physically active in everyday life. Limit the time you spend sitting.

5

Have a healthy diet:

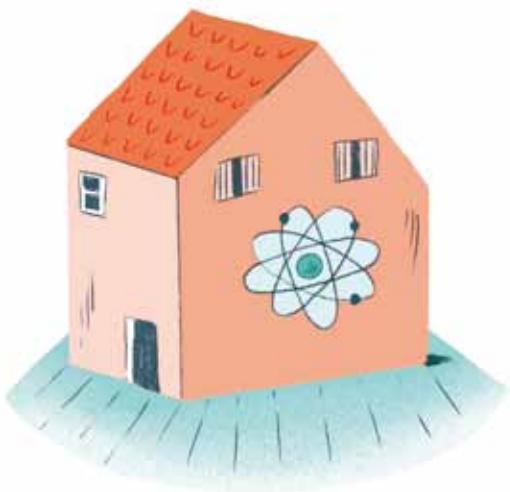
- Eat plenty of whole grains, pulses, vegetables and fruits.
- Limit high-calorie foods (foods high in sugar or fat) and avoid sugary drinks.
- Avoid processed meat; limit red meat and foods high in salt.

6 If you drink alcohol of any type, limit your intake. Not drinking alcohol is better for cancer prevention.

European Code Against Cancer

7 Avoid too much sun, especially for children. Use sun protection. Do not use sunbeds.

8 In the workplace, protect yourself against cancer-causing substances by following health and safety instructions.



9 Find out if you are exposed to radiation from naturally high radon levels in your home. Take action to reduce high radon levels.

European Code Against Cancer

For women:

10

- Breastfeeding reduces the mother's cancer risk. If you can, breastfeed your baby.
- Hormone replacement therapy (HRT) increases the risk of certain cancers. Limit use of HRT.

Ensure your children take part in vaccination programmes for:

11

- Hepatitis B (for newborns).
- Human papillomavirus (HPV) (for girls).

Take part in organised cancer screening programmes for:

12

- Bowel cancer (men and women).
- Breast cancer (women).
- Cervical cancer (women).

Find out more about the European Code Against Cancer at: http://cancer-code-europe.iarc.fr

International Agency Research on Cancer
World Health Organization

These recommendations are the result of a project coordinated by the International Agency for Research on Cancer and co-financed by the European Commission

ECCO in 2016: a renewed organisation with a unique multidisciplinary vision

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

The European CanCer Organisation (ECCO) is embarking on an exciting new path in 2016. We recently took the time to re-evaluate our role in European cancer care, inviting the insights of patients and member societies.

We came out of this process with a vision to improve outcomes for all cancer patients in Europe through multidisciplinarity. Our core purpose is to provide a cohesive platform promoting the concept and practice of multidisciplinarity across all areas of cancer care and to be the united voice of European cancer professionals to address common policy issues.

As a federation of 23 professional societies working in oncology in Europe and beyond, ECCO is fully equipped and best positioned to achieve this purpose. We seek to include all professional societies active in cancer and to unite our members behind a truly multidisciplinary approach to ensure the best care for our patients. ECCO member societies bring their advanced expertise to this work drawing on the huge progress they have made in designing guidelines and delivering education to their own membership.

ECCO is particularly committed to decreasing the unacceptable disparities and inequalities in cancer outcomes across Europe. To prioritise our efforts in this area we need to listen to cancer patients. It is obvious that, in addition to improving treatment-related outcomes, we need to advance cancer care from prevention right through to survivorship. ECCO has placed the patient perspective at the core of its work. Patient advocacy organisations are actively involved through their participation in the ECCO Patient Advisory Committee whose Chair sits on the ECCO Board.

ECCO has adapted its governance to match its new vision and is an open and transparent organisation where all member societies have an equal voice.

Reinforced by our powerful new vision and modern governance model, joined by even more member societies last year, we look forward to 2020 with ambitions to:

- Reinforce our strong community of organisations that represent different professional groups and are committed to ECCO's vision
- Consolidate a sustainable organisation that provides significant added value to its members
- Shape the policy environment and increase our political influence to ensure we achieve our policy objectives
- Identify and develop effective approaches to advance the concept and practice of multidisciplinarity across different cancer settings
- Ensure that the patient perspective informs all ECCO activities

Stay tuned for our progress reports!

For 40 years we've been guided by our values, focusing on developing new solutions to improve the everyday lives of patients.

Today, we're proud of our commitment to build better todays for even more patients worldwide.

HELSINN

Building quality cancer care together

Multiparametric MRI in prostate cancer

Traditionally confined to a role in staging, MRI is increasingly being used along the entire continuum from diagnosis to care and follow up in patients with prostate cancer.

This egrandround was first presented by Caroline Moore, from University College Hospital London, as a live webcast for the European School of Oncology. It is edited by Susan Mayor. The webcast of this and other e-grandrounds can be accessed at e-eso.net

Until the last few years MRI was used essentially as a staging tool in prostate cancer, with imaging being performed after a biopsy to assess a patient's suitability for radical treatment and for assessing extraprostatic extension and disease. However, it has much greater potential, and is now being used at several different stages in the prostate cancer pathway.

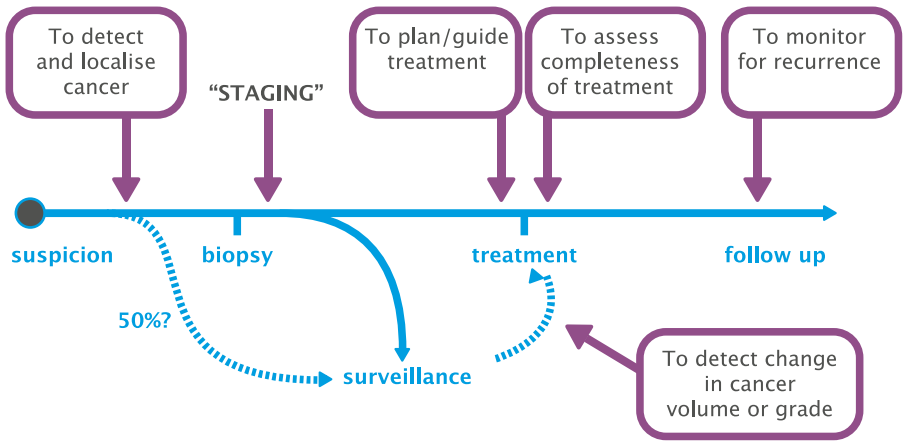
First, and I think most importantly, MRI can be used to detect and localise prostate cancer. As in the past, it can be used to stage prostate cancer, but it can also be used to plan and guide treatment very specifically, to assess the completeness of treatment and to monitor for recurrence. MRI can also be used for surveillance in men with prostate cancer where we consider their disease is not significant enough for treatment and we want to detect change in cancer volume or grade.

Using MRI to help decide who to biopsy

In a systematic review looking at studies comparing MRI-targeted prostate biopsy with standard transrectal biopsy (*European Urology* 2013; 63:125–140) we found MRI-targeted biopsy achieved more efficient sampling, with equal detection of clinically significant disease but with fewer cores, and with fewer men needing biopsy. There was also less clinically insignificant disease detected and more effective assessment of the extent of disease, including cancer core length, representing tumour burden, and Gleason score.

Carrying out an MRI-targeted biopsy alone would miss some men: 51 of 555 men (9%) with a negative MRI had cancer on standard biopsy. However, significant cancer (>4 mm cancer core length, any pattern 4) would be missed in only 2.3% (13/555) of men referred for a biopsy. On the positive side, one in

How MRI can be used in prostate cancer



three men would avoid a biopsy, and the troublesome problem of an insignificant cancer being diagnosed would be avoided in one in 10 men.

Reporting of groups of men who have MRI-targeted and standard biopsies is not always sufficient for us to compare the two different approaches, so we convened an international working group to look at this issue. The group recommended:

- Standard and MRI-targeted cores should be reported separately using separate Gleason scores and maximum cancer core lengths for both.
- A comparison table of clinically significant disease using each approach should be given in studies comparing the two types of biopsy, giving the numbers of patients with no cancer, with clinically insignificant disease, and with clinically significant disease for each biopsy strategy.
- A new definition of clinical significance will be needed for MRI-targeted biopsy studies.

Since these recommendations were made (*European Urology* 2013; 64:544–552), a large study carried out at the National Institutes of Health comparing standard transrectal biopsy with MRI-/ultrasound-guided biopsy in 1003 men included the suggested comparison table (*JAMA* 2015, 313:390–397), which demonstrated that the likelihood of missing an important cancer is much higher with a standard biopsy than with an MRI-/ultrasound-guided biopsy.

Using MRI to help decide how to biopsy

MRI information can enable a biopsy to be carried out much more accurately, which means it can be approached in a different way to the standard template of the transrectal biopsy, where you might decide the number of cores based on the volume of the prostate, but stick to a standard template for how you take those cores.

The most common way of carrying out an MRI-targeted biopsy to sample a lesion seen on MRI is by using visual registration (see figure opposite). The radiologist reports the MRI scan, ideally in a diagrammatic form, drawing the lesion in different sections on the prostate or by annotating the MRI images.

