

# Cancerworld

www.cancerworld.net

Issue 91-95 Spring - Summer 2022





# Sharing Progress in Cancer Care

Sharing Progress in Cancer Care (SPCC) is an independent non-profit organisation, based in Switzerland, dedicated to providing physical and virtual events as well as online services to share and integrate knowledge and information on the latest developments in the Cancer Care Continuum, focusing on scientific progress, innovation and the sharing of best practices.



## PLATINUM SPONSORS



## GOLD SPONSORS



## SILVER SPONSORS





Scan to access our website



*'Beating the odds'*  
by *Maddalena Carrai*

## Contents

**Editor-in-chief**  
Adriana Albini

**Senior Associate Editor**  
Anna Wagstaff

**Core Contributing Writers**  
Adriana Albini, Marc Beishon, Rachel Brazil, Alberto Costa, Simon Crompton, Janet Fricker, Sophie Fessl, Anna Wagstaff

**International Contributors**  
Valeria Hartt (South America), Esther Nakkazi (Africa), Alexandra Nistoroiu (Central and Eastern Europe), Myriam Vidal Valero (Central America), Swagata Yadav (South Asia)

**Publishing Coordinator**  
yStadium

**Graphic Concept and Design**  
Studio TheValentino, www.thevalentino.it

**Printed by**  
Industrie Grafiche Pacini, Pisa

**Cover by**  
Maddalena Carrai

**Illustrations by**  
Sara Corsi, Maddalena Carrai, Alessandra Superina

All enquiries to:  
**SPCC** Sharing Progress in Cancer Care  
Piazza Indipendenza 2  
6500 Bellinzona - Switzerland  
info@cancerworld.net  
editor@cancerworld.net  
© 2022 European School of Oncology.  
All rights reserved

Published by  
Scuola Europea di Oncologia  
Registrazione Tribunale di Roma  
Decreto n. 436 del 8.11.2004  
Direttore Responsabile  
Alberto Costa

- 3** War, reconstruction and the duty of medicine and science
- 5** Beating the odds in colorectal cancer
- 11** Lung cancer screening  
*Time to act on the evidence*
- 18** Tailored exercise  
*A key element in personalised treatments and prevention*
- 24** Trust me: I'm a surgical oncologist!
- 32** PSA population screening is back in favour: here's why
- 38** Pain relief is a right  
*Building confidence in opioid use in oncology*
- 43** Cancer-related fatigue  
*Might research into long-Covid help find causes and cures?*
- 49** Evolution of the doctor-patient relationship  
*From ancient times to the personalised medicine era*
- 54** Bridging the Age Gap in Breast Cancer  
*A treatment selection tool for the over-70s*
- 58** Tackling drug resistance  
*How our commensal bacteria can hinder or help*
- 65** Preventing alcohol-related cancers in Europe  
*Lessons from three countries*
- 74** Decolonising cancer research  
*Why it matters, what can be done*

**Cancer World** is an online-first magazine that publishes weekly news reports and features. The print edition is distributed at major conferences and mailed to subscribers and European opinion leaders.

Subscribe at: [http://bit.ly/CW\\_Subscribe](http://bit.ly/CW_Subscribe)





# Over 20 years of innovation in breast cancer care

Breast cancer is not a singular disease, and neither is our approach to treating it.  
Visit [breastcancervision.com](https://breastcancervision.com) for breast cancer resources and support



Breakthroughs that change patients' lives<sup>®</sup>



# War, reconstruction and the duty of medicine and science

*Adriana Albini – Editor in chief*

**A**s healthcare and economies across the globe were starting to emerge from the impact of the Covid-19 pandemic, in February 2022 the Ukraine war exploded with an unexpected devastation.

More than 4 million refugees have fled Ukraine and keep fleeing the country, with an estimated 7.5 million internally displaced.

Hospitals have been bombed, and other facilities indispensable to the survival of the civilian population, such as food production, drinking water installations and supplies, have been targeted.

The humanitarian crisis implies loss of access to nutrition, running water, housing, heating, electricity, healthcare, and medical supplies.

Besides physical injuries and mental health harms, the sanitary situation provides a worrying breeding ground for infectious diseases – starting, as would be expected, with the resurgence of Covid-19 cases and other infections.

We are looking at two major sets of problems: how to send medication and medical equipment to Ukraine, and how to coordinate the relocation of patients and continuity of care, locally and internationally.

More than 400,000 Ukrainians are currently suffering from cancer and, on average, there are 160,000 new cases every year.

The European Cancer Organisation and the American Society of Clinical Oncology (ASCO) united forces in

March to launch a Special Network on the Impact of the War in the Ukraine on Cancer.

The Network has already been joined by many member and patient organisations, charities, and foundations, and many more are urged to collaborate.

The European Society for Medical Oncology (ESMO) is also encouraging its network of members and industry partners to provide onsite and remote support.

At a time of multiple crises, where our ‘normal’ has been turned upside-down, the “*duty of science*” is to follow the world emergencies and contribute to solving them, as stated by the zoologist Theodore Cockerell in *Nature*, in 1918 after World War I.

Medical journals can help by publishing accurate reports about the health crisis caused by wars, as international journals such as *The Lancet*, *JAMA*, the *BMJ*, *Nature* and *Science* are doing.

Following a general trend, *Cancer World* is also set to become more global, expanding our international panel of journalists to provide better coverage of issues impacting on cancer care beyond Europe.

We will continue to tackle social, economic and cultural as well as medical aspects of cancer, and will step up our presence on social media to better reach an international readership.

We hope that *Cancer World* can be a broad instrument of communication and a messenger of peace, reconstruction and joint actions of collaboration around the world.

esso  
41

Bordeaux  
France

**41<sup>st</sup> Congress  
of the European Society  
of Surgical Oncology**

19-21 October 2022

Treatment tailoring  
in cancer surgery

**Key dates**


**31 May 2022**

Abstract Submission  
Deadline

**15 August 2022**

Early Registration  
Deadline

[www.esso41.org](http://www.esso41.org)

 #ESSO41

  
**esso**  
THE EUROPEAN SOCIETY  
OF SURGICAL ONCOLOGY



# Beating the odds in colorectal cancer

When the odds are 10 to 1 against you, what, if anything, can be done to help tip the balance in your favour? **Anna Wagstaff** put the question to Stefan Gijssels, an advocate who survived those odds, and to Eric Van Cutsem, his oncologist.

**S**tefan Gijssels beat the odds in colorectal cancer. Diagnosed with a cancer of the colon in 2015, a laparoscopic surgery intended to remove what was thought to be a locally contained tumour revealed something much nastier. The cancer had pierced through the colon wall, it had spread to part of the small intestine, and there were metastatic tumours in the lining of his abdominal cavity.

The chances of surviving a diagnosis like that, a stage 4 colorectal cancer, were around 1 in 10. Yet more than five years on, he not only remains cancer free, but says there is literally nothing that he did before he had cancer that he is unable to do

today. Gijssels knows he is extremely lucky to be the one who survived – and survived well.

Had the cancer been of a more aggressive phenotype, or if it had progressed just a little further by the time it was diagnosed, things might have turned out differently. Had he been more frail, or had more comorbidities, he might not have been able to tolerate the radical surgery followed by six months of highly toxic chemotherapy, and his story might have ended differently.

But Gijssels also believes there is more to the story than just luck. There were things that tilted the odds in his favour. One of these is that he was treated at the Digestive

Oncology unit of Leuven University Hospital (in Belgium), under the leadership of Eric Van Cutsem, which, despite handling more than its fair share of challenging cases, delivers some of the best five-year survival outcomes in Europe. This matters, given that, across Europe, quality of care can differ widely between treatment centres in the same country, or even the same city.

Also improving his chances, says Gijssels, was the contribution he himself tried to make, as an active patient, to getting diagnosed (just in time, and doing what he could to maximise the impact of his treatment, promote his recovery and reclaim his life. Gijssels now spends

## Delivery of Care

much of his time working with advocacy groups, policy makers and hospital managers to ensure that knowledge and information derived from the collective experience of patients like him is made available to newly diagnosed patients early on, to give them a chance to be active in tilting the odds in their own favour.

So what can patients themselves do, and what can treatment teams do to maximise the chance of survival with a good recovery? *Cancer World* put the question to Stefan Gijssels and his oncologist Eric Van Cutsem.

### Beating the odds: diagnostics and treatment

There's no magic formula, says Van Cutsem. "You cannot improve your outcome statistics by just changing one thing, you need to address everything. It takes time and a lot of effort."

Thanks to progress in imaging, diagnostic biomarkers, treatment techniques and technologies, and in knowledge of how best to apply them, some patients who would once have been recommended palliative treatment are now potential candidates for treatment aimed at a cure. The biggest disparities in survival statistics are probably related to patients at this curability frontier.

"In many patients with metastatic disease [cure] is clearly not possible," says Van Cutsem. "But it is possible with some." One group he mentions is certain patients who present with metastases in the liver that are clearly not resectable. "If you downsize them you may cure some of them. Even in exceptional cases of stomach cancer, which is a tough disease, you can do that."

Patients presenting with locally

non-operable rectal cancer is another group he mentions, where he says significant differences between outcomes delivered by different hospitals can be seen even for stage 2 and 3 rectal cancers. "With more intensive treatments, with chemo and/or radiotherapy before operation, you can more often go for cure in some of these patients." The quality of surgery also plays a very important role, he adds, together with other aspects, such as the quality of intensive care, for patients who need it.

**"You cannot improve your outcome statistics by just changing one thing, you need to address everything"**

Getting the diagnostic imaging right, to be certain about exactly where the disease is, and how far it has invaded and spread, is absolutely essential to making the call on treatment options, says Van Cutsem. This includes use of standard technologies, such as endoscopy in rectal cancer, to determine how far the tumour is from the patient's sphincter. But for identifying and analysing metastatic spread, for instance, high-quality MRI is essential, he says.

"It's not just a question of doing an MRI, but a high-quality MRI and expert radiologists... In Leuven we have access to the best MRIs, with which you can look very adequately for peritoneal metastases – much better than with CT scans." PET scanning and functional MRI, which

provide information about cells' metabolic or biochemical function, are also needed, after treatment for metastatic disease for instance, to see whether a patient is responding or not.

Part of this comes down to having access to cutting edge equipment – and Van Cutsem stresses the wider importance of access to innovation, including through clinical trials, which are "particularly important for patients with stage 4 cancers". But equally important is the involvement of radiologists who are expert in capturing the right sequences and analysing and interpreting them correctly. The radiologists he works with at Leuven all specialise in digestive cancers – they spend their working lives immersed in visualising and analysing tissues of that part of the anatomy.

Growing knowledge about how the biology of tumours and their microenvironment influence prognosis and response to treatments also requires integrating new layers of expertise around the multidisciplinary team. "You need people in the lab – a team of marker geneticists, marker biologists, marker pathologists who understand the different platforms and different fusions, mutations and variations in different genes – and can do the interpretation and explain its relevance."

This can be important, for instance, in deciding on treatment options in certain cases of pancreatic cancer. "Should we go for more marker testing or not? In many patients it is not needed. But if you can give a call to the geneticist's number, you have the knowledge in this situation."

When Van Cutsem speaks of the importance of working as a



multidisciplinary team, it's clear that he himself relies heavily on the expertise of those around him. "Team work in oncology is not one person, and the team is as weak as the weakest part of the chain. Small hospitals may have good radiologists or good surgeons, but you need the whole team if you are to give a chance for survival."

What counts, he emphasises, is how well and how fluidly members of the team are able to interact to ensure clinical decisions along the entire treatment pathway are informed by the full range of diagnostic and treatment expertise.

And it is that clinical decision making process that Van Cutsem highlights as a final point. Many treatment centres, he feels, rely too heavily on clinical guidelines, which, while extremely important as a general framework, should not be used as a 'cook book'. They don't look hard enough at the specifics of each cancer – imaging, pathology, molecular biology – and of each patient – their health status and priorities – to identify those at the 'curative frontier' who are most likely to defy the odds.

### Beating the odds: the active patient

Stefan Gijssels has nothing but praise for the treatment and care he received once the cancer was diagnosed, and he is deeply grateful to the whole team – including the dedicated nursing staff – who saw him through some dark days and left him seemingly cancer free.

But as a patient advocate he also feels it is important to highlight the contribution people/patients themselves can make to tilt the odds in

their favour. Outcomes will be better when patients actively participate in their treatment pathway, and are given the help and advice they need to do it.

### Early diagnosis

An awareness of signs and symptoms that could indicate a cancer, and of possible genetic predisposition, is probably the single biggest contribution anyone can make to tipping the odds of surviving cancer in their favour.

### Gijssels advises people who have serious concerns not to take no for an answer

But getting doctors to act quickly when patients raise reasonable concerns is not always easy. It's understandable – complaints of the digestive system are things GPs deal with every day, and it can be tricky to identify the small minority that are associated with a cancer. Gijssels advises people who have serious concerns not to take no for an answer.

In his case, the first symptom was acute pain on one side of his abdomen. He doesn't blame his GP for suggesting it could be an inflamed appendix, and trying antibiotic treatment. When, after a second lot of antibiotics, the pain was worse than ever, at his GP's suggestion, Gijssels visited the emergency department at Leuven hospital. He has no good words for the consultant who he says interrupted a more junior doctor in the middle of going

through a list of questions, to ask him: "Do you play sport?" On hearing that Gijssels had been playing tennis the day before, he concluded that the problem was a muscle in his abdomen.

"I said: I've been playing tennis for years, I know what pain in my muscles feels like. And it couldn't have happened yesterday because I've been complaining about it for months." But Gijssels was sent home. "They didn't take me seriously. They didn't do anything. No scan, no X-ray."

Gijssels went back to his GP and told him that both his father and grandfather had died of colorectal cancer. It was almost true: they had both died of cancer. It did the trick, he was referred to an immediate colonoscopy, and that is how his cancer was diagnosed. You do what you have to do to tilt the odds in your favour.

### The right treatment centre

For patients trying to survive a cancer with a poor prognosis, finding a treatment centre that consistently delivers good patient outcomes is the single most important thing that could help them beat the odds. Unfortunately, says Gijssels, hospitals, the medical profession, health systems, don't like publishing that information.

In August 2018 he found information on the [zorgkwaliteit.be](http://zorgkwaliteit.be) (Care Quality) website that showed the five-year survival rates achieved for rectal cancer on named hospital basis, and revealed a difference between the worst and the best of 25 percentage points (62.7% vs 87.7%). Shortly afterwards, he says, the site completely changed, and

## Delivery of Care

such transparent data are no longer available.

Gijssels can see no acceptable reason for denying that information to people whose lives could depend on it. In common with patient advocates everywhere, he is arguing for treatment centres to publish their results, as an exercise in transparency but also quality improvement, and he is hopeful that the argument is beginning to gain some ground (see box *opposite*).

### The right diet

Nutrition is another area Gijssels believes patients can help their recovery chances. He sees himself as someone who always made an effort to eat healthily. “My cholesterol was too high, my sugar content in my blood was at the limit so I really looked at what I ate.” But no-one told him that a ‘healthy diet’ for his pre-diagnosis self might not be what his body needed when it was recovering from radical surgery, missing a chunk of colon, receiving chemotherapy and vomiting quite a bit. As a result, he lost 15 kilos over six months.