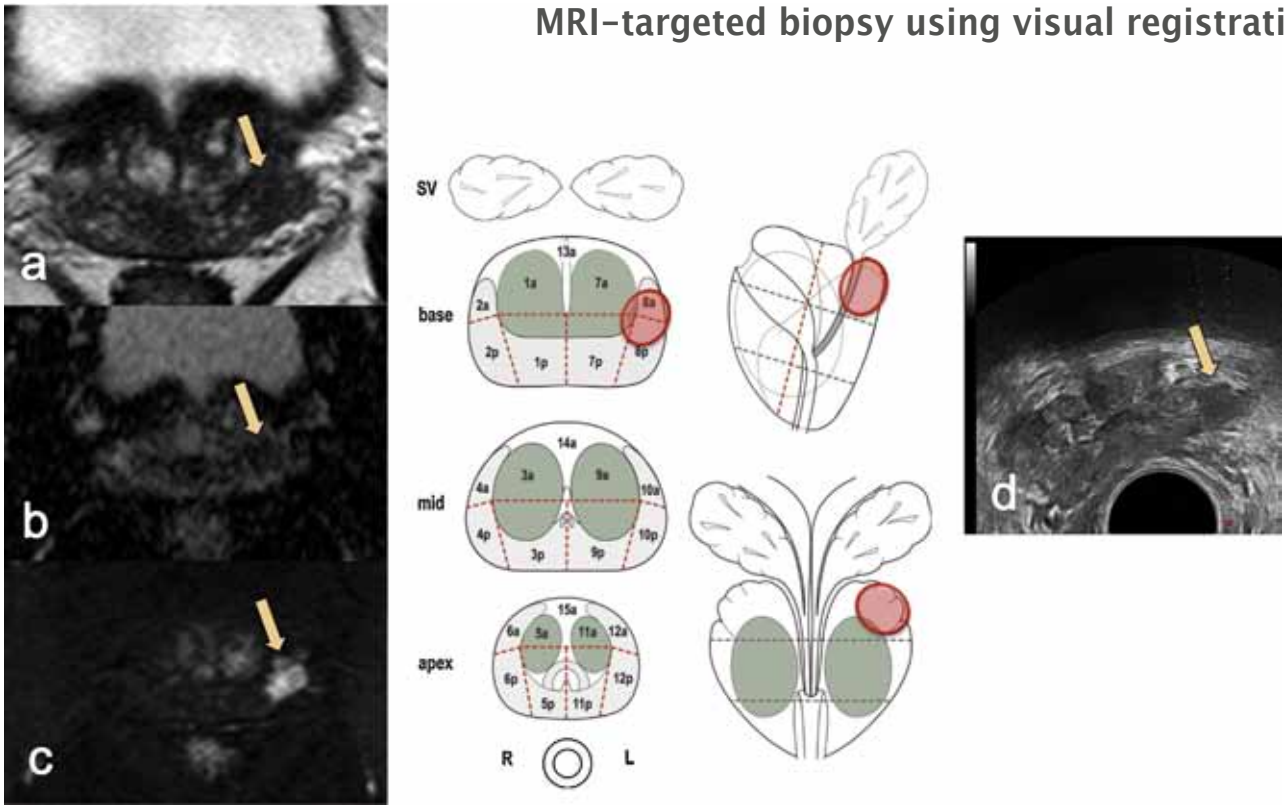
A number of groups, including ours, are using software registration that transposes MRI information onto the ultrasound information used at the time of biopsy. This gives the advantages of an ultrasound clinic-based approach at the same time as allowing the important MRI information to be transferred.

Head-to-head studies of visual registration and software registration suggest there is no clear winner at the moment. It seems to depend on both the tumour – larger tumours being more easily accessed with visual registration – and on the expertise and experience of the radiologist reporting the scans and the operator performing the biopsies.

The third method, less commonly used, is MRI-targeted biopsy using an 'in-bore' biopsy device that allows you to see the needle in the MR machine. Most centres perform a high-resolution diagnostic scan first and then an interventional scan at the time of the biopsy. The diagnostic MR images and the interventional images would be co-registered.

***Question**: If you have a patient who does not have an MRI before biopsy, how long would you wait to perform MRI after biopsy?*

***Answer**: For me, it depends on the cancer you find at the biopsy. If you find, for example, 10mm of Gleason 4+3 high-risk disease and you just want to know about the nodes or extraprostatic extension, I would do that fairly quickly because the nodes will not be affected by biopsy. But if you find 2 mm of 3+3 disease and you think that a man is suitable for sur-*



MRI-targeted biopsy with ultrasound guidance and visual registration. A lesion (*white arrow)* that is highly likely to be clinically significant cancer is seen in the left anterior horn on a) T2-weighted, b) diffusion-weighted, and c) dynamic contrast-enhanced images and depicted in red by a radiologist on a diagrammatic colour-coded report (where red indicates clinical significant cancer is likely to be present). The urologist uses this report to visually register the location of the lesion during the biopsy with transrectal ultrasound guidance. d) The biopsy needle is seen within the lesion on the ultrasound image.

Source: CM Moore et al (2013) *European Urology* 64:544–552, reproduced with permission from Elsevier

veillance based on the standard biopsy, then I would tend to wait at least 3 months before doing an MRI scan. We know that for some men, even at 3 months, there will still be changes that show up on the scan and make it more difficult to interpret.

Question: *UCL have been pioneers in dissemination of template biopsies. Is there still a role for template biopsies in the era of MRI?*

Answer: *It depends what you mean by template biopsy. A 5mm mapping biopsy taken in a detailed and intensive manner should not be necessary in the future, based on data that we have been collecting. It may be necessary in some cases, such as those men who are not suitable to have an MRI scan, those with a worrying PSA where no cancer is evident on MRI or standard biopsy. Our usual approach at UCL is to carry out targeted biopsies and then, for men undergoing a primary biopsy, we might do a less intensive 12-zone transperineal biopsy rather than a full 5 mm mapping biopsy.*

MRI in active surveillance

A systematic review of the literature (*European Urology* 2015; 67:627–636) reveals three different datasets of interest for MRI in men on active surveillance.

Radical prostatectomy data

In men who are suitable for surveillance on biopsy criteria, what sort of disease is found if you go ahead with a radical prostatectomy? The review found for men with a positive MRI there was a 44% chance of upgrading from being suitable for surveillance to being

unsuitable. There was a much lower chance (11%) for men with a negative MRI. There was less of a difference for upstaging based on MRI status as opposed to biopsy status: 25% of men with a positive MRI were upstaged and 10% of those with a negative MRI.

Reclassification biopsies

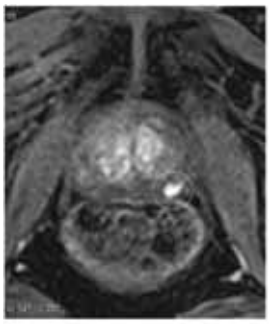
If a man has a biopsy suggesting he is suitable for active surveillance and he has a concordant MRI (a positive MRI with a small lesion or a negative MRI with no specific lesion), then the likelihood of reclassification on repeat biopsy is 17%. If, however, there is a discordant MRI (the MRI suggests more significant disease) then there is a 77% likelihood of reclassification, which is quite a strong driver to perform extra biopsies if the MRI does not match a patient's current biopsy.

Repeat MRI on surveillance

I am particularly interested in this area, which involves looking to see if we can use MRI for active surveillance instead of repeat biopsy. It is essentially looking at radiological progression, which means an increase in volume or in the conspicuity of a lesion on MRI. The data showed that men with a positive MRI at baseline had a one in three (32%) chance of radiological progression over a three-year period. Men with a negative MRI at baseline had an 11% chance of radiological progression over this period.

There is a lot of work to be done to define these elements of progression, but I think this is an interesting area for the future. The challenges are in how we define radiological significance and then how we define progression. The RECIST criteria that we use in a lot of other tumour groups would need a minimum of a 1 cm-diameter tumour, which would be uncommon in a patient put on surveillance for localised prostate cancer. We also need to look at standardised reporting for volume, change in volume, and change in characteristics. We don't yet know how important it is if a lesion becomes visible on diffusion imaging when it was not previously visible, although we suspect it means higher-grade disease and that we should probably be taking action.

Prostate lesion on dynamic contrast-enhanced MRI



Dynamic contrast-enhanced MRI clearly shows a left peripheral zone lesion

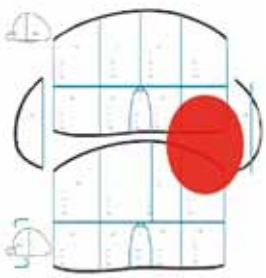
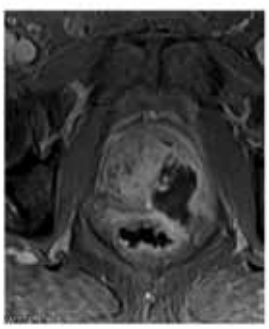


Diagram of the findings of transperineal biopsy targeted on the area shows that the only cores that showed up positive were the targeted cores with 4 mm of Gleason 4+4.



After high-intensity focused ultrasound the lesion is no longer visible

Source: Courtesy of Mark Emberton, *Division of Surgical and Interventional Science*, University College London

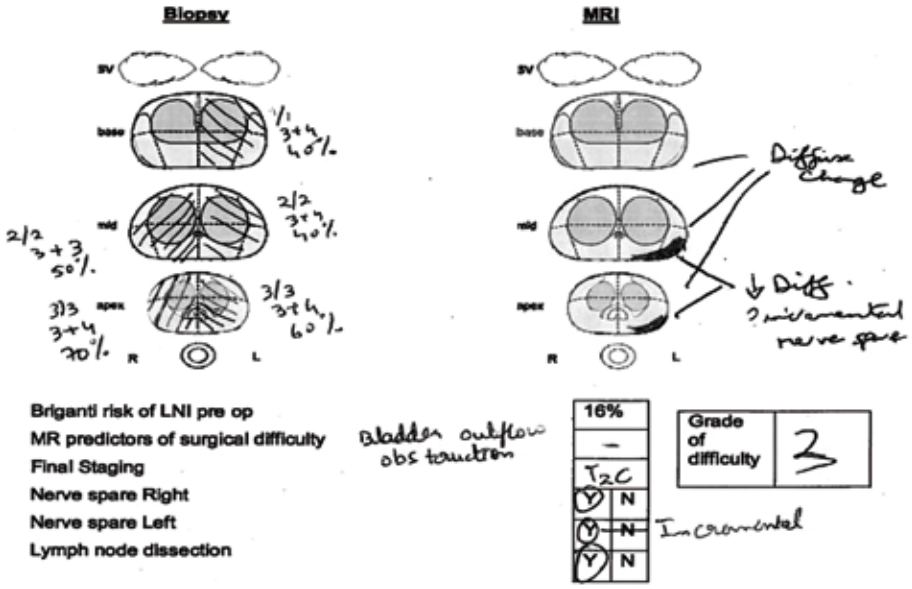
Once we have answered all these questions, the final challenge is what to do with the information for the care of the patient in front of us.

Question: *Is there a minimal volume that MRI can detect or is it always according to grade?*
Answer: *It is grade-dependent. MRI has excellent ability to detect any tumour of 0.5 ml or more when it is a focal lesion. It is still very good in detecting tumours of 0.2 ml and less, particularly if they are high grade, for example tumours of 0.1 ml with primary Gleason pattern 4 element will show up quite well on MRI. This works well for focal lesions, but with diffuse change throughout the peripheral zone you can have a reasonable volume of a low-grade tumour that does not show up on MRI.*

MRI for treatment planning: focal therapy

The figure *left* shows a left peripheral zone lesion that is clearly visible on dynamic contrast enhancement (*top*). This was targeted at transperineal biopsy and compared to the 24-core or 12-zone biopsy (*middle*) and the only cores that showed up positive were the targeted cores with 4 mm of Gleason 4+4. The patient was an ideal candidate for focal therapy based on having a very small, discrete lesion that reaches histological significance. He was treated with high-intensity focused ultrasound and the treatment effect is shown (*bottom*). We are seeing a revolution in the use of focal therapy, with the ability to characterise the prostate and identify areas of prostate cancer.

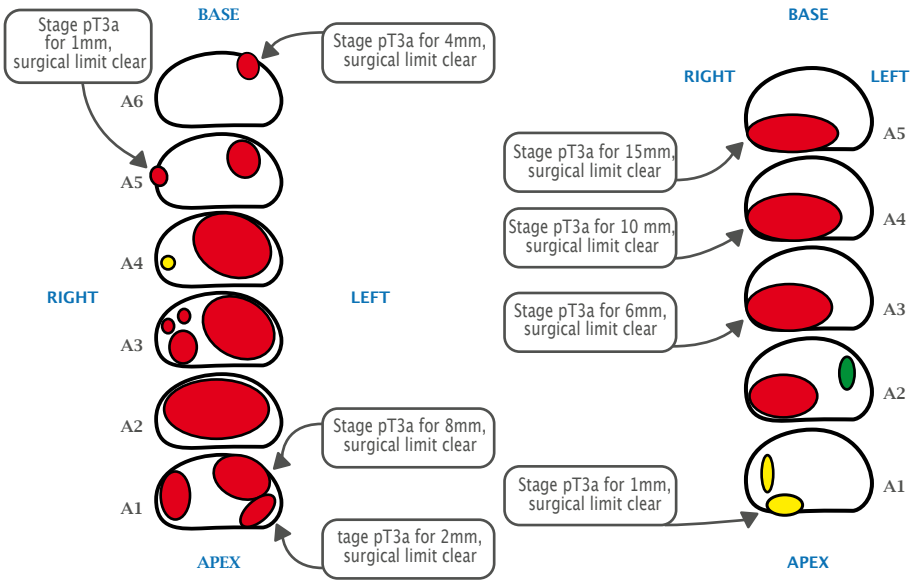
Treatment planning



This planning document is for a larger prostate cancer requiring more radical treatment. It shows schematics of the biopsy findings (left) and MRI findings (right), and defines preoperative risk of lymph node invasion, any MR predictors of surgical difficulty, objectives for nerve sparing and lymph node dissection, and grade of surgical difficulty.

Source: Courtesy of John Kelly, *Division of Surgical & Interventional Science*, University College London

MRI correlated with histology



Postoperative histology in two patients with high volume tumours correlates well with preoperative MRI, using colour coding to show likelihood of clinically significant disease on MRI (red – highly likely, yellow – equivocal, green –unlikely).

Source: Courtesy of John Kelly, *Division of Surgical & Interventional Science*, University College London

MRI for treatment planning: radical prostatectomy

MRI is also very useful for more traditional treatment approaches, including radical prostatectomy.

At our institution we hold robotic surgery radiology planning meetings, where robotic surgeons and radiologists discuss each case, including histological findings, patient characteristics and MRI findings. Each case is assigned a grade of difficulty for surgery (1–3), and the decision is made whether to spare the nerves or not based on MRI findings and the patient's wishes. Plans are made for unilateral or incremental nerve spare; for the margin at the posteriolateral and anterior apex; and for how the fascia will be approached, as shown in the upper figure.

Post-operatively, the histology is correlated with the preoperative MR images. The lower figure shows two patients with quite high-volume tumours who had radical prostatectomy achieving clear surgical limits, despite the disease having spread outside the prostate.

Value of MRI for surgical planning

We consider that MRI adds incremental value to the use of clinical variables alone for staging prostate cancer. This value is greatest for patients with intermediate- and high-risk disease.

Paul Cathcart and colleagues assessed this formally during a quality assurance programme for prostate cancer surgery which included MRI, showing much better return to potency in patients in the programme compared to those treated before the programme had started (see over).

Return of potency: impact of the quality assurance programme

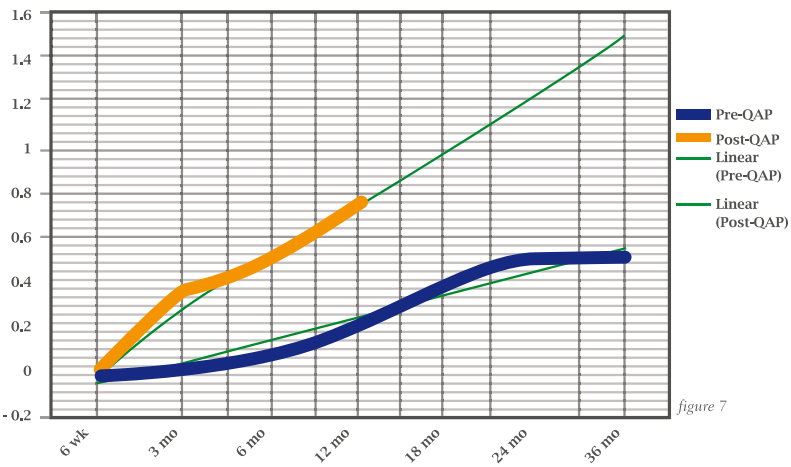


figure 7

A quality-assurance programme (QAP), which was piloted during reorganisation of UK prostate cancer services and includes MRI, showed important benefits in terms of return of potency after bilateral full nerve-sparing surgery

Source: P Cathcart et al. (2015) *European Urology* 2015; 68:22–29, reproduced with permission from Elsevier

Take home messages

MRI is the best imaging modality to detect higher-risk prostate cancer. It will not detect all prostate cancer, but I consider that's a specific advantage of MRI because, in my opinion, we don't want to detect low-risk, low-volume, low-grade tumours.

It is important to use T2 anatomical imaging as well as diffusion and contrast enhancement.

It is important to report standard and targeted biopsies separately and discuss with radiologists. This is best done as an ongoing, learning process. We hold weekly meetings where we look at men having biopsies and focal therapy with radiologists and urologists. We feel this is important because, although we have been doing prostate MRI for a long time at University College London, there is still more to learn.

Question: *Is there a difference between CT scan and MRI for staging nodes?*
Answer: *The difference between CT and MRI in assessing nodal disease is less than the difference between the two techniques for assessing the prostate itself. I think it makes sense to stage, using MRI if available, because it is much better for staging the prostate. But if a patient cannot have an MRI, then CT staging of the nodes is as good. However, CT staging of the prostate is not so good.*
Question: *While you do need a contrast sequence at the beginning, do you consider a non-contrast MRI is suitable for follow-up?*
Answer: *I think it would depend on the patient. If they have a lesion that shows up well on contrast then you will want to repeat that. But if they have a lesion that shows up best on diffusion, you could potentially miss out the contrast. You can run into difficulties if you have a lot of different protocols for MRI in your system and people can get confused, so we have an initial MRI protocol and a protocol for follow-up after focal therapy, where contrast images are very important, and that can shorten the scan time.*
Question: *The Pinto NIH group found you have to biopsy 200 men to find one man with clinically significant disease misclassified by targeted biopsy (JAMA 2015, 313:390–397). Do you think there is still a need for standard biopsy?*
Answer: *In a centre with good MRI and where the radiologist is confident, a patient with a lesion scoring 4 out of 5 and where the rest of the prostate is normal, I don't think you necessarily need a standard biopsy. But for younger men, where the prostate can look quite bright, there is diffuse enhancement and it's hard to say, then you do need a standard biopsy.*
Question: *Which is the best registration system?*
Answer: *It's worth learning visual registration because, whether you are a urologist or radiologist, if you're the person doing the biopsy you should be looking at the MRI scans. Over time you will learn and get better at targeted biopsies. But there will always be some difficult lesions, and it will be interesting to see if software can help with those. The choice of software should be based on whether you offer a transperineal or transrectal service.*
It's important to use deformable registration, because with rigid registration the MR image is transferred directly across and overlaid on the ultrasound image, but the image of the prostate in an MRI scanner is different to how it looks when there is an ultrasound probe in the rectum or when it starts to swell and bleed when you have taken some biopsies.

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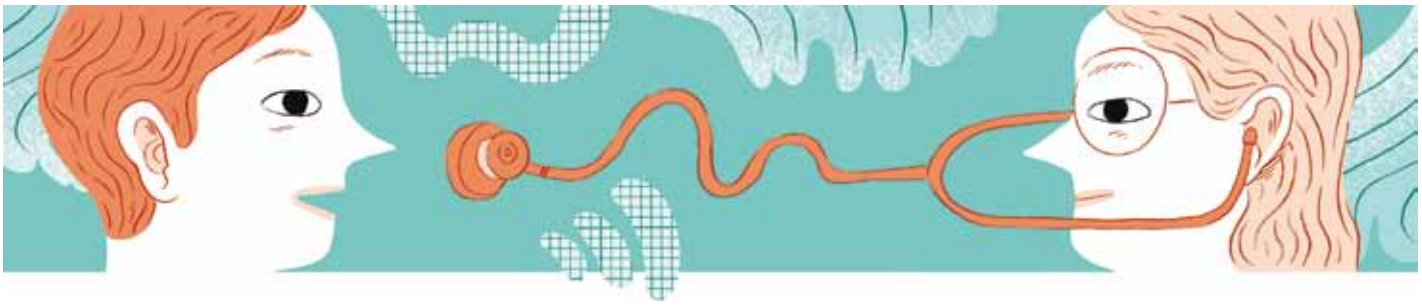


A journey to the heart of the EMA

Flexibility and goodwill have allowed patient involvement in the work of Europe's drug regulators to develop at an impressive pace. But will they be enough to withstand the strains on the relationship exerted by financial pressures, together with demands that patient reps stop seeing industry reps?

Ten years ago, an opportunity arose for Hildrun Sundseth to help develop the patient voice in the European Medicines Agency (EMA), the EU agency responsible for the evaluation of medicinal products. She had long advocated for women's health and saw this as a chance to change things gradually for her cause.

"Women are very much underrepresented in clinical trials," says Sundseth, who was the head of EU Policy at the European Cancer Patient Coalition at the time. This stems from the thalidomide tragedy when they "discovered when a woman is pregnant, the drug can be dangerous for the infant and cause birth defects". Banning women from taking part in clinical trials for their own protection was a natural reaction, she explains – but in real life, women take medicines.