### No one told him that a ‘healthy diet’ for his pre-diagnosis self might not be what he needed while on treatment

Six in every 10 patients with digestive cancers suffer from cachexia, says Gijssels – like him, most of them will not have been given dietary advice, and like him,

they probably won’t know to ask. It matters, he says, not just because your body needs energy to start recovering its strength and fitness, but it can reduce the impact of the treatment. On the one hand, it can reduce tolerance to toxic effects of the chemotherapy, and thereby impact on adherence. On the other, studies show that the catabolic drivers that accompany cachexia also speed the elimination of some anti-cancer therapies, which has been shown to affect survival in some cancers (*Clin Cancer Res* 2018, 24:5841–49).

### The right exercise

Physical activity is another area where good advice and encouragement could help patients tilt the odds in their favour, says Gijssels. Its benefits to people recovering from cancer and cancer treatment have been well documented, but pain and exhaustion can make it hard to get started.

“Don’t overdo things... be very cautious... don’t lift heavy weights,” was the – very valuable – advice he was given on leaving hospital. As he points out, patients are more than happy to comply, “because it hurts”. But you do need to work to get back in shape, he says, “and that was never mentioned – there was no advice on how best to do that.” As luck would have it, Gijssels is married to an experienced physiotherapist, who helped him get on his feet and walk a few steps, in the first days home, and then encouraged his progress.

The severity of fatigue you can feel while on cancer treatment is something Gijssels says his pre-diagnosis self could not have imag-

ined – just the effort of taking a shower could leave him collapsed on the sofa in a sweat. But some days are better than others. After a few weeks, Gijssels was able to take a short walk on most days. As his fitness began to recover, these would typically last an hour or more, and they became a highpoint in his day.

Advice on walking or other forms of exercise is essential in helping patients assist their own recovery, says Gijssels. “Walking is the best,” he believes. “It is easy to do. Natural. Not exhausting. But it gives you back your lung capacity, your energy.”

### Love and friendship

Relationships are another deeply important area of life that can be put under strain – and improve or fall apart – as a result of going through cancer. Here again, talking things through, or getting advice, can help patients steer things in the right direction. It’s easy to get isolated, says Gijssels; friends become awkward, they don’t know what to say, they often just keep their distance. His advice is to reach out to them: “They will appreciate it. You will get energy from it. Don’t isolate yourself because you don’t hear from them anymore.”

He’s learnt to laugh at some of the insensitive things people can say. An example that would infuriate his wife was: “Oh colorectal cancer – my mother died of colorectal cancer.” “What they mean is ‘I can empathise with you,’” says Gijssels, “You have to accept that and be tolerant. People are not trained to deal with people who have cancer. They say the stupidest things.”

Gijssels found his daily walks were perfect settings for conversations that were able to touch on things and feelings that matter – with close friends, with his wife, with his children.

He’s not saying it is a blueprint for everybody, but that relationships can need attention just as much as nutrition and fitness, and helping patients access advice from professionals and from the collective experience of patients who have been through it before, can be invaluable.

The same can be said about the other aspects of life that cancer can disrupt, including your employment and financial stability, your sex life and physical intimacy, and countless others that will be so familiar to people who have been through the experience – and often entirely below the radar for those who have not.

### The best possible outcome

Van Cutsem and Gijssels both agree that there is no recipe for surviving cancer, and surviving it with your life intact. There are things you can do, however, to get the best chance of the best possible outcome. At the medical level, it’s about “and, and, and” – the right infrastructure, the most expert team members who work effectively together, the access to innovation, the personalisation...

At the patient level, it’s about recognising how much you can do to help your own diagnosis and recovery, and knowing where to go for help and advice.

At the health system level – and this is what Gijssels has been working on over the past couple of years – it is about ensuring that the two

## Finding a hospital that can tilt the odds in your favour

Belgium is by no means alone in denying citizens the opportunity to compare outcomes between different treatment centres. Very few countries do so.

- In Germany, the German Cancer Society, the DKZ, publishes comparative data on 31 quality indicators for colorectal cancer, as part of its certification and quality improvement scheme, but it does not name the treatment centres ([bit.ly/DKZ-CRC-indicators](http://bit.ly/DKZ-CRC-indicators)). Patients can therefore see how many centres achieve below – sometimes well below – the target rate of key indicators such as for revision surgery, postoperative mortality, liver metastasis resection rates, quality total mesorectal excision, testing for BRAF and RAS mutations... What they don’t know is whether the centre treating them is among the underperformers.

Some countries have begun to introduce greater transparency.

- In the UK, for instance, the Association of Coloproctology of Great Britain and Ireland publish data by hospital trust, giving data on quality indicators such as negative resection margins and hospital stay, and showing how mortality rates and readmissions by hospital and named surgeon, compare with those achieved by other hospitals and surgeons across the country. The data for Oxford University hospitals, for instance, can be found at [bit.ly/OxUniHosp-CRC-data](http://bit.ly/OxUniHosp-CRC-data).
- In the Netherlands, aggregated ‘medical quality’ data can be found using a scoring system of zero to five, for diseases of the stomach, colon and liver ([bit.ly/NL-qualitydata-CRC](http://bit.ly/NL-qualitydata-CRC)) on the website of the healthcare comparator [zorgkiezer.nl](http://zorgkiezer.nl)
- Gijssels also mentions a recent initiative, Progetto Contact, whereby some Italian hospitals are putting data on various indicators into the public domain – starting with heart failure, breast cancer, diabetes and hip replacements – as part of an accountability and quality improvement initiative ([progettocontact.com/](http://progettocontact.com/)).

sides work together. A new patient pathway guide in colorectal cancer and pancreatic cancer, designed as part of the Innovative Partnership for Action Against Cancer ([bit.ly/CRC-Patient-Pathway](http://bit.ly/CRC-Patient-Pathway)), states that after diagnosis patients should be referred to a disease-specific patient organisation, as these have the expertise and experience to orientate the patient in relation to all aspects of the disease and treat-

ment, and equip them to play an active role in their own treatment and care, to help them tilt the odds in their own favour.

*This article was published on the Cancer World website on 3 February 2022. To comment on or share the article go to [bit.ly/Beating-the-Odds](http://bit.ly/Beating-the-Odds)*

# Cancerworld

**Cancer World magazine** brings perspectives from across the cancer community – professionals, patient advocates, policy makers – to explore ways to improve the quality of care for cancer patients across Europe.

We help readers stay in touch with conversations happening beyond their own discipline and specialism.

Join the conversation: *cancerworld.net*

Scan the QR code to subscribe to the newsletter. **It's free.**



Cancer World  
is funded by

Sharing Progress  
in Cancer Care



# Lung cancer screening

## *Time to act on the evidence*

Targeted screening could hugely improve the chances for lung cancers to be picked up early enough to be cured. Yet lung cancer screening remains a low priority in Europe. **Janet Fricker** looks at the evidence supporting screening, and at the questions regions and countries need to address to develop screening programmes that work for their populations and health systems.

“It’s extraordinary that screening for the biggest cancer killer is not available in most of Europe,” says Anne Marie Baird, President of Lung Cancer Europe (LuCE). “Lung cancer causes more deaths in Europe than breast, colorectal and cervical cancers combined, yet for these cancers, population based screening programmes are readily available.”

Delays in implementing screening for lung cancer have resulted in the loss of many lives, she adds, “Mortality from lung cancer is huge in Europe, accounting for 28% of all cancer deaths. In 2018, 470,000 people in the EU were diagnosed with lung cancer and around 338,000 died from it... These aren’t just statistics, each patient who dies represents an individual

loss to their families and friends.”

Lung cancer is a particularly fatal malignancy because it is so hard to detect in its early stages. Almost three quarters of lung cancer patients present with late-stage disease, where treatments have little effect on mortality. While more than seven in ten people diagnosed with early-stage lung cancer are still alive five years on, for those diagnosed at

a late stage that figure is fewer than one in ten. That explains the importance of an effective screening programme, says John Field, Director of Research at the Roy Castle Lung Cancer Programme at the University of Liverpool, UK. “The overriding objective of lung cancer screening is to shift timing of diagnosis to an earlier point so that disease is localised to the lung allowing surgery or stereotactic radiotherapy to eradicate the cancer.”

With publication of the results of the NELSON trial in January 2020 (*NEJM* 2020, 382:503–513), evidence for the benefit of lung cancer screening with low dose computed tomography (LDCT) is now considered indisputable. “NELSON put paid to objections that lung screening had not shown benefits in a large European trial,” explains Field.

In this Dutch–Belgian trial, nearly 16,000 individuals considered at high risk for lung cancer underwent either four rounds of LDCT or no screening. Results at 10 years show participants in the screening group had a 26% reduction in death from lung cancer compared with those in the control group.

These positive results support the findings of the 2011 US-based National Lung Cancer Screening Trial (NLST), which show a 20% reduction in cancer mortality for those screened with three rounds of annual LDCT screening versus chest X-ray (*NEJM* 2011, 365:395–409). The NLST study is now considered to have underestimated benefits, as all participants had a scan of some kind (either X-ray or LDCT). Other smaller European-based studies demonstrating survival benefits for lung cancer screening include the Multicentre Italian Lung Detection

(MILD) trial, the German Lung Cancer Screening Intervention Trial (LUSI), and the UK Lung Cancer Screening Trial (UKLS).

In 2013, as a direct result of the US NLST trial, the US Preventative Services Task Force (USPSTF) recommended current or former smokers meeting defined criteria should be offered annual screening. The latest US guidance, which was updated in 2021, and is followed by health insurance groups and Medicare and Medicaid, is that people aged 50 or over with a smoking history of 20 pack years (i.e. who have smoked one pack a day for 20 years) should be offered annual LDCT scans ([bit.ly/US-LungScreening-Guidance](https://www.uspreventiveservicestaskforce.org/US-LungScreening-Guidance)).

### Situation across Europe

Europe has proved altogether more wary of lung cancer screening, with countries adopting different attitudes ranging from genuine interest to downright hostility. In October 2020 Croatia became the first country in Europe to launch a national lung cancer screening programme for all eligible citizens. In contrast, countries like the UK, Poland and France have chosen instead to start by setting up pilot schemes at a few centres first, with a view to tweaking the service as they go along, and performing analyses demonstrating cost-effectiveness to convince payers. Other countries, such as Spain, have no pilot initiatives planned, with lung cancer screening available only on a private basis or as part of a European clinical trial.

Referring to Croatia’s decision to offer a national service from the outset, Ante Marušić, a thoracic radiologist from University Hospital Centre, Zagreb, says the small size of

the country was a factor. “While we knew it would be impossible to foresee everything from the start, as Croatia has just four million people and 16 screening centres we felt it would be feasible to adapt the service as we went along.”

Another key factor in the decision to launch straight into the real thing, adds Marušić, was the importance of providing equal access to all eligible people. “We waited 15 years for the results of NELSON and felt it would be unfair to make people wait any longer for widespread screening.”

With a population of around 68 million, introducing lung cancer screening into the UK represents an altogether more complex undertaking, says Field. “To deliver a full national screening service there are multiple aspects that need to be well integrated with each other. Running pilots allows countries to design screening programmes that are both appropriate and cost-effective for their own particular health systems and evolve the service gradually.”

Witold Rzyman, a thoracic surgeon from the Medical University of Gdansk, Poland, agrees that countries need to run their own pilots and cannot just rely on information obtained from pilots elsewhere. “Each country has different healthcare systems, making it necessary to undertake individual cost-effectiveness studies.”

As Field points out, differences in culture can be as important as differences in health systems, when it comes to designing an effective lung screening service. “For optimum uptake you need to consider different ways of approaching people to take part in screening, whether

they respond best to receiving letters or telephone calls, and the best terminology to get across concepts of risk to that particular population.” This can make cross-border collaborations challenging.

In Europe, the only cross-border initiative is the 4-IN-THE-LUNG RUN (4ITLR) study, funded by the European Horizon 2020 programme, which aims to determine whether screening intervals of two years after a negative baseline scan are as effective as annual screening (*Trans Lung Cancer Res* 2021, 10:1052–63). Results of 4ITLR, which plans to screen 26,000 people at sites in the Netherlands, Germany, Spain, Italy and France, will have important implications for containing costs, thereby making screening more attractive to payers.

There are fundamental differences between trials and pilots, explains Michael Davies, who works with Field at the University of Liverpool. “Trials are designed to answer specific questions, whereas pilots are used to demonstrate whether you can achieve good results in the real world when you upscale screening to provide a service.”

The wide-ranging topics that need to be addressed include: Who should be eligible for screening? What should the screening intervals be? How to incorporate smoking cessation? How to deal with incidental findings? – as well as getting the patient information literature right, and establishing central registries. Other challenges include assembling multidisciplinary teams to discuss suspicious results, which would need to include all relevant specialities, including pulmonologists, thoracic surgeons, radiolo-

gists, pathologists and lung cancer nurses. From the radiological perspective, organisation gets even more complicated with the need to standardise diagnostic criteria for screen-detected nodules and implement quality assurance to ensure that CT images are undertaken, recorded and reported to uniform high standards. Training programmes are also needed for radiologists to ensure a suitably trained workforce is in place to deliver the service.

### Balancing benefits against risks

The scale of infrastructure investment involved requires considerable commitment, which may prove a step too far for some European countries, which historically have a mistrust of screening. It should never be forgotten that screening carries risks as well as benefits. Valid concerns include: exposing healthy people to radiation (although the advent of LDCT reduced radiation doses 10 fold); the high incidence of false-positives; the anxiety and stress that can accompany screening; and the risk that people can be exposed to unnecessary procedures such as biopsy, bronchoscopy and surgery. “Caution is needed because lung cancer biopsies are invasive and expose people to complications of pneumothorax. This poses a completely different level of risk from say a breast biopsy,” says Helmut Prosch, a thoracic radiologist from the University of Vienna, Austria. Even when malignancy is accurately detected, there are concerns that, left to its own devices, the cancer might not have gone on to cause symptoms and limit life expectancy.

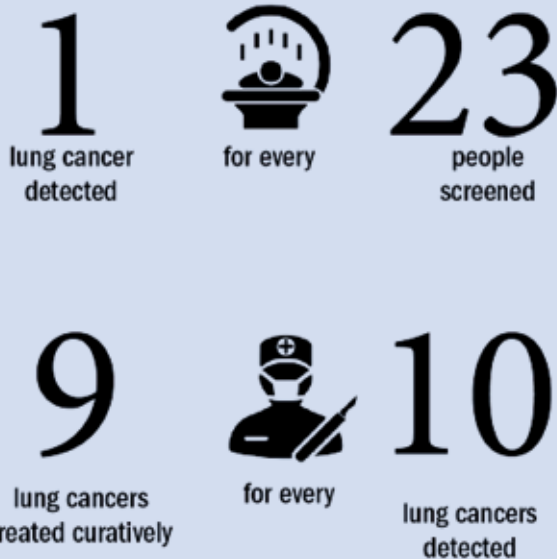
A number of research developments are taking place to boost the likelihood of benefit and lower risk associated with lung cancer screening.

### Targeted screening

One approach to limiting risk is to focus screening on individuals at greatest risk of developing cancer. While the NELSON and NLST studies used criteria based on the number of years participants had smoked (known as pack years), the UKLS study incorporated the Liverpool Lung Project (LLP) risk prediction model 5. (*Cancer Prev Res (Phila)* 2015, 8: 570–75). The model had been generated by Field and colleagues, who compared data from 579 lung cancer cases and 1,157 age- and sex-matched controls. From a Cox proportional hazards model, the team found lung cancer risk factors included age, sex, smoking duration, history of pneumonia, non-lung cancer, asbestos exposure and family history of lung cancer. “Incorporating the model into screening offers the advantage of minimising unnecessary interventions for those at lower risk and providing a more cost-effective programme,” explains Field.