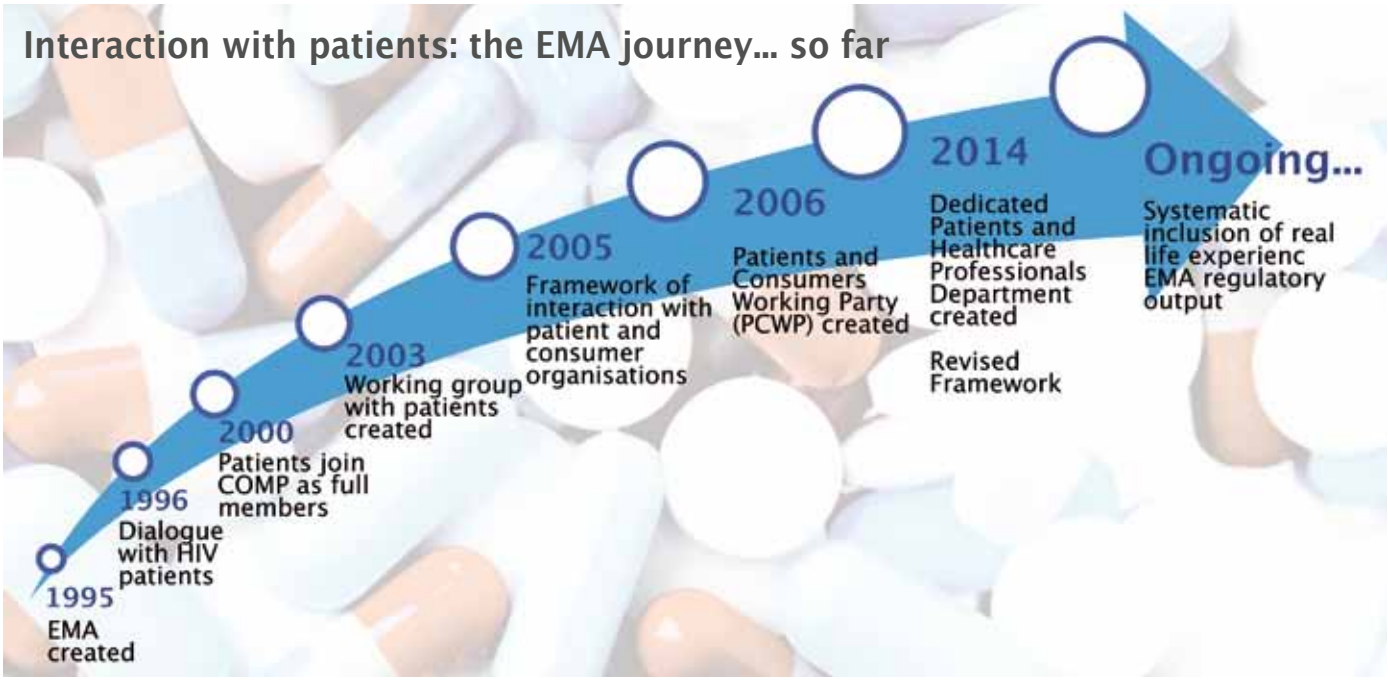
When the EMA set up the Patients' and Consumers' Working Party in 2006, Sundseth says that they "started with a clean sheet of paper". Together with her fellow patient representatives, she contributes real life experience, which she says is very important. This includes "what it feels like [to live] with a disease as well [the impacts of] the medicines you are taking".

The number of patients and consumers involved in EMA activities increased eight-fold between 2007 and 2014, from 76 to 633, according to the EMA's latest report. Sundseth, who is now the President of the European Institute of Women's Health, says this reflects the patient movement generally, but adds that "it's amazing what progress has been made."

This progress includes patient representatives being involved "across the whole medicine lifecycle", according to Nathalie Bere, patient relations coordinator at the EMA. It's been a journey, she says. What started as opening a dialogue has now transformed into involving patient representatives as an integrated part of their work.

"A lot of people didn't really know at the beginning what to expect, having the patient around the table when it is predominantly a scientific discussion." The approach was to start slowly and involve patients bit by bit into the different activities.

Now, patient representatives are voting members in most committees. So



Source: European Medicines Agency

far, however, they have no seat at the table where the recommendations on marketing approval and other issues are decided – the Committee for Medicinal Products for Human Use (CHMP) – and that is where their sights are now set.

"We would very much like to be part of the CHMP," says David Haerry, an HIV/AIDS patient advocate who co-chairs the Patients' and Consumers' Working Party, adding that, "In other committees the patients are very much part of the game." Sundseth agrees. "We've pushed for a very long time to get involved in the CHMP," she says.

As Bere points out, patient representatives already have some input into CHMP assessments via their involvement in scientific advisory group meetings, which are convened by the CHMP (see panel overleaf), but the EMA is open to discussion on how to improve the process.

A pilot is currently underway in which patients take part in the CHMP process as experts on benefit–risk assessments, and other ways of consulting patients through the CHMP are also being explored. Haerry expects this trial period to be over next year, after which the interaction will be analysed to see how to move forward.

Penalties of participation

Achieving high-level input into EMA's decision making processes is not just about getting formal access, however. There is also the problem of financial sustainability for the patient representatives who bring their knowledge and expertise to the table, and this problem is growing more acute as the extent and level of their involvement increases.

"Patients contribute mostly as volunteers, which means we are not paid," explains Haerry. "It is an issue when you are part of a busy committee like the Pharmacovigilance Risk Assessment Committee." He has calculated that patient representatives need to spend between six and eight days per month to keep up-to-date with the workings of such a committee.

Currently patient representatives are compensated for expenses such as travel and meals, but not for lost time. Haerry, who has been involved in the EMA since the inception of the Patients' and Consumers' Working Party, says "you cannot expect people to do this for free," but adds that no solution has been found to date.

"This is something that we're aware of," says the EMA's Bere. "We rely very much on voluntary work from a lot of patients, and it is obviously very much appreciated." She adds that the EMA are constantly investigating to see if there are ways to compensate patient representatives further, but there's nothing concrete as yet.

The European Institute of Women's Health is campaigning for patient organisations to be funded for their work. Sundseth argues that they are providing

a public service, and sees the lack of funding as a legacy issue. When the EMA and European Parliament proposed the amendment to consult patient organisations in the process, she says, they didn't think about how to do it, and "there is no funding for these patient organisations to interact with the agency," as a result.

This is not an issue in some other jurisdictions. The US regulators, the FDA, pay a salary to patient representatives for the time they spend in meetings, in addition to paying for expenses. Most members of FDA advisory committees are appointed as 'special government employees'. The EMA can't pay patients, according to Bere, because "we don't currently have the legal basis for that."

To resolve this issue, a change in EU legislation may be required. Sundseth says this will most likely be at least a five-year process, but she feels "that's something we could do."

Lack of funding not only affects individual patient representatives, who give up their time to attend meetings or committees, but also patient organisations who work or want to work with the EMA. "If you want to have total transparency, and patient organisations that are independent from industry, you have to support them with funding," argues Sundseth.

Currently, there is a set of eligibility criteria against which patient and consumer organisations must be evaluated before they are eligible to work with the EMA. The criteria, as spelt out in a recent EMA report, include a "limitation of the amount of funding that organisations can receive from a single pharmaceutical company, the publication of their yearly financial accounts and adherence to a code of conduct/rules with regards to the relations of an organisation with industry."

The lack of EMA funding can make it hard to meet the criteria, particularly for small, relatively new organisations, such as Melanoma Patient Network Europe. Bettina Ryll, who founded this network three years ago, says that ideally their funding would be split evenly between the regulator, pharmaceutical companies and

Patient representatives and the CHMP

The Committee for Medicinal Products for Human Use (CHMP) sets up scientific advisory groups, as and when they may be required, to provide advice in connection with the evaluation of specific medicines or treatments.

These advisory groups are made up of European experts, including patient representatives. In recent years, almost all scientific advisory group meetings (82% in 2013) included at least one patient representative.

The eight scientific advisory groups currently running encompass areas such as oncology, vaccines, neurology and cardiovascular issues. They are convened for a variety of reasons including where issues may be controversial or involve complex technical assessments, or where major public health interests are expected.

For oncology, typical questions that scientific advisory groups are asked to consider include:

- Whether benefit–risk is negative or marginally positive
- How clinical meaningful are the benefits
- The clinical impact of risks
- Need for further studies
- Guidelines

Patient interactions at these advisory group meetings have proved useful, according to the EMA. They provide a patient perspective to discussions about a medicinal product as well as providing insights into acceptable levels of associated risks. A 2011 survey of patient representatives showed that almost all felt their views were taken into account, and were able to follow the discussions at the meetings.

In September 2014, a pilot project was launched by the EMA to involve patients in the CHMP's assessment of the benefits and risks of medicines. This pilot is intended to mark the next step in bringing patients' views and values to the assessment of medicines throughout their lifecycle.

The first medicine to be included in this pilot was Scenesse, a treatment for erythropoietic protoporphyria, a rare genetic blood disorder that causes intolerance to light. During the approval process, two patients shared their experiences of living with the condition and answered questions from the CHMP. Their inputs were considered by the CHMP as part of its assessment of the treatment.

To date, there have been three cases of patient involvement as part of this pilot. A recent CHMP report said that "involvement of patients has been a learning curve and has improved with experience." It added that, to complete the pilot, at least two to three more cases are needed before being able to deliver a sufficient analysis.

health-technology assessment bodies, but this is not possible as the EMA doesn't fund advocacy.

Since Ryll founded the new network, she is "personally no longer eligible" to take part in certain EMA activities, due to industry funding. "We all have the problem that we rely on pharma funding. It's nearly impossible to get other funding, especially as a starting non-profit."

Haerry, the Patients' and Consumers' Working Party co-chair, says that this is an ongoing discussion, and feels "it has taken some unfortunate turns." Transparency is essential, he says, but he points out that EMA rules about interaction between patient representatives and pharmaceutical companies also mean that those who do work on EMA committees often have to restrict the advocacy work they do outside of the EMA.

He cites his own local work as an example. "In Switzerland, I work on a few things that nobody else in my country works on, so it is important that I can do my local work while being at the agency."

Under the current criteria, however, he cannot attend local advisory meetings with industry, which means an opportunity for patients' interests to be heard and taken on board by industry is being missed.

This may not be an issue at the European level, as other representatives can attend, but it is certainly a problem at country level. "Some of our patient [representatives] are quite rare birds," Haerry points out.

He argues that the European Commission either needs to start funding patient organisations or the overall eligibility criteria need to be looked at again. "As long as the information is out and the organisations are transparent, I don't really see this [as an] issue."

The Patients' and Consumers' Working Party. Patient communities welcome greater involvement – but not the expectation that their expert input should be entirely unpaid

A flexible approach

EMA's Bere says that patients are considered to be experts, and every expert coming to work at the EMA has to declare their interests and have these looked at prior to being involved. She stresses, however, that there are flexibilities. "It depends which activity you want to take part in, and what kind of interactions [with industry] there have been."

For rare diseases, where patient advocates can be particularly thinly spread, there is also an option, which they call an 'expert witness'. This allows patient advocates who have some interactions with industry to come and participate in a discussion and to share their views, with some restrictions.

Even when patients are ruled out due to conflict of interest, or their organisation is deemed ineligible, it is still possible to have some interaction with the EMA, and also take part in certain projects. One such example is a benefit–risk pilot, which is being undertaken by Melanoma Patient Network Europe.

"We have established a really constructive relationship [with the EMA] based on this pilot project," explains Ryll. The network's relationship with the EMA began when Ryll invited them to a conference on adaptive licensing, a new way to approach clinical trials for cancers such as stage IV melanoma.