Another risk model used is the Prostate, Lung Colorectal, and Ovarian (PLCO) programme, (*JNCI* 2011, 103:1058–68) which has a slightly different emphasis, including socio-economic status and body mass index. The NHS England Targeted Lung Health Check Programme ([bit.ly/UK-NHS-LungHealthChecks](http://bit.ly/UK-NHS-LungHealthChecks)) is incorporating both the LLP and PLCO risk models in their pilot, to explore which is the most effective.

## Manchester Lung Health Check pilot statistics



Source: Crosbie PA et al (2019) Second round results from the Manchester ‘Lung Health Check’ community-based targeted lung cancer screening pilot. *Thorax* 74:700–704

“Whatever model is used, it needs to be remembered that risks for developing lung cancer vary over time, due to changes in risk factors, like age. Consequently people who have been deemed ineligible may become eligible, underlying the importance of regular risk assessments,” says Field.

### Engaging the at-risk population

For screening services to be effective they need to engage target populations. The fundamental importance of understanding your target audience is clear from the salutary experience of the uptake of lung screening in the US. “Despite

having national screening programmes endorsed by their medical societies, only around 5% of high-risk Americans took up the opportunity of lung screening,” says Field.

One major obstacle that needs to be overcome is deep-rooted feelings of shame around smoking. “Smokers assimilate the stigma of lung cancer and are afraid to come forward for fear of being judged,” says Luis Seijo, a pulmonologist from the Universidad de Navarra, Madrid. “In asymptomatic healthy people, there’s also a strong instinct to avoid screening due to fears of receiving a life-threatening diagnosis,” he adds.

Simply changing the name to the more neutral term ‘Lung Health Check’ was sufficient to diminish

hesitancy, investigators in the UKLS study discovered. “Dissociating screening from the word ‘cancer’ really helps to frame screening in a more positive light,” Seijo agrees.

Lung Health Checks become as good as their name if the appointment also screens for other tobacco-related diseases, such as chronic obstructive pulmonary disease (COPD) and coronary artery disease. These inclusions again deliver additional benefits of making screening more cost-effective for health services.

Another major challenge is how to reach people in more deprived areas, which is where lung cancer is most prevalent says the thoracic radiologist from Vienna, Prosch. “The problem we perpetually face is that it’s the most affluent members of society who put themselves forward for screening, yet these are the people with least risk of lung cancer.”

Phil Crosbie, a respiratory medicine consultant from Wythenshawe Hospital, Manchester, argues that the experience of Manchester’s ‘Lung Health Check’ pilot (*Thorax* 2019, 74:700–704) shows it is perfectly feasible to reach deprived populations so long as the service is designed appropriately. “Instead of waiting for people to come to us in hospital clinics we designed our service to be as convenient as possible, by taking our LDCT scanners out into the community,” explains Crosbie. “We offered one-stop lung health checks in vans in supermarket car parks, located near to where people live with the added advantage of providing plenty of parking.”

For the initiative, people aged between 55 and 74 years from 14 GP practices in deprived areas were sent letters inviting them for screen-



ing if they smoked. The assessment, conducted by lung specialist nurses, involved a discussion about symptoms, a breathing test (spirometry), and calculation of individual cancer risk. Anyone found to be at high risk of lung cancer was then invited to have an immediate LDCT scan in a mobile scanner.

Results show that one lung cancer was detected for every 23 people who underwent two rounds of LDCT scans. “This level was higher than any of the large international trials, showing additional benefits can be achieved by targeting deprived populations,” says Crosbie.

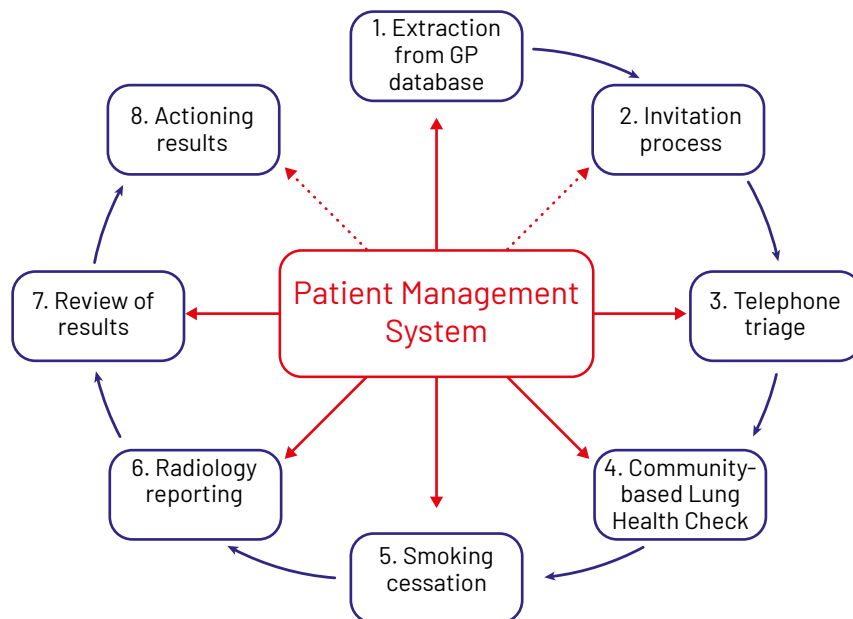
The study also showed almost eight out of ten cancers picked up this way were stage 1 (79%), and almost nine out of ten people diagnosed with lung cancer (89%) were offered curative treatment. The Manchester data proved so inspirational that NHS England announced that they will be operating scanning trucks from supermarket car parks in all their 20 screening pilots.

Aside from the compassionate aspect of saving more people, increasing the yield of lung cancer identification undoubtedly shifts the cost-effectiveness dial positively in the right direction, making screening a more attractive economical prospect for health care providers.

### A teachable moment

Another innovation with potential to both save more lives and make initiatives more cost effective is applying smoking cessation in tandem with screening. Screening offers a ‘teachable moment’, providing an opportunity to motivate individuals to adopt risk-reducing health behaviours. “Screening programmes

## Lung Health Check patient management system



Source: Targeted Lung Health Checks Programme Appendix A. Published online by Luton NHS Clinical Commissioning Group, <https://bit.ly/LungHealthCheckPatientManagement>

need to start supporting smokers properly to quit, not blaming them for their habit,” says Marie-Pierre Revel, a radiologist from Cochin University Hospital, Paris. “We need to research incorporating smoking cessation properly and realise that smoking is an extreme addiction that smokers don’t do on a whim but because they have no choice.”

Results around smoking cessation have proved mixed. Data from the UKLS trial (*Health Technol Assess* 2016, 20(40)) shows enrolment in lung cancer screening programmes had an overall positive effect on smoking cessation, especially for those requiring additional clinical investigations. However, neither the NELSON study nor the Danish Lung Cancer Screening trial found differences in smoking cessation between screening and control groups.

Receiving a normal scan result, it has been suggested, may induce a false sense of security in participants who feel invincible against the harmful effects of smoking.

“But none of these studies had on-site smoking cessation interventions bundled together with screening,” says Matthew Callister, a respiratory medicine consultant from Leeds Teaching Hospital, UK. “On the whole, participants were just given cards directing them to local smoking cessation services. In reality it’s all too easy for people to lose the card or become too busy with other things, so the proportion making contact is likely to be small.”

To increase uptake, the Yorkshire Enhanced Stop Smoking (YESS) study, running in Leeds, is evaluating adding a personalised smoking cessation intervention

to lung cancer screening ([bit.ly/YESS-study](https://bit.ly/YESS-study)). In this study, funded by Yorkshire Cancer Research, participants who are still smoking are offered access to smoking cessation counsellors on the screening van immediately prior to undergoing scans. “It’s opt out, with the smoking cessation room just metres from the scanner, making it easy for people to engage with the service,” explains Callister, adding vans have been specially configured to make space for private smoking cessation rooms.

### **“Screening programmes need to start supporting smokers properly to quit, not blaming them for their habit”**

The smoking cessation programme, provided for four weeks, includes behavioural support over the telephone, nicotine replacement therapy, pharmacotherapy, and/or commercially available e-cigarettes. Then, after four weeks, participants who are happy to take part are randomised to either continue best practice of ongoing support for a further eight weeks or get best practice plus an individualised report on their heart and lung damage that has occurred as a direct result of smoking. “We give them a pamphlet with images from CT scans of their own heart highlighting areas of coronary calcification, and their lungs highlighting areas of damage resulting from emphysema,” says Callister (see [fig.2, \*BMJ Open\*, 2020, 10:e037086](https://doi.org/10.1136/bmjopen-2020-027086)). “The concept is a strong visual mes-

sage – if you stop smoking you’ll prevent other areas of your lung from being similarly damaged.”

### **The case for a concerted European approach**

As the technology and evidence for population lung cancer screening have developed, pilot programmes were started in a number of European countries, some of which were covered by *Cancer World* in January 2022 ([bit.ly/CW-LungScreening-TurningPoint](https://bit.ly/CW-LungScreening-TurningPoint)).

Some of these were quite severely hit by the Covid-19 pandemic. In the US, where lung screening has been widely available for a number of years, a recent study showed annual LDCT screening had dropped to almost one quarter of the levels seen in pre-Covid times.

The absence of any recommendation in favour of lung cancer screening in Europe’s Beating Cancer Plan was seen by many as a missed opportunity. The plan, published February 2021, recommended that EU member states ensure that nine in ten of those eligible for breast, cervical and colon screening receive it by 2025. The issue of whether additional cancers, such as lung or prostate, should be screened for, however, was put on hold pending a review of the evidence by the European Commission’s Group of Chief Scientific Advisors (GCSA).

That Scientific Opinion, published on 2 March 2022 ([bit.ly/SAPEA-ScreeningUpdate](https://bit.ly/SAPEA-ScreeningUpdate)), recommends that lung and prostate cancer should both be added to the screening programmes that the European Commission recommends Member States to implement. The Commission has indicated this it will take

this advice on board in drafting proposals to update the 2003 Council Recommendation on cancer screening, which are due to be put forward for approval by the end of 2022 ([bit.ly/EC-Screening-Statement](https://bit.ly/EC-Screening-Statement)).

For the lung cancer community in general, and advocates like Anne Marie Baird of Lung Cancer Europe, such a formal European recommendation cannot come too soon. Currently only a small minority of countries are running pilot schemes, while many other are holding back, either because lung cancer is not seen as a policy priority or because of scepticism hanging over from the early trials of lung cancer screening. The hope is that the strong signal coming from the rigorous objective assessment of the evidence by the Commissions group of scientific advisors will galvanise countries into action, and make 2022 a turning point for lung cancer in Europe.

*The opening image shows participants in the NHS England Lung Health Check pilot schemes, which offer low-dose CT scans to people deemed to be at high risk of lung cancer. Pictured is Bill Simpson, who was diagnosed with early stage lung cancer in October 2017 via a screening pilot in Strelley, Nottingham, and was successfully treated. With him are members of the Citycare respiratory team, Joanne Adkin and Emma Waring, together with Safiy Karim, Clinical Commissioning Group (CCG) Cancer Lead for Nottingham City.*

*This article was published on the Cancer World website on 3 February 2022, [bit.ly/CW-LungScreening-Evidence](https://bit.ly/CW-LungScreening-Evidence). It has been updated to take account of developments relating to European policy.*



## When We Stand Together, Cancer Stands No Chance

There are few diseases that trigger quite the breadth and depth of emotions as cancer. A diagnosis can prompt everything from fear and anger, to stress, sadness, and loneliness. Some of us have experienced these first-hand. Others have watched loved ones reeling from one sensation to the next. What we all share, however, is a profound conviction that we must unite forces against this unforgiving disease. Working together is our only path to success, as working in isolation leaves us vulnerable to the continued spread of disease and countless more lives lost. If we are not to fail in reducing cancer deaths, we must become fellow warriors in the fight against it.

Many of us are patients, survivors, advocates, healthcare providers, policy makers and more. We each have a vital role to play, we all bring our different perspectives to the issue at hand, but we each share a common ambition: a world free of cancer, once and for all.

With years of my life spent providing care to cancer patients, I now feel honoured to be working in partnership with you as the new President of the European Cancer Organisation (ECO) – the first with a background in cancer nursing.

The spirit of patient-centred collaboration, equality and transparency as core values of ECO, are always embodied within the organisation's activities. Everything we do, we do together. We recognise the value of your input and support. It has enhanced and expanded so many of our initiatives, and the results

were readily apparent during the annual European Cancer Summit.

Last November, our hybrid event focused on critical aspects of the cancer care continuum within 12 sessions, inspired by ECO's Focused Topic Networks, Europe's Beating Cancer Plan and the EU Mission on Cancer.

The Summit theme, From Plans to Action, was well timed as Stella Kyriakides, European Commissioner for Health and Food Safety, officially announced the release of the implementation roadmap for Europe's Beating Cancer Plan during her address.

Building upon the momentum of fresh publications, several outputs from our Focused Topic Networks were highlighted during the sessions, these included our latest papers and projects on improving access to and uptake of screening, HPV vaccination, delivering the promise of digital for cancer care and the Time To Act campaign's 'Data Navigator'.

The European Cancer Organisation's many new efforts, including the European Cancer Summit 2021 Report and Declaration, as well as the essential requirements for quality pancreatic cancer care published shortly after the Summit, are all available on our website at [europeancancer.org](http://europeancancer.org).

We did this together and we will continue to do so with more intensity. There is so much more we can do when we are united and committed.



# Tailored exercise *a key element in personalised treatments and prevention*

The health benefits of exercise have been known about for millennia. Research shows its impact on multiple types of cancer, across prevention, treatment and survivorship settings. So why are oncologists, and the wider medical community missing opportunities to help patients help themselves, asks **Adriana Albini**, and what is needed to improve efforts to promote more physically active lifestyles?

**T**he expression ‘couch potato’ conjures up images of a world-wise, self-mocking type who leaves the rat-race to others, while happily cuddling up in front of

the TV with snacks and drinks. Yet the consequences of such a lifestyle are dire. Physical inactivity is one of the leading causes of preventable death worldwide, triggering or exac-

erbating conditions such as heart attack, stroke, hypertension, depression, obesity, osteoporosis, respiratory problems, type 2 diabetes, sleep apnoea, and many forms of cancer.

Physical activity has an important role in cancer prevention for various reasons. Biologically, exercise affects systemic functions that lower the risk of many types of cancer, e.g. insulin/glucose metabolism, immune function, inflammation and sex hormones (CA *Cancer J Clin* 2020, 70:245–71). Inhibiting cancer cell proliferation and inducing apoptosis and regulating metabolism and the immune environment are the main mechanisms of the benefits of physical exercise in cancer prevention and treatment (*J Sport Health Sci* 2021, 10:201–10).

Its association with reduced risks of colon and breast cancer has been known for some time. In recent years, however, the range of cancers for which exercise regimes have shown to have a promising effect on prevention has been extended to more than 13 types, including endometrial, bladder, oesophageal adenocarcinoma, kidney, and gastric. In association with diet, physical exercise helps maintain a healthy weight. According to the European Association for the Study of Obesity, between 7% and 41% of certain cancer burdens are attributable to overweight and obesity. Exercising also has the inherent advantage of reducing sedentary time.

We humans are built to be active. But establishing the intensity, duration, and type of activity most effective to promote health is quite complicated. We often talk about exercise, physical activity, fitness, and sport as if they were interchangeable terms. They are not, though they can overlap or complement one another to result in the right level of exertion.

The WHO's definition of 'physical activity' is "any bodily movement produced by skeletal muscles

that requires energy expenditure". In other words, any movement, from walking to gardening, cleaning, redecorating, etc. 'Exercise', on the other hand, is movement that is planned, structured, and repetitive. It builds and maintains physical fitness.

The main components of fitness are aerobic endurance, muscular endurance, strength, and flexibility. Balance, power, speed, agility, body composition, coordination and reaction time are also maintained and improved through physical exercise. Sport shares most of the benefits of exercise, with the extra bonus of forming social relationships in the case of team sports. It is often of a competitive nature, however, which can potentially push participants beyond their limits.

### **Exercise regimes have shown to have a promising effect on prevention in more than 13 types of cancer**

Exercise induces a response from the body, which works to maintain an appropriate level of homeostasis for the increased demand in physical, metabolic, respiratory, and cardiovascular effort. Time, consistency, and progression are fundamental to 'convince' the body that it needs to adapt to increased demand. Paradoxically, someone can be both sedentary and active, for instance, if after a day at their desk they cycle or go to gym classes, while a bartender can be non-sedentary, yet physically inactive, if after a day standing on

their feet they go home and rest until the following day.

### **The history of exercise and health**

"Exercise is a voluntary movement that induces deep, frequent breathing. Its proper, moderate use prevents physical illnesses." This quote could come from any contemporary health publication. In fact it comes from Ibn Sina, commonly known in the West as Avicenna, a Persian polymath who lived at the dawn of the first millennium, and wrote more than four hundred books, including at least 40 medical texts, drawing from the knowledge of Indian and Persian medicine, in addition to the Greek and Roman medical literature.

It is uncertain when the association between physical exercise and preventing illness was first made. Evidence of competitive and leisure activities such as swimming, dancing and ball games dates back many thousands of years. Yoga has been around for at least 5,000 years. Our remote and more recent ancestors built muscle tone, endurance, flexibility, and stealth through physical training and war-related games, such as running, fighting, marching, jumping and javelin throwing. The purpose of training could be military, competitive, recreational, or even aesthetic, as in achieving a well-sculpted body. Physical training was usually the domain of a dedicated instructor, not a medical doctor.

The first physician known to prescribe physical exercise for health was not, as is often assumed, Hippocrates, who lived in the 4th century BCE and is known as the 'father of medicine'. It was Sushruta, an Indian doctor and surgeon, believed to have

## Delivery of Care

lived during the 6th century BCE. In his vast compendium, the *Sushruta Samhita*, he repeatedly advocates moderate exercise to maintain or re-establish health, seen as a balance of humours. Because needs vary according to personal history, condition and circumstances, exercise needs be tailored accordingly. Excessive exhaustion is counterproductive.

### **Hippocrates believed a balanced prescription of exercise should be based on the patient's condition, food intake, body mass, age and environment**

In Greece, Hippocrates was a strong promoter of 'regimen', that is, of combining diet and exercise for health. "Eating alone", he wrote, "will not keep a man well, he must also take exercise, because food and exercise, while possessing opposite qualities, yet work together to produce health." (*On Regimen* I.ii. 22). On similar lines to Sushruta, Hippocrates believed that a good physician must balance the prescription of exercise based on the patient's condition, food intake, body mass, age, environment and so on.

As the study of medicine was not canonised in Ancient Greece, there were many schools of thought among physicians, and much bickering and slander, but overall, the focus was similar: prevention, in the form of diet, exercise and hygiene, was favoured over cure, and cure over surgery – not surprisingly, perhaps, when we think of the 'heroic' nature of some of the treatments.

But it was Galen in the 1st century CE who exercised the most lasting influence on Western medicine. His theory of what became known as the 'non-naturals' survived in European medical thought for nearly fifteen centuries. The 'non-naturals' referred to things that are not innate, but over which humans could and should have control: air, food and drink, rest and exercise, sleep and waking, excretions and retentions, and emotional affections. Galen also saw exercise as vital to well-being, but he stressed the need for moderation in the intensity and duration – do enough, but do not overdo it.

### **The meaning of moderation, then and now**

Herodicus was a Greek physician in the 5th century BCE who, even before Hippocrates, stressed the importance of exercise for health. If we are to believe Plato (who was apparently not a great fan), Herodicus' idea of moderate exercise was walking from Athens to Megara and back – a trek of about 20 miles. "Herodicus, being a trainer, and himself of a sickly constitution, by a combination of training and doctoring found a way of torturing first and chiefly himself, and secondly the rest of the world." (Plato's *Republic* III, 406). Aristotle was not that impressed either: "Bodily excellence is health, and of such a kind that when exercising the body, we are free from sickness; for many are healthy in the way Herodicus is said to have been, whom no one would consider happy in the matter of health, because they are obliged to abstain from all or nearly all human enjoyments," (Aristotle, *Rhetoric*, book 1, chapter 5). In his treatise *On Exer-*

*cise with a Small Ball*, Galen recommends the small ball as the best form of exercise for health, as it is a total workout, it is portable, and its intensity can be adapted as required. If the small ball is to be identified with the *harpastum*, it was a game similar to rugby... not exactly the gentlest of activities.

From the 17th century, when major discoveries in the field of medical science brought the development of drugs and treatments that were progressively more efficient and less invasive, scientific interest shifted from prevention to cure, and exercise gradually reverted to the domain of trainers and physical education instructors. The focus also became more on sports and less on moderate exercise.

The ever-increasing speed of technological development in the 20th and 21st centuries progressively lifted the 'burden' of physical exertion, reducing the need for movement, and sowing the seeds of the 'couch potato pandemic'. With chronic non-communicable diseases now topping the mortality charts, the medical community is rediscovering the need to focus more on prevention, balance, moderate diet and exercise.

To promote healthy changes in our bodies (and minds) we need to do regular physical exercise, with quantifiable intensity and duration. Because the results are not immediate and the activities are not necessarily that gratifying or interesting *per se*, adherence is an issue. The good intentions are there, but discouragement sets in quickly, especially if exercise is seen as something we are obliged to do, rather than a pleasurable activity. Attendance at the gym typically falls dramatically after the first few

months, and those who drop out earliest are often the ones who most need to improve their fitness.

In a gym, exercise class, or outdoor structured physical activity, individuals with low levels of fitness might feel physical and mental discomfort, due to early onset of breathlessness, fatigue, fear of failure, and body image issues. Introduction to healthier lifestyles need be gradual and individually tailored.

To test, prescribe and evaluate exercise, a unit of energy expenditure was agreed upon – the metabolic equivalent of task (MET) – which, despite limitations, provides a useful and versatile way to measure activity intensity. 1 MET is defined as the energy expended by a subject at rest (resting metabolic rate, RMR) and is roughly equal to 1 kilocalorie per kilogram of body weight per hour. There are standard parameters of recommended intensity available, and charts calculating the energy expenditures of everything from walking to surfing, painting walls, and mowing lawns. This allows for a move away from a ‘one size fits all’ definition of ‘moderate exercise’ towards tailoring of physical activity regimes that take into account an individual’s condition, environment, interests and needs.

### From guidelines to personalised exercise interventions

The benefits of physical exercise are not limited to prevention. Its critical contribution to the treatment of diseases has been known for a long time: it improves cardiovascular and respiratory efficiency, muscular strength, balance, reflexes, and so on. It also reduces fatigue, depression, and low self-

esteem. Yet, until recently, the value of physical activity in people living with and beyond cancer was poorly investigated. One reason could be that cancer used to be associated with poor outcomes, and it was deemed unlikely that patients who were undergoing or had completed intensive treatments, would be able to engage in an exercise routine. The usual medical advice was to rest and avoid strenuous activity. Some clinicians may still be giving that advice today.

### The medical community is rediscovering the need to focus more on prevention, balance, moderate diet and exercise

But the scenario has now changed drastically, due to the progress made in cancer research, early detection, and newer treatments. According to the *Cancer Atlas*, in 2018 there were almost 44 million cancer survivors diagnosed within the previous five years ([bit.ly/CancerAtlas-Burden](http://bit.ly/CancerAtlas-Burden)). Together with the increase in survival rates and longer life expectancy, the field of exercise oncology has also grown. There is now strong evidence that exercise provides benefits in quality of life and muscular and aerobic fitness for those living with and beyond cancer. It may also reduce the risk of cancer mortality and recurrence, as it helps to counteract some side effects of treatment, such as cardiotoxicity, and can reduce the sensation of fatigue and nausea, thus allowing for higher treatment completion rates. Further-

more, improved fitness has been associated with better surgical outcomes, and less complications and morbidity. Exercise may contribute to reducing inflammation and to building a stronger immune system. It is also believed to have a role in preventing metastases, as it alters the microenvironments in the body where metastatic cancer cells may be dormant.

It is now widely recommended that cancer survivors avoid inactivity and engage in regular exercise. Several cancer and sports organisations have endorsed exercise guidelines, including the American Cancer Society, the National Comprehensive Cancer Network, the American Society of Clinical Oncology, the European Society for Medical Oncology (ESMO), the American College of Sports Medicine, Exercise and Sports Science Australia, and the British Association of Sport and Exercise Science.

However, these guidelines tend to be rather generic, such as those published in the ESMO Handbook on Rehabilitation Issues During Cancer Treatment and Follow-Up, which say, “Adult cancer survivors are advised to engage in either at least 150 minutes per week of moderate intensity or 75 minutes per week of vigorous intensity aerobic physical activity, or an equivalent combination of both. Muscle-strengthening activities involving all major muscle groups are recommended at least two sessions per week,” ([bit.ly/ESMO-RehabHandbook](http://bit.ly/ESMO-RehabHandbook)).

More research is needed to develop physical activity programmes that work best for different types and grades of cancer (*J Sport Health Sci* 2021, 10:201–10). These should also take into account

## Delivery of Care

the effects of the different treatments undertaken, and differences in patients' medical history, circumstances, and personal tastes. They would also need to address the many obstacles to widespread and sustained adherence. A 2021 paper published in *BMC Cancer* (vol 21, article 643) highlighted the need for robust measurement and reporting of implementation outcomes to help to identify what strategies are essential for successful implementation of exercise interventions.

Thankfully, the days of compulsory Lycra fitness gear and aerobic exhaustion have been largely consigned to history, along with prescriptions to walk from Athens to Megara. We can all do something to become fitter and healthier. Even the act of standing up as often as possible from a resting position on a couch or chair makes a difference.

Fitness professionals need to be acquainted with the patient's condition, symptoms, and side effects of treatments, to evaluate exercise tolerance and prescribe a safe and effective exercise programme. But the most important change has to start within the medical community. The correlation between physical exercise and carcinogenesis is still too often overlooked by oncology teams and other health professionals, with the result that exercise interventions are not routinely provided to people who have been diagnosed with cancer. This is particularly the case in advanced cancer settings, but it also holds true in early cancer settings, where there may be opportunities to help prevent secondary neoplasms, and also in the wider setting of cancer prevention.

Physicians should prioritise encouraging people, and specifically

cancer patients and survivors, to be active, test their fitness levels, and help them build, or refer them to, exercise programmes, possibly also combined with dietary advice.

Making a difference at a societal level, however, will require public, private and community organisations to work together to create structures, initiatives and environmental changes to provide safe, enjoyable, and accessible opportunities for physical activity for everyone, regardless of their economic and social condition.

*With the contribution of Francesca Albini*

*This article was published on the Cancer World website on 14 July 2021. To comment on or share the article go to [bit.ly/CW-TailoredExercise](https://bit.ly/CW-TailoredExercise).*

UPDATES ON DIAGNOSTIC AND TREATMENT APPROACHES

OVERVIEW OF THE LATEST ADVANCES IN LUNG CANCER

CLINICAL CASE DISCUSSIONS

1-3 SEPTEMBER 2022  
VODICE - CROATIA

**Eastern Europe Refresher Course  
on Lung Cancer**

40 years European School of Oncology

ES CO

EE Eastern European Programme

APPLICATION DEADLINE  
**1 JUNE 2022**

[www.ESO.net](http://www.ESO.net)



# Harnessing data for better cancer care



A policy report by All.Can

For All.Can, efficient cancer care delivers the best possible health outcomes using the human, financial, infrastructural and technological resources available, with a focus on what really matters to patients and society.




A global, nonprofit and multi-stakeholder initiative launched in 2016, All.Can strives to inform and generate political and public engagement on the need to improve the efficiency of cancer care to make equitable, high-quality care a reality for everyone affected by cancer, while contributing to health systems' overall sustainability.




To be efficient means to learn. Efficient healthcare systems must be resilient and adaptive in an ever-evolving world if they are to deliver the best possible health outcomes for cancer patients, particularly in the wake of the COVID-19 pandemic. Collecting robust data, integrating them into clinical care, and using them to draw meaningful insights to guide decision-making is vital to achieve this goal.



"Harnessing data for better cancer care" is All.Can's latest policy report offering policymakers, care providers, patients, and decision-makers a forward-looking view of how to ensure that high-quality health data are systematically collected and used to improve care and patient outcomes across the entire cancer care continuum.

Download the report and find out more about All.Can via [www.bit.ly/allcanData](http://www.bit.ly/allcanData)

 [www.all-can.org](http://www.all-can.org)  
 [@AllCanGroup](https://twitter.com/AllCanGroup)  
 [@All-Can](https://www.linkedin.com/company/all-can)

 [secretariat@all-can.org](mailto:secretariat@all-can.org)  
 [@AllCanGroup](https://www.facebook.com/AllCanGroup)  
 AllCan International



Changing cancer care together



# Trust me: I'm a surgical oncologist!

Cancer patients need confidence that their surgeon understands cancer and all treatment options, as well as having technical expertise in the often complex procedure they will be performing. Training and certification should play a central role in ensuring high standards, but getting agreement on a harmonised approach in Europe faces obstacles, as **Marc Beishon** reports.

**S**urgery has been the mainstay for treating solid tumours since the dawn of cancer treatment, and recent decades

have seen a huge increase in the complexity and multidisciplinary demands of carrying out cancer operations. So it can come as a sur-

prise to hear that, in most countries, anyone who qualifies as a surgeon can take on cancer patients.

“Surgical oncology as a dis-

cipline doesn't exist in most of Europe," says Lynda Wyld, a British breast surgeon and someone closely involved with developing surgical breast oncology standards. "Surgeons are accredited in categories such as general, thoracic, orthopaedic and plastic, and there is no mention of whether that includes cancer," says Wyld, who is a consultant breast surgeon in Doncaster and professor of surgical oncology at the University of Sheffield. "There isn't such a person as a cancer surgeon in most countries in Europe."

Of course, there are comprehensive cancer centres at which surgeons are often exclusively dedicated to operating on cancer patients within multidisciplinary teams (MDTs), and a very few countries do recognise surgical oncologists. A survey by the European Society of Surgical Oncology in 2018 found just four such countries – the Netherlands, Ireland, Poland and Turkey ([bit.ly/ESSO-Survey](http://bit.ly/ESSO-Survey)).

There are training curricula for some specialists, such as gynaecological oncologists in the UK ([bit.ly/RCOG-CoreCurriculum](http://bit.ly/RCOG-CoreCurriculum)) and in Europe ([bit.ly/ESGO-curriculum](http://bit.ly/ESGO-curriculum)). These surgeons also tend to be the ones developing and refining surgical cancer techniques, wearing multiple 'hats' in being able to also deliver medical therapies, and leading MDTs in all aspects of care.

But many patients do not attend these centres, at least for common cancers such as lung, breast and colorectal, and the extent of cancer specialism among surgeons and MDTs in hospitals can vary greatly both among countries and within them, as can be seen in variance in procedures and outcomes (for

example in lung cancer in England – see e.g. [bit.ly/CW-Ending-Sub-standard-Treatment](http://bit.ly/CW-Ending-Sub-standard-Treatment)).