Her interest in this step-by-step approach to licensing began when her husband took part in a number of randomised trials before he died of melanoma. Ryll says these trials were violating the Helsinki Declarations governing ethical research, as "one arm was better than the other" – the experimental treatment having already been shown to be highly efficacious at the phase 1 stage. She feels that, "from a patient perspective, that's obviously not acceptable."

Ryll organised an initial conference on clinical trial designs in 2014 (http://tinyurl.com/trials-we-want). Since then, she says, the Network and the EMA have "achieved a really good mutual understanding".

It was this relationship that led to the benefit–risk pilot project, which involved a survey of patients with stage IV melanomas, carers and advocates. It also included a group of regulators.

"We got some quite interesting preliminary results, and based on that we decided to make it into a full project," explains Ryll. The initial findings of the pilot showed that patients are much more willing to accept risk than either carers or advocates. "It actually turned out that advocates were more risk averse than regulators," which Ryll feels has had a big impact on those who participate in the EMA.

Meaningful involvement

Francesco Pignatti, who is head of oncology, haematology and diagnostics in the EMA, has seen first-hand the extent to which patient involvement has had an impact on decisions. Though he can't give specific examples, as discussions happen under confidentiality, he says that patient contributions have changed the outcome of benefit–risk assessment and risk minimisation measures in some instances.

A recent EMA report states that 40–50% of patient input is included in the final advice letter. As the report explains, while these figures are impressive, they "do not capture the benefit of each occasion where patient input has led to relevant interesting discussions or been in agreement with the advice provided by the working party."

The creation of a network of young patient experts is the result of one of these interesting discussions at the Patients' and Consumers' Working Party. At an EMA meeting, Rafal Swierzewski, a fibrosarcoma survivor and board member of the European Cancer Patients Coalition, talked about the work ECPC was doing with young cancer patients, especially teenagers and young adults, to set up an advisory group within the Coalition.

The discussion led to Swierzewski being asked to help set up a similar advisory group within the EMA, and he is now involved in the creation of a new patient network. "The EMA like innovative projects," says the cancer advocate. He welcomes the support he is getting from the regulatory body, with three EMA committees having now expressed their full backing for the youth programme. "It is important for me that the project has such a great support," he says.

The EMA's Bere feels that, "if the medicine [is] for young people, then we should be speaking to them as the end users." She says that they are in early discussions at the moment, and hope to set up a framework where teenagers can potentially be consulted.

There are some issues to work through, such as the legal aspects of involving minors, but Bere says they are looking into that. They are also trying to work out the best way to interact with young people by "trying to set up a network, so that we have contact with youth groups across different disease areas in Europe." Social media, facetime, and video conferences are all communication methods currently under discussion.

"A recent EMA report states that 40–50% of patient input is included in the final advice letter"

Swierzewski says it is important that this new group of patients is involved, because their experience is often neglected. His past work in a children's cancer organisation in Poland led him to witness many conversations between children as young as five.

"They were exchanging perfect professional information about their state of health in the corridors," says Swierzewski, who argues that young people have an amazing knowledge about their disease and treatment. "But of course it's never heard, as they only exchange the information between themselves." This is what Swierzewski hopes to change, with the help of the EMA.

One change that is soon coming into force, involves the cause that Sundseth, long-time patient advocate and policy expert, championed for a number of years. This May, a new EU clinical trial regulation (EU No 536/2014) will be implemented, and this will ensure that women will be included in statistically significant numbers in clinical trials.

It's a big step forward, but Sundseth already has her eyes on the next improvement: the use of medication in pregnant women. In her previous job at the ECPC, she often spoke to newly diagnosed pregnant cancer patients who were worried and stressed because no information was available on the safety of their treatment options. "This is an area that we need to make headway in," she insists. This means her involvement in the EMA is far from over.

So what else is in store for patient representatives at the EMA? Nathalie Bere says they are "talking about trying to consult patients even earlier in the assessment process." Francesco Pignatti says that "more and more involvement is the natural evolution, which is still continuing." David Haerry is determined to make sure that it does – as he says, "There's more to be done."

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The road to global cancer care

Richard Sullivan is Director of the Institute of Cancer Policy and Conflict and Health Programme at Kings Health Partners Comprehensive Cancer Centre. He will address a specific challenge in global cancer care in each issue of *Cancer World*.

The world is experiencing new and powerful forces in global health, from the Sustainable Development Goals, and 'grand convergences' to what is now the central totem in global health – universal health coverage. For cancer control, context is everything, and it still needs to find its place within these wider agendas.

Cancer is a very new addition to global health, which has been built almost entirely on the platforms of infectious disease, including HIV/AIDS, child and maternal health and other health aspects of the development agenda. Infectious diseases have been the main drivers of global health, where concepts such as immediate good and disease eradication have been powerful motivators for action and funding.

The problem is that cancer doesn't score so highly on either concept, because it is as much about control as cure and outcomes are a complex convergence of multiple different factors. So while we in the cancer community might understand how things work, to outsiders – even other healthcare professionals – the treatment pathways are a bewildering black box.

Many countries already struggle to provide the very basic packages of health services. Adding cancer care systems in the context of other global health goals can seem like a bridge too far, particularly given that many countries are faced with having to deliver care for not only non-communicable diseases but all the 'old' enemies – continuing threats to maternal and child health, malnutrition and infectious diseases.

It's now clear that disease eradication programmes, such as those for malaria, lymphatic filariasis, dracunculiasis, and onchocerciasis, are difficult and risky and will probably require a lot more effort, time, and money than initially expected. Between 1986 to 2015, for example, it cost an estimated $350mn to bring the number of dracunculiasis cases down from 3.5 million to under a thousand cases in three countries – Mali, Chad and South Sudan (*NEJM* 2013, 368:54–63).

This tells us two things. There's still a huge amount of time and effort required to achieve the most fundamental population health interventions and, if Ebola and antibiotic resistance has taught us anything, you can never take your foot off the neck of infectious disease. In comparison, cancer control looks expensive and complex. And it is. The cost of basic treatment for a range of common cancers for the population treated in the dracunculiasis eradication programme would have been $118 bn. And that doesn't include the capital costs.

National cancer control plans look rational and affordable in the context of high-income countries, but when it comes to countries with struggling economies, fragile public finances, poor social determinants of health, and multiple co-existing disease burdens from infectious diseases, chronic diseases and violence and trauma, national cancer plans are harder to deliver.

This poses a real challenge for how we approach

global cancer control. The economic, structural and cultural reality for many countries is that the basic systems of healthcare, prevention and development are insufficient foundations upon which to build cancer control. Domestic funding and overseas development aid needs to be far more creative in the way that services are built up to provide the backbone for fully developed cancer care systems in the future. And this needs to be a public cancer system where private interests serve the greater good.

A public good

Global health is a public good and cancer control must be as well. All of this will require an open, two-way process of global cancer, engaging with and educating other parts of global health, be they development agencies such as USAID, or disease-specific groups such as HIV/AIDS, as well as a willingness of these other actors to positively engage with the complicated planning required for cancer control.

Cancer presents a challenge to the traditional structures and cultures of global health. Traditionally, norms and standards are set by the WHO, with operational responsibilities being a matter for governments or NGOs. But because of the breadth and depth of preventative measures and treatments needed for cancer control, many other actors are now setting norms and standards. This may be in site-specific areas, such as the Breast Health Global Initiative (*Lancet Oncol* 2014, 15:1421–23) or across domains, such as Global Surgery 2030 (*Lancet Oncol*. 2015, 16:1193–1224).

Some countries are developing their own quality standards, pathways and systems, such as the National Cancer Grid of India and the Chilean Cancer Forum (*J Ind Soc Med & Paed Oncol* 2014, 35:226–227). All this begs the question about long-term strategy and structures for supporting the development of affordable and equitable systems of cancer control within global health.

Progress outside high-income countries has been made through taking a wide and varied approach to building capacity and capability. There is no 'one country' model for building cancer systems, with much of the literature anyway a descriptive narrative rather than critical scrutiny. The real successes are heterodox solutions that build on political commitments in countries that are open, democratic and have transparent governance for sustainable health and development.

The tragedy of Libya and Syria, both of which had been held up as global models of how to deliver good health outcomes for low cost, is a cautionary warning about just how dependent global cancer control progress is on socio-political factors (*J R Soc Med* 2011, 104:490–492). Despite a lot of grandstanding no one 'owns' the cancer agenda in global health or has the universal solution to national cancer control plans. Instead we see a rich tapestry of creative ideas to tackle the problems we know exist and are becoming more adept at quantifying. It is easy to see how high income hegemony around global cancer, including some powerful vested interests in specific areas such as medicines, can distract us from looking beyond the usual suspects.

Long-term twinning partnerships between institutions have proved to be particularly effective for both adult and childhood cancers. A good example of the former is the AMPATH twinning model, between USA and Kenya (*JCO* 2016, 34:36–42); while the work done by St Jude's Children's Research Hospital (*JCO* 2016, 34:53–61) and by World Child Cancer (*J Cancer Policy* 2013, 1:e8–e19) are good examples of the latter. Building operational capacity using modality-specific approaches, as the Global Taskforce on Radiotherapy is doing, has also started to prove its worth as a focal point for action.

Much of the real progress, however, is being made through the collaborations between low- and middle-income countries, such as the recent high-level partnership betwen India's Tata Memorial Centre and Mongolia, and the work of University of Zambia–University of North Carolina to build up gynaecological-oncology surgery in other African countries such as Malawi. Cuba's contribution to medical training is also rarely recognised, even though workforce capacity in cancer care is the single biggest issue facing most countries and the Cuban medical schools have been superb at providing a global health workforce (*The Lancet* 2009, 374:1574–75). It is to these places and people that we should look for how we can achieve universal coverage of global cancer care.

Progress through collaboration. Lameck Chinula (centre) can now perform curative surgery on women in Malawi with early cervical cancer, thanks to a regionally based training programme

Marc Beishon

Bridging the gap in metastatic breast cancer

Every two years the metastatic breast cancer community convenes to assess what needs to be done to bridge gaps – gaps in scientific/clinical knowledge and in service provision, and gaps between the patients and professional communities.

More than one in four people say they would prefer it if people with advanced breast cancer kept it to themselves and did not talk about their condition to anyone but their doctor. This was one of the findings of the *Global Status of Metastatic Breast Cancer Decade Report 2005–2015*, and it helps explain many of the report's other key findings: namely, that far too many people living with advanced breast cancer are still not getting the information and support they need.

That's not to say that nothing has improved over the 10-year period covered by the report. It has, and nowhere is this more evident than at the ABC (Advanced Breast Cancer) conference, where clinicians, patient advocates, researchers and support professionals from across the world gather in Lisbon every two years to identify key issues, and build a consensus on what needs to be done and the political will to make it happen.

Over the past four years the conference has set out a stall on the world stage to establish international guidelines for the treatment and care of women, and some men, with advanced disease, and has added substantially to these recommendations at each conference.

This is no small achievement given that, until quite recently, some oncologists were arguing that such guidelines were not possible, because metastatic breast cancer is too complex and individual. That objection now seems to have been overcome. The ABC consensus panel includes the world's top breast cancer specialists, and since ABC2, the consensus guidelines have been published jointly by ESO (the European School of Oncology, which organises the conference), together with ESMO (the European Society for Medical Oncology) – the support from ESMO also demonstrating the 'buy in' to the process.

The rise of a vocal, if still fragmented, patient advocacy movement for survivors of metastatic breast cancer, particularly in the US, is also well-reflected at the ABC conference. While patient advocates are now involved at some level in almost all the international breast cancer conferences, including San Antonio, the European Breast Cancer Conference (EBCC) and the St Gallen consensus meeting on early stage breast cancer, ABC is unusual in the extent to which patients and support specialists are integrated into the programme on the main stage; patient advocates also participate as equals in the consensus panel.

Also well represented are specialists other than medical oncologists, whose involvement within multiprofessional teams is key to meeting the full range of care and support that people living with metastatic breast cancer need to sustain a good quality of life.

Jorge Nogueira/Hugo Silva

Consensus. Expert patients vote on changes and additions to the guidelines alongside international leaders in metastatic breast cancer

So it was fitting that the third ABC conference, which took place last November, should be the platform chosen by Pfizer to launch their comprehensive *Global Status* of *Metastatic Breast Cancer* report into the unmet needs of people with metastatic breast cancer, and how perceptions and realities – clinical, scientific, policy and advocacy – have changed over the past decade.

In her now customary opening address, co-chair Fatima Cardoso, the medical oncologist who has led the development of ABC, reminded the audience that efforts to achieve this level of focus on metastatic breast cancer only started around ten years ago, and were built on surveys that highlighted how forgotten and isolated patients with metastatic disease have been.

She paid tribute to Novartis and Pfizer as the major supporters of researching unmet needs at global and European levels, a counter to the criticism often levelled at the pharmaceutical industry, and its focus on early stage disease. And she warmly welcomed the *Global Status* report, which was published in partnership with ESO and ABC, and is the most comprehensive report to be published in this field so far. It is based on evidence drawn from multiple sources, including substantial surveys of patients and the public conducted across 34 countries.

"Innovation in breast cancer is now lagging behind other tumour types such as lung cancer and melanoma"

The strapline of the ABC conference is 'Bridging the Gap' and Cardoso highlighted a number of priorities that need to be addressed in order to meet the needs documented so clearly in the *Global Status* report – and to improve patient satisfaction with their oncologists.

Key among these, she argued, is communications training for healthcare professionals (one in two doctors who responded to the survey had been given no such training), and greater involvement of patients in decisions regarding their care (fewer than half of the patients surveyed reported being involved in decision making).

She highlighted in particular the importance of talking to patients about end-of-life and supportive and palliative care: "Our ABC recommendation

The Expert Eye

Last year, the European Parliament explicitly extended to patients with metastatic disease its 2003 call for all breast cancer patients to have the right to be treated by a multidisciplinary team of experts at a specialist centre (2002/2279(INI)). In practice, many member states are still a long way from complying with this policy, despite a deadline set for this year.

A manifesto setting out the imperative for specialist breast units will be presented at the European Breast Cancer Conference (EBCC) in Amsterdam this March. Even in countries where the principle of specialist centres has been embraced, some patients with metastatic disease are still being treated exclusively by medical oncologists, without input from other specialists. The lack of agreed training or accreditation for 'breast cancer specialists' is also a concern.

'The Expert Eye' (left), painted by two-time breast cancer survivor Shirley Bianca Mueseler, is the symbol of a campaign for a Global Licence in Oncoplastic Surgery, which was presented at ABC3. A collection of Mueseler's paintings, titled Messages of Hope, can be found on YouTube.

is for it to start early, but in 65% of cases it happens very late, when it's difficult to have these discussions," said Cardoso.

CJ (Dian) Corneliussen-James, co-founder and president of the US advocacy group METAvivor, brought a patient perspective to this topic, describing how many doctors are still failing to communicate bad news promptly, and their patients consequently do not fully understand the implications of being diagnosed with metastatic disease. She also questioned the emphasis on messages about healthy living, from both doctors and parts of the advocacy movement, which she says results in some women blaming themselves for their disease, and contributes to the prejudice they face.

A particular concern for everyone in the advanced breast cancer community is the slowing pace of progress in survival rates. Cardoso spelt out the worrying reality that, despite the field having pioneered new treatments, such as trastuzumab (Herceptin) – the first targeted agent for treating solid tumours – innovation in breast cancer is now lagging behind other tumour types such as lung cancer and melanoma.

"Among the most frustrating issues for oncologist is the lack of studies that define the optimal sequence of agents"

This is reflected in survival rates, which remain poor, with only one in four people diagnosed with advanced breast cancer surviving for five years or more. With global rates of breast cancer rising fast, this means that the current number of deaths – around 500,000 in 2015 – will rise to 800,000 by 2030, said Cardoso.

What's new?

The conference took a close look at the latest scientific advances in treating advanced breast cancer. The headline news is most positive for HER+ disease, where progress is continuing thanks to treatments such as the 'dual blockade' of trastuzumab and pertuzumab (Perjeta), and T-DM1 (Kadcyla). A number of inhibitors are in trials for use in ER+ disease, with one drug palbociclib, (Ibrance), which inhibits certain enzymes implicated in tumour growth, already approved in the US. Like many such drugs, however, there is still no biomarker to show who will benefit most. The least encouraging headlines are for triple negative disease, which still has no targeted therapy, only chemotherapy.

New therapies bring with them new side-effects. The conference heard about some of these from Lesley Fallowfield, of Sussex Health Outcomes Research and Education in Cancer, (UK), who also spoke of the need to develop patient-reported outcome tools that can drive research into the

best way to prevent or ameliorate them. Survivorship issues, supportive and palliative care and affordability of drugs all had dedicated sessions, as did clinical dilemmas, such as whether and when to remove a primary tumour in patients with metastatic disease.

The implications for practice arising from these presentations will be reflected in new or modified statements in the ABC3 guidelines, as agreed by the concluding consensus panel session.

Among the most frustrating issues for oncologists, which will be covered in a new statement, is the lack of studies that define the optimal sequence of agents in different types of metastatic breast cancer. As Cardoso argues, trials should compare sequences of drugs in one order and then the reverse, but neither regulators nor companies accept this crossover trial design, because it decreases the chances of observing a positive outcome. "But what we need to know in the metastatic setting is the value of adding a new agent to what we already have, and to know how best to incoporate it," says Cardoso. "We need the regulators on our side in this."

There are also problems with early approval of drugs at phase II, such as with the new inhibitor, palbociclib, as results often fail to hold up at phase III, the stage at which drugs for early breast cancer are usually approved. "We want to make sure a drug is really useful and not just given because it's a new drug," says Cardoso.

A call to use objective tools, such as ESMO's Magnitude of Clinical Benefit Scale or ASCO's Value Framework, to evaluate such therapies, will therefore be issued in another new statement from the ABC consensus panel.

A new set of statements was also agreed on support for palliative care symptoms, such a fatigue, neutropenia and dyspnoea. The latter condition, breathlessness, is one of the hardest to control. As Matti Aapro, a geriatric oncology specialist at the Genolier clinic, Switzerland, told the conference, this is partly because it has so many possible causes in people with advanced cancer, and very few effective treatments exist.

An overview of the additions and modifications agreed to the ABC guidelines is published on p59. The full consensus guidelines will be published in *The Breast* and *Annals of Oncology.*

One guideline for the globe?

The big question, of course, will be how to 'bridge the gap' between the published guidelines and the real world of clinical practice. Talking with oncologists at ABC3 it seems there is no substitute for 'ambassadors' to present the guidelines around the world.

There are also major challenges in how they can be applied in different settings. In Germany, for example, the country's guidelines group has assessed the ABC consensus alongside its own and actually added to it, whereas in low-income countries there are aspects of care that are far from achievable.

No one knows this better than Alexandru Eniu, a medical oncologist in the breast unit at the Ion Chiricuta Cancer Institute in Cluj, Romania, who is involved in a survey of cancer drug availability in Europe and globally, run by ESMO together with the WHO and other organisations.

"It is striking to see that many countries, including my own, lack access to some cancer treatments on the WHO's essential drugs list," he says.

These aren't the new targeted agents, which are also not available in many emerging countries, but some basic and cheap agents such as tamoxifen and 5FU, which Eniu says are simply not economical for companies to distribute in some markets. He is also of course an advocate for ESMO's new Magnitude of Clinical Benefit Scale to show the value of new drugs.

He stresses, however, that addressing drug availability may be the easy bit. The key and ultimate aim throughout Europe and elsewhere must be establishing multidisciplinary specialist breast units, and this will involve complex issues that will vary according to the country. In Romania, he says that access to radiotherapy is the biggest concern – "It is estimated that only about 25–50% of Romanians have access, owing mainly to lack of equipment," he says.

"The key and ultimate aim throughout Europe and elsewhere must be establishing multidisciplinary specialist breast units"

Alexandru Eniu: basic treatments such as tamoxifen are unavailable in many countries

"In breast cancer, this means that surgeons will often propose a mastectomy because they can't offer radiotherapy," he adds, "and this can really impact the quality of life for patients." Volume of surgery is also an issue, and Eniu is hopeful that a voluntary breast unit accreditation scheme, under development at EU level, will eventually improve matters.

"In my centre I am lucky to work with a large multidisciplinary board, but that just isn't possible in other areas at present," he says. "We have a grant from ASCO to set up an online board where outlying hospitals can send us a request to have cases discussed at our institute, although there are challenges in data privacy and timely management. But it is a step forward in bringing multidisciplinarity to smaller centres where they can't build a breast team."

Given that most people with metastatic breast cancer are being treated in health systems that are no more advanced – and often far more basic – than Romania's, could the ABC guidelines be seen as so ambitious they become, in effect, irrelevant in most settings?

Cardoso believes this could be a danger, and she strongly advocates adopting 'stratified guidelines' that define the second best option, which will offer a good standard of care that could be deemed more immediately achievable, but will still enable advocates to argue with their governments that 'second best' is just not good enough.


Lillie Shockney

A pioneering survivorship service

"I've felt that it's not right to only start survivorship care after treatment ends, instead of at the point of diagnosis, where you can find out what a woman's life goals are. It's about finding out what brings joy in their lives."

These are the words of Lillie Shockney, oncology nurse, two-time survivor of breast cancer, and head of the breast cancer service at the renowned Johns Hopkins Hospital in Baltimore, Maryland.