### Centralisation and audits

The need to centralise and specialise in high-volume centres is hardly a new cause, and there has been significant progress in some countries such as Denmark, where the number of centres carrying out lung cancer surgery has been pared down to a handful.

Across Europe there are a number of audits and indicators for surgery and multidisciplinary performance according to clinical guidelines and targets.

### Many cancer operations are highly complex and subject to rapidly evolving research

Surgery has long been the focus of auditing, owing to the ease of quantifying it in volume and outcomes such as mortality, and reoperation and complication rates – although in some cancers, such as lung and pancreatic, curative-intent surgery is carried out only in a minority of cases, as most patients present with advanced, inoperable disease.

It has been audits of outcomes that have put pressure on healthcare systems to centralise cancer care; surgical outcomes have often been a major driver, but survival rates (mostly at five years) as detailed in the Eurocare study series have also played a big role ([eurocare.it](http://eurocare.it)).

Yet the focus on processes and

outcomes misses the status of training and lack of accreditation in cancer surgery among surgeons.

As with the other two pillars of cancer treatment, medical and radiation oncology, there have been efforts to raise the profile of surgical oncology in Europe, but progress has been slow. Unlike medical oncology, which, after years of lobbying was recognised as a medical specialism by the European Commission in 2011, there has been little advancement of the idea of a board certified cancer surgeon, although the European Society of Surgical Oncology (ESSO) says that it is not realistic to expect a surgeon to cover oncological operations in widely different organs.

Many cancer operations have become highly complex and subject to rapidly evolving research; they demand both latest technical skills and oncological knowledge, and also coordination of an MDT that also has essential skills and knowledge.

Cancer treatments are becoming increasingly multimodal over longer pathways with a surgical direction towards less radical and more organ-sparing procedures, already seen in breast, cervical and rectal, as a Commission on the Future of Surgery by the UK Royal College of Surgeons notes ([bit.ly/RCS-Future-OfSurgery](http://bit.ly/RCS-Future-OfSurgery)).

Specialist organ surgeons are of course a staple of hospitals, such as for gastrointestinal (GI) and cardiothoracic procedures, and gynaecologists and urologists have long had command of organs in their remit. But can a cancer patient be confident that a surgeon spends sufficient time on cancer operations within a workload that can include many

other conditions, and that she or he has up to date skills and knowledge within an expert cancer MDT?

For certain cancers and in certain countries, patients are almost guaranteed specialist surgeons working in such MDTs. These tend to be for rare cancers such as sarcomas, and operations where there is a long and compelling history of the superiority of specialists, such as gynaecological oncologists in advanced ovarian cancer surgery (*Gyn Oncol* 2007, 105:801–12).

A team of expert surgeons with various skills may also be needed for ‘ultra-radical’ operations on cancers where multiple organs are involved (again, advanced ovarian cancer is a good example).

But it is comprehensive cancer centres or departments mainly in teaching hospitals, and not individual surgeons, that tend to get accredited or recognised as specialist, according to audits and indicators such as a minimum volume of cases. They are often members of a national or European network of audited centres – for example the German Cancer Society’s certification programme ([bit.ly/ECC-Certification](http://bit.ly/ECC-Certification)) or the Organisation of European Cancer Institutes ([oeic.eu](http://oeic.eu)) or, for a specific cancer-type example, the centres of excellence accredited by the European Neuroendocrine Tumor Society ([bit.ly/enets-CoE](http://bit.ly/enets-CoE)).

### Weighing up the evidence

As Kjetil Søreide, a GI surgeon at Stavanger University Hospital in Norway, and professor at the University of Bergen, who sits on ESSO’s training committee, comments, the evidence base for establishing what

makes such centres ‘excellent’ is not set in stone. “We are still debating the effects of high volumes of cases with a high proportion of surgery. Should we also be setting thresholds for number of surgeons, number of surgeries they each perform, or maybe other factors such as the number of patients in the catchment area for a hospital?”

### Can a patient be confident that a surgeon spends sufficient time on cancer operations and has up to date skills and knowledge?

The choice of what indicators to use to judge levels of excellence also varies by type of surgery. Some operations are high risk, which makes mortality and complication rates important outcomes indicators. While these have generally improved in recent decades, mortality in particular remains a key indicator in surgical treatment of pancreatic cancer, for instance, where 5% is currently seen as a maximum acceptable rate. In breast cancer, by contrast, surgical procedures are highly unlikely to lead to death, but as Wyld points out, certain breast operations such as complex reconstructions can now take as long as a Whipple procedure for pancreatic cancer, and they too demand high levels of expertise, which need to be judged by different indicators.

Assuming mortality will drop as volume rises may be wrong though. A study on pancreatic surgery in

Italy (*Br J Surg* 2020, 107:1510–19), where there are a lot of hospitals carrying out procedures, found that although many hospitals had low volume that was associated with high mortality, applying a minimum volume of 10 or 25 operations a year would still give a mortality rate higher than 5% in a substantial number of hospitals and more than 10% in some. The authors report that, without considering a mortality threshold, hospital selection based only on surgical volume could prove inadequate.

As Søreide comments, given the supportive environment needed in an MDT where such surgery is performed, the focus is often rightly on the institutional capability to take care of complex cases rather than on an individual surgeon. Pathologists and radiologists contribute to crucial decisions before surgery, such as the operability of borderline cases, and intensive care specialists and anaesthetists, interventional radiologists, gastroenterologists, expert nurses and others span perioperative care, minimising complications and mortality.

This is probably why a study in England found that, even with a more challenging patient mix, high-volume centres, which are usually at the more prestigious hospitals, performed better with lung cancer than smaller centres. But it is also true that the best surgeons may be at the top hospitals, as they are often also referral centres for the most difficult cases.

Take the thoracic surgery department at UZ Leuven in Belgium, which has reported improving quality in oesophageal cancer operations – a major high-risk procedure ([bit.ly/UZLeuven-complications-news](http://bit.ly/UZLeuven-complications-news)). There has been a big drop in com-

plications such as pneumonia. But it is hard to say whether one particular factor has been a main contributor. One clear factor is that it is a high volume centre no doubt with top surgeons, but as Philippe Naftoux, a surgeon in charge of oesophageal care notes: “The increase in the number of minimally invasive interventions (keyhole surgery) and the introduction of a new postoperative care programme also play a significant part.”

What is clear is that the 30-day mortality rate for patients operated at Leuven has been less than one-third of the national average – 1.3% vs 4.8%; and after 90 days, 5.5% vs 9.9%. (See also a ‘plea for centralisation’ of pancreatic and oesophageal surgery in Belgium; *Ann Oncol* 2018, 29(Suppl 8): 562–75.)

A review of reviews on the relationship between surgeon volume and outcomes (*Syst Rev* 2016, 5(204)) has found that, in cancer, the most clear-cut evidence for the effect of volume is in colorectal and breast cancer.

A recent study has found an association between surgical technical skills and long-term survival in colon cancer, as assessed by video reviews of operations (*JAMA Oncol* 2021, 7:127–29); other such studies have focused on short-term outcomes. Another *JAMA* study has shown substantial differences in skills and outcomes in rectal cancer (*JAMA Surg* 2020, 155:590–98).

The introduction of new surgical techniques can be particularly challenging as they are often introduced without ‘gold standard’ randomised controlled trials. There can also be a steep learning curve that can result in unacceptable outcomes, such as with the relatively recent transanal total mesorectal excision in rectal

cancer – a difficult procedure – (*Colorectal Dis* 2021, 23:2020–29); and while frameworks for safe implementation exist (*BMJ Surg Intervent Health Technol* 2019, 1:e000004), there can be a tendency to introduce new procedures too quickly.

In some countries, data on individual surgeons is also available, such as in the UK, where patients can check the reported outcomes for named surgeons in various specialties, including mortality after colorectal cancer surgery. When this was proposed, there were concerns that surgeons would opt out of operating on high-risk patients or ‘game the data’ by deeming patients to be more urgent cases than perhaps they were, and so excluding them from elective surgery classification in audits.

### **The 30-day mortality rate for patients operated at UZ Leuven has been less than one-third of the national average**

But a study in the *BMJ* did not find adverse effects of public reporting, and even found improved outcomes in colorectal surgery, although this may have been because MDTs started to perform better to support surgeons.

Compliance with clinical guidelines can be a more detailed way of tracking performance, building on data captured by quality indicators – see for example a US paper on concordance with gastric cancer guidelines from a large clinical registry database (*Curr Oncol* 2021, 28:138–51). Structured operative

and pathology reports can capture more reliable data. Guidelines differ though among health systems, and MDTs have variation in decision making when presented with the same cases, such as whether to perform pancreatic cancer surgery in borderline cases (*Br J Surg* 2019, 106:756–64).

A concerning side-effect for surgery is the unintended consequences of the use of new technology, especially robots, now widely used in prostate cancer but also in other urological cancers, rectal and lung. A new generation of surgeons is being trained mainly on minimal invasive and robotic techniques, but the equipment, especially robots, may be promoting inequalities in access, as smaller, outlying hospitals may not be able to afford the equipment and resources.

As Richard Sullivan and Ajay Aggarwal noted in an IARC publication, ‘Reducing Social Inequalities in Cancer’ ([bit.ly/IARC-Social-Inequalities](http://bit.ly/IARC-Social-Inequalities) see chapter 18), a quarter of locations in the UK that were carrying out radical prostatectomies have closed, as patients, possibly the more affluent and more able to travel, choose robotic centres, even though the long-term benefit of robotic surgery is unproven. A further effect is that surgeons who lack open surgery experience may not be able to visit or return to poorer countries that lack such equipment to help with cancer work.

### **Routes into cancer surgery**

The way doctors become surgeons is similar in most countries, as Wyld describes. There is probably at least five years in training, which may include some cancer oper-

ations, and for those wanting to pursue a career at a cancer centre in the UK, a further training fellowship in cancer is likely to be a prerequisite. “But it’s an informal process, and lot of surgeons doing cancer around Europe won’t have done a period of more specialist training,” she says.

Sørdeide agrees, although he says the days of the general surgeon doing ‘head to toe’ operations is long gone, and in Norway surgeons who develop an interest in say GI surgery are channelled into subspecialists, mainly colorectal, hepato-biliary-pancreatic and gastric-oesophageal which are typical routes in most countries. “But in Norway GI surgeons also cover acute and trauma surgery and relatively minor operations such as laparoscopic hernias and gall bladders – not every specialist has the luxury of choosing one organ and focusing only on that. Cancer needs to be seen in context with other conditions that reduce quality of life.”

### **“The most difficult thing is to know what all the options are... and what to do when an option fails or if a patient does not fit the guideline”**

He adds that operating on non-cancer conditions may use similar techniques, and it is important to gain wide experience. Norway has, over time, consolidated expert cancer care among various regional centres according to care

pathways, he says. “But this hasn’t come from a focus on training surgeons as oncologists. It’s about systems that implement the standard of care.”

Decision making, he adds, is the central issue. “Of course you need technical skills as a surgeon, but the most difficult thing is to know what all the options are – what to do and what order to do them. And what to do when an option fails or if a patient does not fit the guideline for a particular condition.” That is the essence of surgical oncology and being part of an MDT.

### **Towards harmonised qualifications: breast leads the way**

ESSO has a core curriculum in surgical oncology, which was first proposed in 2008, with the most recent version published in 2021 ([bit.ly/ESSO-CoreCurriculum](https://bit.ly/ESSO-CoreCurriculum)). There is also a position paper on a global surgical oncology curriculum. The European Board of Surgery of the Union of European Medical Specialists ([uemssurg.org](https://uemssurg.org)) is the main umbrella body for qualifications, and currently conducts exams in general surgical oncology and also breast cancer surgery, both with curriculum input from ESSO. (ESSO also has two specialist schools, in soft tissue sarcoma and peritoneal surface oncology, run jointly with associated societies.)

The UEMS exams judge only knowledge, although applicants do have to submit a logbook of operations. Wyld and colleagues are now taking European breast cancer surgery to the next level with BRESO, a certification platform that aims to

review training comprehensively as well as test knowledge ([breast-surgeoncercertification.com](https://breast-surgeoncercertification.com)).

The breast cancer community has long been in the vanguard of calling for and implementing dedicated resources such as breast units. The latest ‘requirements of a specialist breast centre’ from EUSOMA and ECCO specify that such units must have two surgeons available, each spending at least 50% of their time on breast disease. Similar requirements are made in other tumour types in the European Cancer Organisation Essential Requirements series ([bit.ly/ECO-ERQCC](https://bit.ly/ECO-ERQCC)).

Wyld notes there is good reason for the cancer focus in breast – “About 80% of our procedures in breast are on cancer.” BRESO draws on ESSO’s curriculum and that of other bodies (*Eur J Surg Oncol* 2020, 46:717–36).

As Wyld adds, review of a putative breast surgeon for eligibility for BRESO will specify at least two years spent working at breast units, one at a high-volume centre, and a wide range of evidence will be taken into account to reflect differences in European healthcare training systems.

A formal qualification in breast practice is required such as the UEMS breast exam; others that can be considered are the University of East Anglia’s Masters in oncological surgery – which has a fee of about £7,500 (€8,700) – and the European School of Oncology’s Certificate of Competence in Breast Cancer, developed with Ulm University in Germany ([bit.ly/ESO-BC-Certificate](https://bit.ly/ESO-BC-Certificate)). The partners in BRESO also see it as a key part of the lobby to improve breast

care in Europe, as advocate Shirley Bianca wrote in *Cancer World* ([bit.ly/CW-A-Job-for-Specialists](http://bit.ly/CW-A-Job-for-Specialists)).

In the UK, says Wyld, while breast still comes under the ‘specialism’ of general surgery, the country has gone further than most to develop a pathway for breast surgery to become a subspecialism, not least because oncoplastic procedures were introduced into training some time ago.

### **“The aim... with BRESO is to embed a widespread pathway to being a certified breast cancer surgeon”**

Through the Intercollegiate Surgical Curriculum Programme platform ([iscp.ac.uk/](http://iscp.ac.uk/)), trainees can develop a portfolio of formally assessed breast cancer surgeries, she says. “For example, the other day I was supervising a trainee doing a breast reconstruction with axillary clearance. After the surgery, she sent me a link where I gave her a detailed assessment of how she performed the operation and how much support she needed from me. In this way we can see the trainee gaining skills and becoming more independent. They can build up a portfolio of specialist ‘index’ operations as they near the end of the training, attesting to their competence before they are allowed to practise independently.” The ISCP system is excellent and the result of many years of hard work to set up and perfect, notes Wyld.

Discussions are ongoing as to whether breast surgery becomes a

fully fledged speciality that integrates plastic procedures, which could free trainees from also being ‘on call’ to do emergency and other non-relevant work after deciding on a career as an oncoplastic breast surgeon.

There is a new UK surgery curriculum (*Surgery (Oxf)* 2020, 38:601–606) that will see oncoplastic surgery start to diverge from mainstream general surgery part way through training, resulting in better trained breast cancer specialist surgeons. (See also a paper by Wyld and colleagues on the status of breast surgery training in the UK and elsewhere; *Breast Care* 2019, 14:366–372.)

So the aim in the UK and with BRESO, says Wyld, is to embed a widespread pathway to being a certified breast cancer surgeon rather than it being an adjunct to general surgery – and in so doing to address the gaps in breast surgery training and in care that are still common in Europe (*Eur J Surg Oncol* 2019, 45:567–572). “A lot of older surgeons are not trained in oncoplastic reconstructions, so many women are being offered only mastectomies, and some are also suffering bad outcomes from lumpectomy because surgeons don’t understand therapeutic mammoplasty,” she says. A lack of knowledge of the latest research on neoadjuvant medical therapy (before surgery) is another shortcoming.