They wanted someone who 'walked the walk' as well as talking the talk, she said, explaining how it was that someone from her background was seen as ideal to take charge of the service.

Under her leadership, the hospital has developed a pioneering survivorship programme that is capable of helping patients with a full spectrum of support needs, as well as integrating survivorship concerns into the treatment plan.

A case in point: a woman who didn't enjoy her bank job much, but loved playing the piano – "I realised if I didn't intervene before she saw the medical oncologist she could be given a drug that caused peripheral neuropathy, and that could be avoided."

Another example: patients can plan for coping with fatigue. The literature indicates that 'power walks' can reduce it by as much as 70%. Patient navigation – helping women through their journey with such information – is another way Shockney and her team can help.

Treatments can be planned around work, too, if that's important. Johns Hopkins itself walks the walk here, with a programme, Managing Cancer at Work, in place for its own staff – of the more than 42,000 employees in the hospital and university, about 800 have been diagnosed with cancer.

For patients with metastatic disease, Shockney has organised a retreat at Johns Hopkins, where women and their partners can spend a few days in peace and plan to fulfil life goals, even though they may not be there physically, such as by preparing cards for key moments in their children's lives (she ran a video on the retreat in her conference presentation). "We have boxes of cards for all occasions – birthdays, bar mitzvahs, weddings," she said. "I had a call recently from a 24-year-old woman who got married and whose mother died when she was ten, under our care. She thanked me for helping her mother to still be part of her life."

"It's about finding out what brings joy in their lives"

Summary of consensus statements at ABC3

The consensus process works by amending existing statements from ABC1 and ABC2, where new evidence has emerged, and adding new ones. These then will be published alongside the unchanged statements later this year in *The Breast* and *Annals of Oncology*. Summaries of the new ABC3 statements are as follows (the full statements await final approval):

- The ABC community strongly calls for **clinical trials** addressing important unanswered clinical questions in this setting, and not just for regulatory purposes. Clinical trials should continue to be performed even after approval of a new treatment, to provide real world data on performance of the therapy**.**
- Use **objective scales to evaluate benefits** of new treatments, such as ESMO's Magnitude of Clinical Benefit Scale and ASCO's Value Framework.
- Use **telemedicine** to help manage patients in remote places.
- 'Strong consideration' should be given for using **patient-reported outcome measures** as a regular part of clinical practice – but they must be easy do, say with iPads.
- With survival improving for many patients, health professionals should **consider survivorship issues**, by being ready to adapt treatment strategies according to patients' circumstances. Patients should have the opportunity to work, should they want to. Breast reconstruction should be an option for women with stable disease.
- In **HER2+ disease**, the optimal duration of treatment isn't known, but stopping it after several years of remission may be considered for some patients. If pertuzumab is not given, first-line treatments can include trastuzumab combined with vinorelbine or a taxane, and in later lines trastuzumab can be given with several chemotherapy agents. Chemotherapies to combine with the dual blockade of trastuzumab and pertuzumab are paclitaxel or vinorelbine.
- The addition of **palbociclib** to an **aromatase inhibitor** at first line has shown benefit in postmenopausal patients, but phase III results are needed before recommendation. Palbociclib with fulvestrant beyond first line is an option, but overall survival results are awaited.
- In **non-BRCA, triple negative disease**, all chemotherapy recommendations as for HER2– disease apply, as there are no data or specific recommendations. Regardless of BRCA status, carboplatin is an important option for patients previously treated with anthracyclines with or without taxanes.
- In HER2– disease, **anthracyclines** can be reused under certain conditions.
- For BRCA-associated disease in patients with triple negative or luminal metastatic breast cancer, **genetic counselling** and possibly BRCA testing should be discussed with the patient if the results can impact treatment decisions and/or clinical trial entry.
- In **HER2+ patients with brain metastases** and stable extracranial disease, systemic therapy should not be changed. Where brain metastases are the only site of recurrence it is not known whether adding chemotherapy will alter the disease course and it is recommended that trastuzumab be restarted if stopped.
- **Metronomic chemotherapy** (low dose given very frequently, e.g. daily) is a reasonable option for patients who do not require a rapid response.
- **Multigene panels**, such as those obtained using next-generation sequencing, on evolving changes in metastatic tumours **have not proved to be beneficial** and should only be used in an investigational setting.
- In **supportive and palliative care**, there are new statements on managing cancer-related fatigue, neutropenia, non-infectious pneumonitis, mucositis/stomatitis, dyspnoea, nausea and vomiting, and mTor inhibitor endocrine toxicities.
- Two new definitions are on **oligometastatic disease** (low volume disease that could be treated to achieve remission) and patients who suffer from **multiple chronic conditions**.

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Cognitive effects of endocrine therapy

The impact chemotherapy can have on the ability to think clearly is well recognised. Less is known, however, about the cognitive effect of endocrine therapies, which in the adjuvant breast cancer setting are being prescribed for up to 10 years. Wilbert Zwart, Sanne Schagen and colleagues from The Netherlands Cancer Institute, review the evidence.

This is an abridged version of W Zwart, H Terra, S Linn, S Schagen. Cognitive effects of endocrine therapy for breast cancer: keep calm and carry on? ***Nature Reviews Clinical Oncology*** *(2015) 12:597-606. It was abridged by Janet Fricker and is published with permission.*
 doi:10.1038/nrclinonc.2015.124

nature REVIEWS CLINICAL ONCOLOGY

Three quarters of breast cancer patients are eligible to receive endocrine treatments – tamoxifen and aromatase inhibitors (letrozole, exemestane and anastrozole). It is therefore very important to understand their potential adverse neurocognitive effects, particularly now that the guidelines are recommending increasing the duration of therapy from five to 10 years.

Increased awareness of the importance of oestrogen in stimulating neuroplasticity and improving cognitive performance has focused research on evaluating the cognitive effects of breast cancer endocrine treatments.

A recent review that summarises more than a decade of research indicates that cognitive decline affects 20–60% of patients after chemotherapy (*CA Cancer J.Clin* 2015, 65:123–138). Patients show changes from pre to post chemotherapy with regard to learning and memory, speed of information processing, and executive functioning. However, most studies have not been designed to address the effects of endocrine therapy, either alone or in combination with chemotherapy.

Studies that explore the influence of endocrine therapy on cognition are often underpowered, with flawed designs, that ignore relevant factors such as the use of hormone replacement therapy

(HRT) and age at menopause.

Any effects of endocrine therapy in breast cancer patients, independent of chemotherapy, need to be explored. Furthermore, since guidelines permit the choice between different endocrine regimens, knowing how each option could potentially impact on cognition might influence the decisions made in individual cases.

Oestrogen effects on brain physiology

Both oestrogen receptors, ERα and ERβ, are expressed throughout the brain, although ratios vary. In general, ERβ is expressed at high levels in the hippocampus and temporal cortex; while ERα is expressed at higher levels in the amygdala and hypothalamus.

Multiple studies have indicated that aromatase inhibitors (AIs) and tamoxifen can cross the blood–brain barrier and enter the brain. All AIs inhibit both ERα and ERβ activity. By contrast, tamoxifen has a mild stimulatory effect on ERα function and completely blocks ERβ activity (*Cancer Res* 2001, 61:2537–41). It is the ratio of ERα to ERβ that may influence the effect of tamoxifen on neuronal function.

Preclinical data on cognition

Animal models of oestrogen deprivation (ovariectomy) show impairment of cognitive function: rodents and monkeys illustrate decreased cognitive performance in spatial memory and working and reference memory.

In these preclinical studies, the effects of tamoxifen and AIs on cognition have proved less conclusive. Mouse studies report adverse effects for tamoxifen, including impairment of memory consolidation and retrieval. In rats, AIs improved spatial learning and memory, but impaired hippocampus plasticity. Furthermore, in ovariectomised rodents, tamoxifen possessed oestrogen-like agonistic effects on the serotonergic system, neuroprotective functions in the dopamine and acetylcholine system, and increased hippocampus plasticity.

ER knockout studies suggest adverse effects of endocrine therapy may be largely mediated by ERβ: mice lacking ERα showed no difference in neuronal morphology, while those lacking ERβ had cognitive deficits, such as reduced context–cue memory (*Mol Endocrinol* 2007, 21:1–13).

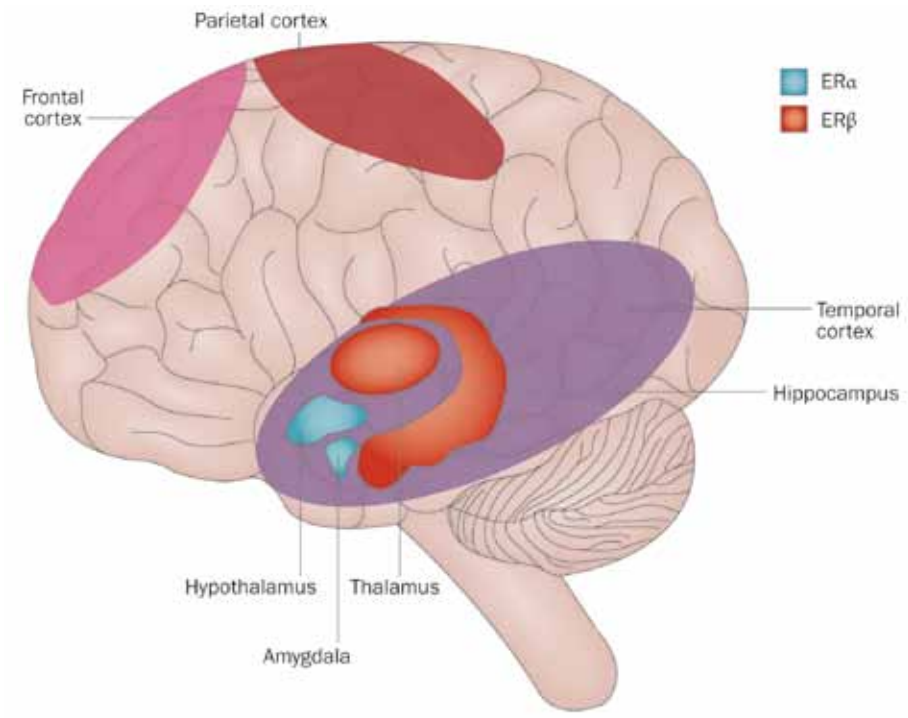
The neuroprotective functions of oestrogens and tamoxifen may be explained, in part, by the prevention of neuronal cell death, controlled partially by ERs (*Endocrinology* 2003, 144:306–312).

Hormones and cognition in healthy women

Studies have explored hormonal influence on cognitive function at different stages in the reproductive lives of healthy women.