As Wyld notes, a complex breast reconstruction with LD [latissimus dorsi] flap can take more than five hours, as can bilateral therapeutic mammoplasty. “Many general surgeons don’t know how much more complex breast surgery has become.” (See also a paper on

knowledge gaps in oncoplastic breast surgery by the Oncoplastic Breast Consortium; *Lancet Oncol* 2020, 21:E375-E385.)

It’s early days for BRESO, but Wyld can envisage a time where European women will be able to visit the site to find a certified oncoplastic breast surgeon, and a number of surgeons are already signed up. Taking a formal exam in breast surgery is also becoming more popular. As an indicator of numbers, there were about 70 applicants for the most recent UEMS breast exam and the pass rate is usually about 60–70%.

Also, from the cancer side, a society that has made much progress is the European Society of Gynaecological Oncology (ESGO), which has had a certification programme for ovarian cancer surgery centres since 2016. In 2021 it launched a new curriculum for trainees, who must have two or three years training at an accredited gynaecological oncology unit. The impact of doing an accredited fellowship is discussed in a 2017 paper (*Int J Gyn Cancer* 2017, 27:819–25).

### **Models from the US – and finding common ground**

The US looks to be a leader in surgical oncology certification. For example, the BRESO team cites a breast surgery fellowship in the US ([bit.ly/SSO-BC-Fellowship](http://bit.ly/SSO-BC-Fellowship)) overseen by the Society of Surgical Oncology (Australia and New Zealand also have breast fellowship schemes). In 2011, the American Board of Surgery introduced certification for what it terms ‘complex general surgical oncology’ ([bit.ly/US-ComplexSurg-](http://bit.ly/US-ComplexSurg-)

OncolFellowship). It's a two-year fellowship that, apart from surgical management of cancer, includes multidisciplinary care, basic research and clinical trial design, patient counselling and even oncology leadership.

It's certainly ambitious, as it aims for experience in surgery with most organ sites, but a more recent article on how to implement it recognises that an oncology related subspecialty such as breast may be a more appropriate pathway in some institutions (*J Surg Oncol* 2020, 122:15–20).

The authors also note that the journey to recognise surgical oncology at this level has been a long one in the US – unofficial fellowship training dates back as far as 1947.

### **The journey to recognise surgical oncology at this level has been a long one in the US – unofficial fellowship training dates back as far as 1947**

An aspect raised by such fellowships is the role of surgeons in research, as there are concerns that the 'surgeon scientist' is becoming an endangered species amid pressures on time, support and funding, including in cancer (*Nat Rev Clin Oncol*, 2019, 16:327–332). Surgical oncology does not seem to be as widely recognised as an academic discipline as it should be, but appears to be on more solid ground in the US.

Another initiative in the US is the Commission on Cancer, a con-

sortium of organisations including the American College of Surgeons, which has set standards for accreditation for cancer programmes. Among them are surgical oncology standards for sentinel node and axillary lymph node procedures in breast cancer, excision of primary cutaneous melanoma, colon resection, total mesorectal excision (TME) in rectal cancer and pulmonary resection.

To achieve these standards, reviewers need to see synoptic (not narrative) operative and pathology reports, and it is a developing programme – as new procedures have only recently been added – with a deadline for organising more reporting systems set for 2023.

This all sounds like basic oncology and similar standards are in place in some European countries. Raising the level to the gold standard across Europe is a big challenge, however, as Søreide confirms. "Many countries are still stuck in the old general surgery paradigm, but when we start to encourage subspecialty training it is hard to find common pathways, because there are so many specialist interest organisations."

By this Søreide means the organ societies such as the European Society of Coloproctology, which has a large number of members and multiple interests, with cancer being only one. "It can be hard to get a consensus on surgical oncology," he says. "I'm on the training committees of ESSO and the European-African Hepato-pancreato-biliary Association, but even though we have common interests there are so many other issues that it is sometimes hard to find common ground."

This isn't to say that the organ societies are not engaged with cancer – the European Respiratory Society, for example, has been a leader in uncovering shortcomings in European lung cancer care in recent years, and UEMS is currently calling for harmonisation of thoracic surgery in Europe, within which thoracic oncology probably accounts for about 50% of the workload (*J Thorac Dis* 2021, 13:2021–28).

**"When we start to encourage subspecialty training it is hard to find common pathways, because there are so many specialist interest organisations"**

But progress is often slow in Europe, and people and initiatives come and go.

The common ground must be that no matter how the health system is organised, cancer patients must be on a pathway that finds them operated on by surgeons trained and assessed, and with ongoing education, in the standard of oncological care as part of an expert MDT.

*This article was published on the Cancer World website on 4 June 2022, [bit.ly/CW-TrustMe](https://bit.ly/CW-TrustMe). It has been updated to take account of the most recent version of the ESSO core curriculum.*



# TIME TO ACT.

## Time To Act Data Navigator

The Covid-19 pandemic has had major consequences for cancer care and cancer patients across Europe. The Time To Act Data Navigator gathers available information to provide the data intelligence to quantify this impact in Europe.

Countries

Pan-European Data

Eastern Europe

Western Europe

Entry by Category

Submit New Data



Contribute to the evolution of the Data Navigator.  
Visit the website and click on the submission button  
to share new data.

[timetoactcancer.com/data-navigator](https://timetoactcancer.com/data-navigator)

#TimeToActCancer #DataNavigator

european  
cancer  
ORGANISATION



## PSA population screening is back in favour: here's why

PSA screening for prostate cancer ran into trouble 20 years ago, as the extent of overdiagnosis and overtreatment that hurt men's quality of life became clear. Yet today clinicians and advocates are campaigning for population PSA screening programmes across Europe. **Simon Crompton** asks them: what's changed?

**F**ive years ago, the idea of national screening programmes for prostate cancer had gone cold. The benefits of PSA (prostate specific antigen) blood testing, introduced as a screening tool in the 1980s, had long been fiercely debated. But by 2015 the United States Preventive Services Task Force had recommended against PSA-based screening, and research had indicated that the potential benefits of reducing mortality probably didn't

outweigh the risks of overdiagnosis, overtreatment – and a resultant damage to men's quality of life.

Even Europe's urologists weren't recommending systematic screening. "Screening for prostate cancer is one of the most controversial topics in the urological literature," said the European Association of Urology (EAU) in its 2015 guidelines. "The impact on the patient's overall quality of life is still unclear. It appears to be minimal in some

subgroup analyses, but significant in others. This has led to strong advice against population-based systematic screening in all countries, including Europe."

How times change. In the past two years, the EAU has been trying to convince Europe's politicians that PSA-based early detection programmes should be implemented at a population level across Europe. The language surrounding PSA-based screening is still heated, but

now it is the heat of the campaign.

“There are now game changers that cancel out all the anti-PSA propaganda that we’ve heard over recent years,” says Hein Van Poppel, Adjunct Secretary of the EAU. “It is now possible to overcome all the disadvantages that the use of PSA has brought in the past.”

In March, as a result of campaigning by a coalition led by EAU and the prostate cancer patient organisation Europa Uomo, the European Commission’s ‘Beating Cancer Plan’ included a promise to update the European Council’s recommendation on cancer screening – including the possible addition of prostate cancer – by 2022. The following month, Hein Van Poppel gave evidence to an EU Beating Cancer consultative session on early detection.

### Three game changers

His message about why the game had changed was clear. First, prostate cancer deaths are rising in Europe and something needs to be done urgently to turn this around: 107,000 men died from prostate cancer in the European Union in 2018 compared to 92,000 in 2010.

Second, objections to PSA screening are outdated, because they are based on research that pre-dates the introduction of MRI prostate scanning as a follow-up to raised PSA levels. This reduces the need for potentially harmful biopsies and ensures that the biopsies that do take place are more effective at identifying dangerous cancers, because guided by MRI scans.

And third, the use of new

risk stratification algorithms can ensure that only men most at risk of severe disease are targeted, reducing the number who will be investigated or treated for prostate cancer when the risk to life is small.

### The use of new risk stratification algorithms can ensure that only men most at risk of severe disease are targeted

“The biggest argument against blanket PSA testing for men is the risk of overdiagnosis and over-treatment,” says Van Poppel. “The arrival of multiparametric MRI [mpMRI] is the most important counter to this argument. It means we can ignore insignificant cancers and detect more significant cancers before embarking on biopsy, which can cause complications, and treatment, which can have damaging side effects on men’s quality of life such as urinary incontinence and erectile impotence.”

There’s no doubt that the publication of major trials – PROMIS (*The Lancet* 2017, 389:815–22) and PRECISION (*NEJM* 2018, 378:1767–77) – in 2017–2019 demonstrating the effectiveness of mpMRI at diagnosing prostate cancer was a turning point (see e.g. [bit.ly/CW-New-Dawn](http://bit.ly/CW-New-Dawn)). This prompted the EAU to change its guidelines on prostate cancer diagnosis in early 2019, recommending mpMRI after a raised PSA reading, thus opening the way for a review of screening.

### Not just about survival

The new knowledge base has brought renewed support for PSA-based screening programmes from beyond urology – most significantly from patient organisations. Europa Uomo formally decided to back the case for a Europe-wide PSA-based screening programme for prostate cancer shortly after the EAU changed its guidelines. But it has also decided to avoid the word ‘screening’ in its campaigning: it is too strongly associated with population-wide testing, as opposed to testing of specific, well-informed groups – which is what they are calling for.

For Europa Uomo, which represents prostate patient groups in 27 countries, the case for early detection programmes is intricately linked with the need to improve quality of life of men with prostate cancer throughout Europe – not simply reducing mortality.

“It’s very clear from the data that the more advanced the prostate cancer at diagnosis, the worse the effects of treatment on quality of life,” says Europa Uomo Chairman André Deschamps.

“We must realise that more than 50% of prostate cancer patients in Europe are diagnosed in a metastatic phase, at which stage treatment is expensive, limited in effectiveness and brings very unpleasant side effects,” said Deschamps. “This is due to the lack of early detection programmes.

“We have the scientific knowledge today to prevent prostate cancer deaths and give patients a much better quality of life. It is the duty of policy makers to make that happen.”

Van Poppel recognises that hav-

## Early detection of prostate cancer in well-informed\* men



Blueprint for PSA screening programmes in Europe (simplified version)

Source: adapted from European Cancer Patient Coalition, Europa Uomo, European Association of Urology (2021) *Early detection of Prostate Cancer: Facts and scientific update for the EU Cancer Plan*, published on the ECPC website ([bit.ly/Factsheet-MEPs](http://bit.ly/Factsheet-MEPs)), downloaded 21 April 2021

ing patients as allies is vital in convincing European politicians that the case for prostate cancer screening programmes must be reconsidered. “We urologists do not have a good voice to claim that we should do more early detection,” he says. “People think we want it because we have a vested interest in more men being diagnosed. The fact that patients want it as well is very important.”

Together with Europa Uomo and the European Cancer Patient Coalition, EAU has submitted white papers and scientific evidence, and spoken to many MEPs about the need for early detection ([bit.ly/EU-EAU-wp](http://bit.ly/EU-EAU-wp)). The message has

been crafted to reflect changing times. “Compared to the classic diagnostic strategy (that is, PSA and direct biopsies), we can use PSA more cleverly, apply MRI and further risk stratification tools in men at increased risk,” says a factsheet for MEPs ([bit.ly/Factsheet-MEPs](http://bit.ly/Factsheet-MEPs)). “This combined approach in well-informed men will allow a substantial reduction of the number of men that need to undergo biopsy (up to 70%) and over-diagnosis up to 20%.”

The campaigning has borne its first fruit with the Beating Cancer Plan announcement opening up the possibility of adding prostate cancer to the current European Guidelines on population screening pro-

grammes. But now comes the hard part. The European Commission cannot implement screening across Europe, even if it wanted to. It can only encourage member states to take action. And should the same actions be recommended across all member states? What can realistically be achieved?

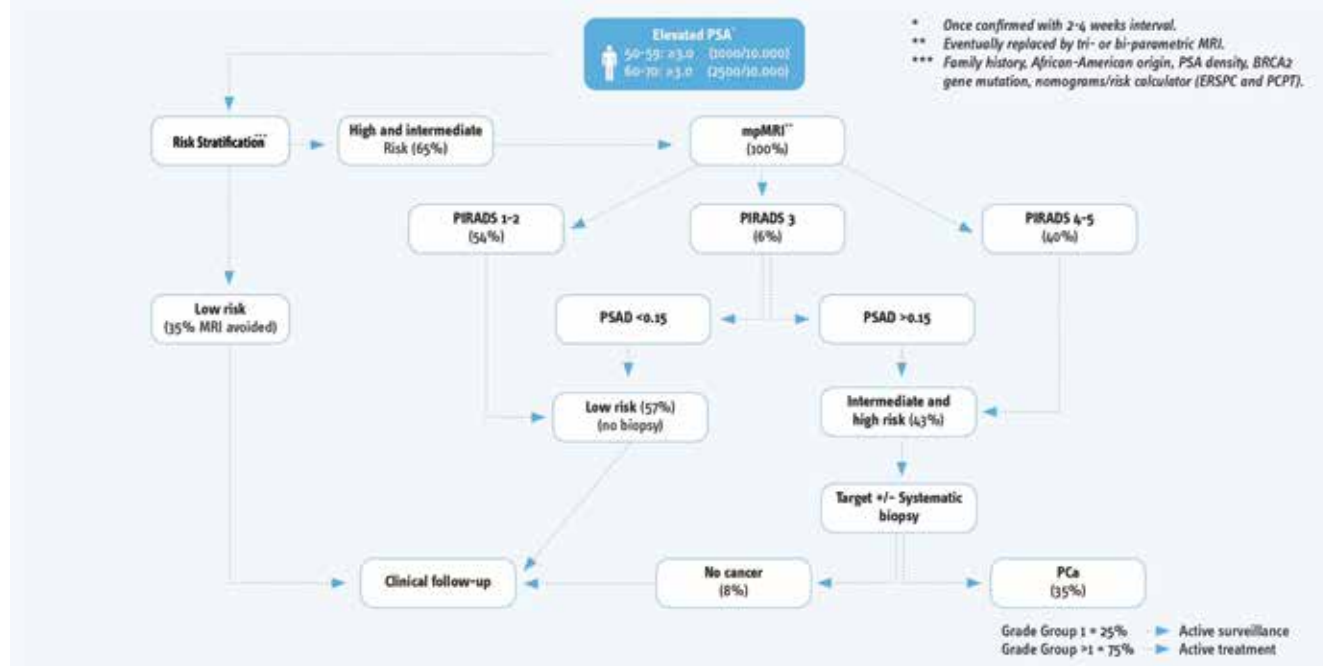
### A blueprint

A blueprint for EU action was set out in a paper published in *European Urology* written by Van Poppel and other urologists and academics, including Monique Roobol, who is Professor in Decision Making in Urology at Erasmus University Medical Centre, Rotterdam (*Eur Urol* 2021, 79:327–329). It sets out a recommended early detection process (or ‘algorithm’), starting with PSA testing among groups at higher risk, with further actions to follow a raised PSA reading, again varying according to age group and risk factors. A key recommendation is for men to receive counselling on the potential harms and benefits of early detection, before undergoing testing.

**“Dependent on resources, all countries should introduce some sort of stratified screening”**

But a problem has immediately become apparent to European politicians who, having accepted the need for screening in principle, are now faced with cold practicalities. Variations in technologies and skills across European countries are so great that a one-size-fits-all recom-

## Prostate cancer: Risk-Stratified Early Detection



mpMRI – multiparametric MRI, PIRADS – Prostate Imaging and Reporting Data System, PSAD – PSA density, PCa – prostate cancer.

Source: Downloaded from the EAU website on 21 April 2021 ([bit.ly/EAU-PCaScreening-call](http://bit.ly/EAU-PCaScreening-call))

mendation on screening will simply be impossible. For example, mpMRI scans – already part of the prostate cancer diagnostic process in many northern European countries such as England and Norway – are currently beyond the reach of many countries in central and eastern Europe.

Hein Van Poppel says that these issues were discussed in recent conversations with Stella Kyriakides, European Commissioner for Health and Food Safety since 2019.

“I think she understands the challenges very well. But we are not asking for all men to be given an mpMRI. Yes, we want risk-stratified PSA-based early detection programmes in every country. But, before that we need awareness cam-

paigns among the population and education of GPs, so that everyone understands the risks and benefits of screening based on recent evidence.”

Then, dependent on resources, all countries should introduce some sort of stratified screening. Roobol, who has also joined discussions with European Commission representatives to put the case for screening, says: “We should try to get some kind of programme everywhere. Let’s say that, if you have MRI available you can go for the platinum level algorithm. If you do not have that, you go for the gold algorithm, using other risk indicators such as PSA density. Anything that stratifies risk is better than leaving PSA testing as opportunistic.”

### Winning over the sceptics

The new emphasis on using PSA testing in a strategic way, following up only those most at risk, is bringing many who had previously been worried about national screening programmes – oncologists and radiotherapists as well as urologists – over to the cause.

Three years ago, for example, Riccardo Valdagni, Director of the Prostate Cancer Programme at Fondazione IRCC at the National Cancer Institute in Milan, Italy, told *Cancer World* of his worries about diagnostic processes that effectively made biopsy a last resort ([bit.ly/CW-NewDawn](http://bit.ly/CW-NewDawn)). He said that men with a higher risk of prostate can-

## Prostate cancer screening timeline

**1980s:** Prostate-specific antigen (PSA) blood tests introduced. PSA is a protein produced by the prostate gland that is detectable in blood. PSA levels rise when there is a benign enlargement of the prostate, an infection of the prostate, prostatitis or prostate cancer.

**Early 1990s:** Incidence of prostate cancer peaks as more men tested with PSA, leading to concerns about overdiagnosis. However, prostate cancer mortality also begins to decline.

**Late 1990s:** Concerns grow that too many men are being diagnosed with prostate cancer, leading to unnecessary treatments with unpleasant side effects, when the disease is not significant enough to kill them or affect their quality of life. Use of PSA testing declines in Europe.

**2000s:** Declines in mortality from prostate cancer level off, with rises in some countries. Mortality in the UK increases 17% in 10 years. Research evidence grows that broad-brush screening of men using PSA tests leads to unnecessary biopsies and treatment, because of the difficulties of discriminating between significant cancers (which might kill a man) and insignificant cancers (which might never affect their lifespan or quality of life).

**2010 onwards:** Development of risk

calculators, using multiple factors such as age, family history and PSA density alongside PSA, make it possible to identify those most at risk of serious disease, who may need further investigation and active treatment. Active surveillance is increasingly recognised as an alternative to active treatment.

**2017–2019:** Results from two major trials (PROMIS and PRECISION) show that using multiparametric MRI (mpMRI) scans after a raised PSA reading and before biopsy is the most effective way of detecting significant prostate cancer. The scans effectively guide biopsies, leading to significantly more harmful prostate cancers, and fewer harmless cancers, being diagnosed.

**2018:** British Medical Journal publishes systematic review and guidelines tentatively recommending against prostate cancer screening programmes, on the basis that harms and benefits are closely matched.

**2019:** EAU updates its early detection guidelines to recommend mpMRI after PSA testing and before biopsy.

**2021:** The European Commission announces it will consider the possibility of “extending targeted cancer screening beyond breast, colorectal and cervical cancer to include additional cancers, such as prostate, lung and gastric cancer”.

cer (for example because of family history or a PSA level above a certain threshold) should have a biopsy even after a negative mpMRI scan, to minimise the possibility of false negatives.

The risk stratification algorithms being proposed put some of those worries to bed. “I agree with the concepts,” he says. “I think it’s an excellent way to arrive at individualised, risk-stratified prostate cancer screening, combining improved biological and clinical knowledge, and better use of new technology such as mpMRI – not in opposition to biopsy but to improve decision-making on performing biopsies.”

However, there still is resistance to structured PSA screening, mainly from general practitioners. According to Van Poppel, this is a considerable barrier – and is frustrating because, he says, it is often the result of simply clinging on to old beliefs. “They are not well informed,” he says.

Roobol agrees that GPs are fundamental to current problems with early detection. She believes that any official algorithm to guide testing – even if it cannot embrace mpMRI – is better than the current situation, where the influence of personal opinion is often making PSA testing erratic, opportunistic, and likely to lead to both overdiagnosis and under-diagnosis.

“It is known that men are being screened who are too old, or too young, or that screening is done every year or even every six months,” says Roobol. “A GP in one village may never screen anyone, but a GP in the village next door screens every man aged 40 and over.”

GPs aren’t the only barrier. Some

key policy makers and influencers still need to be won over. “We have to try and convince people in Brussels and the World Health Organization that what is currently going on is not good. And, you know, they’re currently not convinced. For example, some still think that screening is not being done at the moment. That’s wrong. It is being done and overall it’s doing more harm than good.”

There’s no easy way of changing minds – partly because there’s no definitive piece of research showing that the pro-screening lobby is right. The only completed and authoritative research that exists is all based on wide, non-risk stratified testing of men who were given biopsies after PSA. And they indicate, not surprisingly, that overtreatment is a significant risk.

This is a problem, acknowledges Roobol. There has simply been not enough time to conduct similar long-term studies looking at the effects of risk-stratified screening. She herself was one of the leaders of the European Randomized Study of Screening for Prostate Cancer (ERSPC), which reported that overdiagnosis occurred in at least 40% of the screen-detected cases, indicating a high risk of overtreatment with unavoidable adverse effects (*The Lancet* 2014, 384:2027). This has provided ammunition to those suspicious of PSA.

But Roobol emphasises that overdiagnosis was the result of the study not selecting according to risk and using systematic biopsies after raised PSA findings. The important point which policy makers need to take away from ERSPC is that it showed that early detec-

tion could be effective – reducing prostate cancer mortality by 27% at 13 years. Another smaller study of the same cohort indicated an even greater effect: a mortality reduction of 52% at 19 years (*Eur Urol* 2019, 75:374–77).

**“Some still think that screening is not being done at the moment. It is being done and overall it’s doing more harm than good”**

“What we learned from ERSPC was that we can use the PSA test and make a huge difference. You just need the right risk stratification system afterwards, whether that uses advanced techniques such as MRI, or just uses the PSA level in a smart way, adding if possible prostate volume or digital rectal examination, for example, into the equation.”

### **Where next for EU policy?**

In March 2022 the European Commission’s Scientific Advice Mechanism SAPEA published its report on Improving Cancer Screening in Europe, which concluded there is strong evidence in favour of introducing prostate cancer screening ([bit.ly/SAPEA-ScreeningUpdate](https://bit.ly/SAPEA-ScreeningUpdate)). The European Commission has stated that it will take the evidence into account when it updates its screening recommendations, due by the end of 2022 ([bit.ly/EC-Screening-Statement](https://bit.ly/EC-Screening-Statement)).

No-one believes the Commission

is about to serve up a fully-formed prostate cancer screening programme ready for Europe-wide implementation. Realistically, what adherents like Van Poppel and Roobol are seeking is movement: a forceful European initiative to educate, correct misunderstandings, and set the foundations for national systems based on the realities of risks and benefits. Even international initiatives to educate men so that they can understand the issues would be a welcome start, says Roobol.

“Then, on that basis, a well-educated man can decide: ‘I really want this’. And then they can enter a national system where they can use an algorithm which is suitable for the setting in that country.”

The coming months will see an intensification of debate and consultation. It’s an opportunity not to be missed, believe Europe’s prostate cancer patient representatives.

“Our campaigning and informing work needs to continue,” says André Deschamps. “The door is half open, but we need to work hard this year to ensure that it is not closed again.”

*Declaration of interest: Simon Crompton is a freelance journalist who provides communications services to many organisations, one of which is Europa Uomo.*

*This article was first published on the Cancer World website on 23 April 2021 ([bit.ly/CW-PSA-Screening](https://bit.ly/CW-PSA-Screening)).*

*It has been updated to reflect the publication of the SAPEA recommendation in favour of introducing prostate cancer screening.*



# Pain relief is a right

## *Building confidence in opioid use in oncology*

Fears about unintended consequences of taking opioids, including addiction, now account in large part for unnecessary suffering among people with severe cancer-associated pain. **Sophie Fessl** talks to experts in palliating cancer pain about how, in many countries, attitudes have become a bigger barrier than red tape. She asks them what can be done to increase knowledge and confidence about opioid use among doctors and patients.

**O**pioid analgesics are essential for pain relief and pain treatment in patients with active malignant disease. Yet, in 2011, the World Health Organization estimated that, worldwide, 5.5 million people living with terminal cancer suffered from moderate to severe pain, because of inadequate access to controlled medicines (*Lancet Oncol* 2016, 17:E13–E22). Since that time, the consumption of opioid analgesics

has increased globally, particularly in western countries, including western and central Europe. But access remains a problem in some countries and can be very patchy within countries, particularly where national pain and palliation services are underdeveloped or nonexistent. Many GPs and oncologists remain reluctant to prescribe opioids, and many patients remain resistant to taking them, despite strong evidence of their safety

and benefit and authoritative guidelines on how they should be used. As a result, unnecessary suffering caused by poorly controlled cancer-related pain continues to be a problem.

“Pain relief is a fundamental human right,” emphasises Tomasz Dzierżanowski, Vice-President of the Polish Society of Palliative Medicine. Dzierżanowski, whose day job is Assistant Professor at the Laboratory of Palliative Medicine at the



Medical University of Warsaw, has been tracking the availability and accessibility of opioid analgesics in Poland since 2000. Over the past 20 years, per capita consumption has increased in Poland by more than four-fold, rising steadily from 36 mg oral morphine equivalents (OME) in 2000 to 103.4 mg in 2015, with the figures for 2020 showing a further rise to 150 mg. The latest indication is that consumption levels were stable in Poland from 2018 to 2020. “All strong opioids are now available in Poland, with the exception of hydromorphone,” says Dzierżanowski.

A big change in opioid prescribing patterns was brought about two years ago when bureaucratic procedures involving special prescription forms for opioids were replaced by a mandatory electronic prescription system. Prior to that, the growth in opioid consumption had been accounted for largely by fentanyl patches and, later also by buprenorphine, which in 2007 was approved as the only strong opioid available on regular prescription forms. “Every physician in Poland is [now] allowed to prescribe all available opioids, so this is no longer a barrier,” says Dzierżanowski, though buprenorphine and fentanyl transdermal formulations remain the most frequently used strong opioids in Poland, in terms of OME.

### Regulation is no longer the main obstacle

Dzierżanowski sees the reduction in red tape involved in prescribing opioid analgesics as an important step in making available suitable analgesics for people suffering severe, and often chronic, pain. But other barriers remain, he says, which need to be tackled. One of them is anxieties

around use of opioids that stem in part from prejudice, but often from a lack of knowledge and confidence in how to use them safely. “The barriers now are opiophobia, and especially morphinophobia, which is a slightly different aspect, on both doctors’ and patients’ sides... and an insufficient working knowledge of the principles and guidelines for the treatment of cancer pain – I think these are the biggest impediments to optimal pain treatment,” he says.

Reimbursement regulations can also present an obstacle, he adds, as they are not always compatible with guidelines for pain relief in cancer patients. He cites the cases of tapentadol, which is only reimbursed when morphine appears ineffective – “An absurd situation, as tapentadol is a weaker opioid than morphine. So we need to accept that tapentadol is not reimbursed for most cases of cancer pain.”

The Polish experience bears out observations made by the International Narcotics Control Board (INCB) in its 2018 report. Taking a global perspective, the report states that: “Comparing the responses provided in 1995, 2010, 2014 and 2018, it is possible to observe a decrease in the number of times that onerous regulations are mentioned as impediments to availability.” Fear of addiction as an impediment, it notes, declined sharply between 1994 and 2014, but increased from 2014 to 2018. “Lack of training and awareness of health professionals was the factor most often mentioned as an impediment in both 2014 and 2018, followed by fear of addiction.”

Experiences in Serbia tell a similar story. Snežana Bošnjak is now Professor at the Institute for Oncology and Radiology of Serbia and

leader of its Supportive Oncology and Palliative Care Service. When she started work at the Institute, back in 1992, there was no such supportive service, and the situation regarding pain relief was dire: only tramadol and transdermal fentanyl were available for cancer patients in Serbia, and the country faced an acute shortage of oral morphine.

In 2006, Bošnjak was selected for an International Pain Policy Fellowship at the WHO Collaborating Center for Pain Policy and Palliative Care at the University of Wisconsin’s Carbone Cancer Center, which involved addressing regulatory barriers to cancer pain treatment with opioids. “When I started my fellowship, I needed to change laws and to change policies. For one physician, without any knowledge about policies, this was frightening, but also inspiring and challenging. It was quite a journey.”

By that time, however, she had already spent years trying to address patients’ unmet need for pain relief. “At the beginning, patients suffered in silence. They thought cancer must be painful and hesitated to report pain. When I mentioned morphine, patients started to cry, because they associated morphine with end-of-life care, with death,” Bošnjak recalls. “And there was no service to treat pain in patients who received anti-cancer treatment, only the management of cancer pain at the end of life was recognised.” In these years, Bošnjak worked to highlight the need of cancer patients to receive proper pain management during anti-cancer therapy. “It was about bringing the patient experience into the focus, to ask cancer patients about pain and enable a service to respond to their needs for pain management.”

## Delivery of Care

Improvements in Serbia were lauded by the INCB in its 2010 report ([bit.ly/INCB-2010Report](http://bit.ly/INCB-2010Report)). The Institute for Oncology and Radiology of Serbia recognised the value of the consultations for hospitalised cancer patients experiencing pain, by establishing a dedicated supportive and palliative care service. This now employs specialists from a wide range of disciplines to treat pain and other side effects of cancer and cancer treatment. Such a multidisciplinary approach is necessary, says Bošnjak, because pain is multidimensional, “but opioids treat only the somatic side of pain”. In addition to treating this somatic side, psychologists, social workers and a priest in the team also provide psychological, social and spiritual care for patients.

Thanks to her work with the International Pain Policy Fellowship, Serbia endorsed the medical use of opioids for treating pain in a new law on psychoactive-controlled substances. A new National Palliative Care Strategy was also implemented that recognised opioids as essential for palliative care. This has been accompanied by a significant change in attitudes and knowledge among doctors and patients about the use of opioids as analgesics, says Bošnjak. “Now, in Serbia, the topic of pain is recognised. It is understood that cancer patients need proper management of pain, not only when they are at the end of their life, but throughout their journey, including survivorship.” All opioids recommended by the guidelines for treating cancer pain are currently available in Serbia and relief of pain and suffering is recognised as a patient right she adds.

However, regional differences persist. The IORS where Bošnjak is practising, situated in the Serbian

capital Belgrade, is an ESMO designated centre for integrated oncology and palliative care. The Supportive Oncology and Palliative Care Service treats every patient with cancer pain, and includes an acute Intensive Care Unit for intensive pain treatment, an outpatient service and a mobile consultation team.