During the menstrual cycle, higher levels of oestrogen can have a subtle impact on cognition, with beneficial effects for functions where women excel (such as verbal fluency) and unfavourable effects for cognitive functions where men generally excel (such as spatial function). Studies in post-menopausal women suggest those with higher oestrogen have better verbal memory and retrieval efficiency; while those with lower oestrogen have better visual memory.

Three large cohort studies suggest premature menopause affects verbal



ER expression levels. Expression levels of ERα (blue) and ERβ (red) in specific regions of the brain are depicted

CASE STUDY

Cognitive impairment following endocrine treatment

A 55-year-old postmenopausal elementary school teacher with breast cancer, treated with breast conserving surgery, radiotherapy and tamoxifen, became aware of cognitive difficulties including problems with name retrieval, organisation skills, distractibility, and need for increased mental effort to memorise instructions. A neuropsychological examination revealed she had diminished ability to learn new information (corresponding to the 1st percentile), lower than expected recall of previous learned information (corresponding to the 7th percentile), and underperformance of lexical and semantic fluency (corresponding to the 16th and 14th percentiles, respectively). Interventions were offered including learning compensatory strategies to reduce interference of cognitive difficulties at work, regain resilience and diminish stress.

fluency and visual memory in later life and may increase dementia risks. One study, for example (*Neurology* 2007, 69:1074–83), showed women undergoing oophorectomy before the onset of menopause have increased risks of cognitive impairment and dementia (HR=1.46 compared to reference populations).

In contrast to several observational studies showing reduced risk of Alzheimer's disease in HRT users close to their final menstrual period, the Women's Health Initiative Memory Study (WHIMS) reported HRT (oestrogen plus progestin) significantly increased dementia in women aged 65 years or older (*JAMA* 2003, 289:2651–62). For women receiving only oestrogen, no significant effects were found.

The WHIMS study supports the 'critical window' hypothesis, where the benefits of HRT on cognition are limited to early initiation of treatment. While a 'critical window' has also been observed in animal studies, mechanisms underlying such effects remain poorly understood.

Against this background, there is a need to understand how breast cancer endocrine therapies may affect brain health and to investigate clinically relevant cognitive risks.

Evaluation of such adverse effects remains challenging due to other factors affecting cognition, including chemotherapeutic agents. Cognitive testing is now being incorporated into the design of several clinical trials, allowing opportunities to further explore such issues.

Neuropsychological examinations

Studies of other patient populations with cognitive problems (such as traumatic brain injury) indicate that 'self-reported cognitive function' provides an insufficient proxy, since it is weakly associated with tested cognitive function, and strongly associated with individual mood.

Together with neuropsychological assessment, such information is, however, critical to the differential diagnosis of a cognitive disorder and introduction of intervention strategies.

Oestrogens and cognition: clinical data

Cognitive studies conducted as part of randomised clinical trials in postmenopausal women suggest a potential adverse influence on cognition of tamoxifen but not AIs, though these results are inconclusive.

In the Arimidex Tamoxifen Alone or in Combination (ATAC) study, involving the AI anastrozole alone, tamoxifen alone, and combination of tamoxifen plus anastrozole, patients with cancer scored significantly worse on verbal memory and processing speed compared to controls without cancer (*Psycho-Oncology* 2004, 13:61–66). No distinctions were made between different endocrine therapies.

In the Tamoxifen Exemestane Adjuvant Multinational (TEAM) study, neuropsychological assessment at one year showed tamoxifen users performed significantly worse than controls without cancer, with regard to verbal memory and executive functioning, and worse than exemestane users on information processing speed. Exemestane users did not perform significantly worse on any domain compared to controls. (*JCO* 2010, 28:1294–1300).

The BIG 1-98 trial found that patients treated predominantly with letrozole achieved better cognitive scores than those treated predominantly with tamoxifen (*Breast Cancer Res Treat* 2011, 126:221–226).

Finally, in the International Breast Cancer Intervention (IBIS) II prevention study, where postmenopausal women were randomised to anastrozole or placebo, cognitive function did not differ between treatment groups (*Lancet Oncol* 2008, 9:953–961).

These studies suggest tamoxifen but not AIs may affect cognition, but

results are less clear regarding the effects of endocrine therapy *per se* on cognition, as some studies (such as BIG 1986 and ATAC) report worse performance for all patients on endocrine therapy (either tamoxifen or AIs) compared with controls. It is noteworthy that relevant information on background hormone use, previous HRT, and age since menopause has not been systematically taken into account.

Observational studies

The four observational studies evaluating cognitive effects of endocrine therapy in patients who were chemotherapy naïve found post-menopausal women using tamoxifen performed worse on verbal abilities than non-cancer controls. One study including 14 postmenopausal women taking anastrozole found that women taking anastrozole, in particular, had greater cognitive decline in processing speed and verbal memory, but since this group was particularly small, results should be interpreted with caution (*Psycho-Oncology* 2009, 18:811–821).

Five additional studies have evaluated the influence of endocrine therapy on cognition, but also included patients who received prior chemotherapy. Two studies did not find adverse effects for endocrine therapy. The third study showed a negative effect of anastrozole on visual and verbal learning as well as memory (*Menopause* 2007, 14:995–998). The fourth study showed patients taking endocrine therapy reported increased language and communication complaints compared to cancer patients not undergoing such therapy, and furthermore this was associated with diminished psychomotor function (*JCO* 2014, 32:3559–67). Finally, for a subset of patients, the fifth study showed regionally specific changes in metabolic brain function on PET scans following AIs (*Clin Breast Cancer* 2014, 14:132–140).

Conclusions

With multiple clinical trials indicating prolonged adjuvant endocrine therapy improves outcomes for breast cancer patients, the value of these treatments in managing breast cancer remains beyond doubt. Nevertheless, studies suggest endocrine therapy can potentially have adverse effects on cognitive function.

Attention needs to be paid to whether the observed changes in cognition associated with cancer therapies adversely impact aspects of everyday functioning that matter to patients, such as employment. Elucidating the clinical significance of side effects further would help to identify the therapies that have least impact on physical and mental morbidity.

A core set of cognitive tests measuring memory, executive function and processing speed have been developed by the Response Assessment in Neuro-Oncology (RANO) working groups and the International Cognition and Cancer Task Force (ICCTF). The incorporation of these tests, already widely adopted by the EORTC, RTOG and other consortia, into clinical trials for endocrine therapy could help elucidate potential adverse cognitive effects.

Future development and implementation of predictive biomarkers might enable identification of patients who have excellent prognosis and are unlikely to derive sufficient benefit from adjuvant endocrine treatment to justify their use.

IN SUMMARY

Take home message

Studies involving neuropsychological assessments before treatment are needed to determine the potential cognitive effects of endocrine therapy and identify patients who might be at risk of treatment-associated cognitive decline. As current guidelines permit choice between different endocrine regimens in treating breast cancer, identifying potential cognitive effects associated with different options might influence individual choice of therapy.

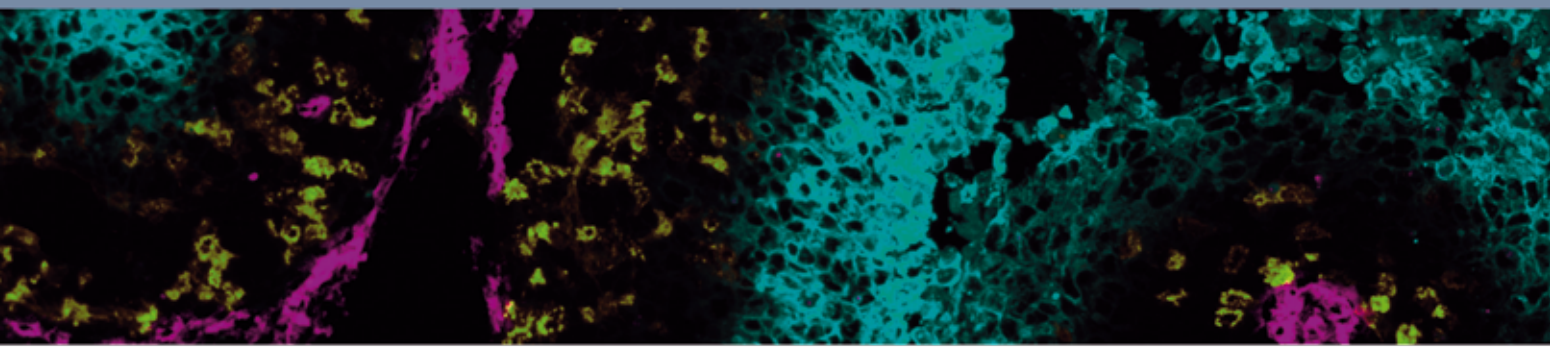
Clinical implications

The continuing search for biomarkers that predict selective benefit from adjuvant endocrine therapies is likely to identify breast cancer patients who have an excellent prognosis and would be unlikely to derive sufficient benefit to justify their prescription. For those who do benefit from endocrine therapy, more research is needed on the potential impact on cognition. At this stage no clinical practice implications are justified, as our knowledge on the actual incidence and severity of cognitive changes associated with endocrine therapies is too limited to be included in clinical guidelines.

Future studies

Standardised testing of cognitive function should be better incorporated into clinical trial design for endocrine treatments, with outcomes related to effects on quality of life. Variables on hormonal background (including HRT, age, age at menopause, and chemotherapy) should be well documented.

nature REVIEWS CLINICAL ONCOLOGY



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2016 - 2017

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EVENTS	SAVE THE DATE
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EACR 24	**9 – 12 July 2016** *Manchester, United Kingdom* EACR24 24th Biennial Congress of the European Association for Cancer Research
ESSO 36	**14 – 16 September 2016** *Krakow, Poland* ESSO36 in partnership with the Polish Society of Surgical Oncology
EORTC NCI AACR 2016	**29 November – 2 December 2016** *Munich, Germany* ENA2016 28th EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics
ECCO	**27 – 30 January 2017** *Amsterdam, The Netherlands* ECCO2017 European Cancer Congress From Evidence to Practice in Multidisciplinary Cancer Care

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ESO EDUCATION 2016

European School of Oncology
Learning to care

MASTERCLASSES

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- 10-14 JUNE - Belfast, United Kingdom
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  ESMO-ESO Course on Medical Oncology for Medical Students
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- OCTOBER - NOVEMBER - Munich, Germany
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INSIDE TRACK CONFERENCES

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- 19-20 MAY - Madrid, Spain
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- 10-12 NOVEMBER - Lugano, Switzerland
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- 25-26 NOVEMBER - Rome, Italy
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PUBLICATIONS

- Cancer World Magazine
- Critical Reviews in Oncology/Hematology (CROH)
- The Breast
- Nature Reviews Clinical Oncology (NRCO)

OTHER ACTIVITIES

- Breast Centres Network

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
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Further information available at:

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