But not all cancer patients in Serbia benefit from this patient-centred, integrated care. “We would like to be a model for other cancer centres in Serbia, for them to recognise the need to integrate tumour-directed and patient-directed approaches in oncology. When these two approaches are integrated, patients live longer and better. The main focus now is to integrate these two approaches in all cancer centres.”

### Fear of morphine persists

Nowadays, patients react differently when morphine is prescribed. “Morphine and other opioids are accepted as essential and effective pain medication,” she says, but adds that fear of morphine is still an issue: “They prefer when their analgesic is not called morphine.” Added to the perceived connection with end-of-life, she feels many patients are still afraid of becoming addicted. “Sometimes, they perceive morphine as so strong that you have to have very severe pain in order to get morphine. They don’t understand that morphine can be given for patients with moderate and severe pain, on the so-called second and third step of the analgesic ladder as per the guidelines.”

In Poland, Dzierżanowski experiences similar reactions. “When I say ‘morphine’, patients say ‘no, no, no, not morphine’. When we switch to oxycodone, that’s okay. Or fentanyl?

which is 100 times more potent? That’s okay. But morphine – no.”

Recently, Dzierżanowski surveyed the attitudes of palliative care specialists and other physicians towards opioids. “In palliative care, we don’t have opiophobia on the doctors’ side. But other specialists hesitate to prescribe opioids.” One reason he identified was the fear of respiratory depression caused by direct or indirect overdosing. “That said, morphine also brings the connotation of drug dependence, and doctors do not want to produce drug dependency in their patients.”

### Building knowledge and confidence

Bošnjak and Dzierżanowski both see raising awareness and promoting education about opioids’ role in pain management – among both health-care specialists and patients – as an important element in improving pain control, together with expanding palliative care services. “We need post-graduate, continuing medical education programmes on pain treatment,” emphasises Dzierżanowski.

Although the European Society for Medical Oncology and the US National Comprehensive Cancer Network have published guidelines for treating cancer patients who experience pain, these international guidelines remain inaccessible for many doctors, Dzierżanowski adds. “Most regular doctors do not know those guidelines, that they exist or what they mean. We need them free-of-charge, available to everybody, translated and disseminated by local organisations – otherwise, they will be only a scientific article somewhere in the cloud.”

The emphasis on access to knowl-

edge is strongly echoed by Silviu Brill, Director of the Pain Institute at the Tel Aviv Medical Center, and Honorary Secretary and Chair of the Cancer Task Force at the European Pain Federation (EFIC). “We need patient education, we need to lead them through social media, through the cancer institutes, through all avenues, so that they recognise the right of patients to be treated. We need education also for young doctors and trainees, teaching about cancer pain, pain assessment and pain treatment. I think those can really make a difference for adequate pain treatment.”

As he points out, the addiction crisis that blew up in the US has made that task harder. “The reluctance and fear we see towards opioids, both from patients and doctors, are a result of the opioid crisis that crossed the ocean, from America to Europe. But for severe pain, opioids are still the gold standard of treatment.”

Across the continent, countries and healthcare systems face different challenges, he argues, which may also differ between hospitals.

“There is not just one thing to address. We should go in every country, or every big cancer centre, to visualise the barriers. Because they can be very different: not enough doctors, not enough nurses, doctors without knowledge about adequate pain treatment, and cultural differences – where one doctor might be very open towards treating patients with opioids, another one, in a nearby hospital, might never give opioids”

A position paper on the Societal Impact of Pain Platform – an initiative by EFIC and Pain Alliance Europe, the European umbrella organisation for people with chronic pain – argued that pain needs to be included among the indicators for

## Cannabinoids – the new(er) kids on the block

While patients are sometimes afraid or reluctant to take morphine, attitudes towards cannabinoids tend to be vastly different. “Somehow, patients are more open towards using cannabinoids than morphine or other guideline-based opioids,” Snežana Bošnjak, head of Supportive Oncology at the Institute for Oncology and Radiology in Belgrade, observes. “Of course, we are very open to explore every possibility to find new medications to treat pain. But patients are maybe too optimistic about, or not careful enough with cannabinoids, and the actual data about their efficacy in cancer pain management.”

In early stages of cancer, cannabinoids might be seen as an option, says Dzierżanowski, Vice-President of the Polish Society of Palliative Medicine. “They may appear an alternative for moderate pain and accompanying symptoms such as chemotherapy-induced nausea and vomiting, spasticity, seizures, mood disorders or loss of appetite.” However, the evidence is still too weak to recommend their use as a first-line treatment for chronic pain, he says. “Approaching cannabinoids, we should avoid the reluctance that was typical towards opiates in the past decades, which appeared not rational. But we still do not have standardised cannabinoids, and oral formulations like pills or solutions, which would be easier to administer. And further randomised clinical trials are necessary to confirm or redefine the role of cannabinoids for the treatment of cancer pain and in palliative care settings.”

assessing the quality of a healthcare systems across Europe ([bit.ly/SIP-Position](http://bit.ly/SIP-Position)). Brill points out that pain does not just cause discomfort, it can also impact severely on people’s social life and ability to function. “Assessing also the social impact of pain, not treating only the pain, but looking multifactorial at the quality of life and activity of patients, will be a strong thing that can improve the quality of our treatment,” he says.

Similar to the approach Bošnjak is championing at the IORS, EFIC is proposing a multi-professional approach towards treating cancer pain. “Treating only pain is an old-fashioned way of looking at the issue. We need to treat the patient as a whole; this needs other professions, such as psychologists, physiotherapists, and also rehabilitation – all the resources available.

“We would need to set high standards that can be easily measured: Are patients asked, every time they see a doctor, whether they experience pain? How long does it take for patients to be seen in a pain unit? And how long until their pain is reassessed? Are patients asked about side effects of pain treatment? These are examples of quality indicators that can be easily implemented and can make a difference. Once we have quality control and set a high standard, the issue will be improved dramatically.”

*This article was published on the Cancer World website on 20 May 2021. To comment on or share the article go to [bit.ly/CW-Pain-Relief-Confidence](http://bit.ly/CW-Pain-Relief-Confidence).*



capo.ca | @CAPO\_ACOP  
ipos-society.org | @IPOSPsychoOncol

IN-PERSON AND VIRTUAL

# IPOS 2022 WORLD CONGRESS

REIMAGINING PSYCHOSOCIAL ONCOLOGY:  
EMBRACING VOICES FROM AROUND THE WORLD



**TORONTO, CANADA**  
AUGUST 29 TO SEPTEMBER 1, 2022



Covid-related fatigue

Cancer-related fatigue

# Cancer-related fatigue

## *Might research into long-Covid help find causes and cures?*

Chronic fatigue blights the lives of many cancer patients long after treatment is ended. **Simon Crompton** reports on hopes that this under-researched condition might finally get the attention it needs, due to the surge of interest and funding currently being poured into understanding long-Covid.

**L**ong-term emotionally and physically debilitating fatigue is a fact of daily life for many who have had cancer. Awareness is low, causes mysterious, and physicians are often sceptical or plead powerlessness – even though a growing body of research attests to its prevalence and devastating effect on quality of life.

One study indicated that up to three-quarters of prostate cancer patients experience fatigue (*Support Cancer Care* 2013, 21:1761–71), and another study, published in 2020, showed that fatigue levels are “significantly higher” than the general population in patients across 15 cancer types (*Cancer Med* 2020, 9:8053–61).

Groups representing cancer patients and other people who suffer from chronic fatigue are therefore following with interest all the attention and research funding that long-term fatigue and other symptoms associated with Covid-19 infection are now attracting.

According to André Deschamps, Chairman of the Europa

Uomo prostate cancer patient coalition, one of the most striking findings of the coalition's recent EUPROMS quality of life study is that long-term discomfort, tiredness, and insomnia have such a strong influence on the quality of men's lives after treatment ([bit.ly/EUROPROMS](https://bit.ly/EUROPROMS)).

"These important areas do not receive sufficient attention from physicians, support services and researchers," he says. "Yet the significant effects that post-Covid fatigue can have on people are now being well-publicised and recognised."

In the UK, for example, where in May 2021 one million people reported they were experiencing sustained symptoms following Covid, the Government announced that 15 new studies will investigate what is now becoming known as 'long-Covid' ([bit.ly/UK-Long-Covid-Research](https://bit.ly/UK-Long-Covid-Research)). This research, they said, will "support thousands of vulnerable people, backed by nearly £20 million through the NIHR [National Institute for Health Research]". In February, the World Health Organization Director for Europe called on all countries and institutions in Europe to come together "as part of an integrated research agenda," on post-Covid conditions "using harmonized data-collection tools and study protocols" ([bit.ly/WHO-Call-LongCovid](https://bit.ly/WHO-Call-LongCovid)).

So the question now being raised is: will the flood of attention, research and funding being directed towards the devastating effects of long-Covid finally throw the spotlight onto causes and cures for other fatigue syndromes such as cancer-related fatigue?

Martina Schmidt from the German Cancer Research Centre certainly hopes so. "Fatigue can be one of the most burdensome symptoms for cancer survivors, and about a quarter of cancer survivors experience it long term," says Schmidt, a senior scientist who over ten years has researched widely into quality-of-life issues for people with cancer, during and after treatment.

### **They are intrigued by similarities with the fatigue associated with long-Covid**

In a large survey of more than 2,500 cancer survivors conducted by the Deutsches Krebsforschungszentrum (German Cancer Research Centre), almost six in ten respondents reported that they lacked good information about fatigue, and more than four in ten reported that their treating physician had never asked them whether they were fatigued (*Support Cancer Care* 2021, 29:2063–71).

"There needs to be a change," she says. "Physicians, healthcare providers and insurance companies do not address it, and families and friends aren't always understanding because they want to think the cancer is cured. It's really a burden."

In 2020, her team published their research looking at fatigue across 15 cancer types, and found that age- and sex-standardised physical fatigue prevalence ranged from just over 30% among prostate cancer patients to more than 50% among liver cancer patients. They

are intrigued by similarities with the fatigue associated with long-Covid. But they are also aware that the term 'fatigue' is very general, covering many different conditions and causes.

### **Not all chronic fatigue is the same**

"We need to make distinctions," says Schmidt. "Chronic fatigue syndrome [CFS], for example, may have similar symptoms to cancer-related fatigue, but also has other physical issues such as sore throat, muscle pain, and exercise intolerance, and it often seems to be associated with viral infection. It might be that fatigue after Covid is more related to CFS: I think this is still not clear. But even so, there are likely to be overlaps."

She points out that the fatigue of long-Covid is often associated with depressive, sleep, and cognitive symptoms – all also associated with fatigue after cancer treatment. The immune system and inflammation processes might be involved in the different fatigue syndromes.

The important thing, says Schmidt, is that there is growing attention on fatigue in general. "We need people to consider fatigue in terms of its different causes, biological mechanisms, and manifestations. That may help us get a better understanding of how it can be effectively treated."

Umberto Tirelli, senior visiting scientist and former Oncology Chief at the Oncology Referral Centre at Aviano, Italy, and a specialist in chronic fatigue, is among the scientists who believe that there may be pathological links between what we call cancer-related fatigue

and what we call long-Covid. But like Schmidt, he believes it is important to draw lines and make distinctions wherever possible.

“I think that the research that is now being conducted into long-term fatigue symptoms after Covid-19 might have relevance for the world of cancer,” says Tirelli, who is Director of the Clinica Tirelli Medical Group, which specialises in cancer, chronic fatigue, Covid-19, and preventive medicine. He believes that there are important distinctions to be made within both cancer-related fatigue, and post-Covid fatigue.

### **The overlap suggests that investigating the causes of long-Covid has the potential to throw light on cancer-related fatigue**

Two types of fatigue might be being experienced by cancer patients. Some will be experiencing fatigue as a direct result of the cancer and its treatments: there may be different underlying causes including anaemia, endocrine and metabolic disorders, and cardiovascular and renal dysfunction. Others, he believes, may be experiencing a particular type of fatigue similar to that experienced by people with CFS or myalgic encephalomyelitis (ME), with symptoms including: severe fatigue associated with memory and concentration problems, lasting tiredness after exercise, muscle and joint pain, headaches, and unrefreshed sleep. This kind of cancer-related fatigue could be considered a sub-

type of CFS, says Tirelli.

“This kind of cancer-related fatigue for me is an illness in those cured of their cancer and unrelated to metastatic disease or ongoing cancer drugs. It is similar to CFS/ME, possibly due to immunological abnormalities.”

Interestingly, he also believes there are two types of long-Covid sufferers, along similar lines. One group is suffering fatigue as a consequence of long-term damage to lungs, heart, liver, kidneys or brain resulting from Covid infection. The other is suffering debilitating symptoms such as tiredness and lack of concentration, even though there is no organ damage, and this second condition again has many similarities to CFS/ME.

The overlap suggests that thoroughly investigating the causes of long-Covid has the potential to throw light on both CFS/ME and cancer-related fatigue. There is already some evidence that CFS/ME is linked to issues in energy metabolism, nervous function, and immune response, says Tirelli.

### **Who will fund research across disease areas?**

But is such wide-ranging research likely to take place, and how successful is it likely to be?

So far, one of the leading UK research projects has been a twins study at King’s College London, which has used the Covid Symptom Study app (covid.joinzoe.com/about) to examine long-lasting symptoms, using volunteer questionnaires to try to define post-Covid syndrome, while also tracking blood markers to shed light on the immune mechanisms

### **“It is highly plausible that long-term cytokine response is at the root of all these fatigue syndromes”**

that might contribute to long-term symptoms. Its work has been supported by European as well as UK funds.

In June 2021, based on early findings, the researchers proposed a new model for identifying individuals at risk of long-Covid for trials investigating prevention and treatment. In parallel, King’s College researchers are also investigating potential triggers to changes in immune activity in CFS, particularly the role of cytokines (proteins involved in regulating the immune system).

According to Frances Williams, from the Department of Twin Research and Genetic Epidemiology at King’s, there are links between all these strands of work. But funding tends to be focused on particular discrete research questions, rather than exploring larger questions such as connections between fatigue syndromes.

“It’s exactly the sort of research we are keen to do,” she says. “There’s already some controversy over whether you can draw parallels between what we call long-Covid and post-viral fatigue, and it’s a contentious area. But in order to sort out the science in contentious areas, we need some funding to do some really well-designed studies across all areas.

“What I would like to do would be to collect some cancer patients,

### Definitions

#### What is long-Covid?

Definitions of long-Covid have been issued by both the British National Institute for Health and Care Excellence (NICE) and the National Institutes of Health in the United States.

The NICE definition ([bit.ly/UK-NICE-LongCovid](https://bit.ly/UK-NICE-LongCovid)) explains post-Covid-19 syndrome as:

- Signs and symptoms that develop during or after an infection consistent with Covid-19, continue for more than 12 weeks, and are not explained by an alternative diagnosis.
- Usually presents with clusters of symptoms, often overlapping, which can fluctuate and change over time and can affect any system in the body

Symptoms include:

- psychiatric problems
- generalised pain
- fatigue
- persisting fever

#### What is cancer-related fatigue?

The European Society for Medical Oncology 2020 practice guidelines on cancer-related fatigue ([bit.ly/ESMO-CRF](https://bit.ly/ESMO-CRF)) say it is characterised by:

- A distressing, persistent, subjective sense of physical, emotional and/or cognitive tiredness or exhaustion that is not proportional to recent physical activity and that interferes with usual functioning.
- Its severity and persistence compared to other types of fatigue, and the inability to alleviate it through rest or sleep.

root of all these fatigue syndromes.

“It is certainly clear that it is often a cytokine storm that means Covid patients require intensive care. This is something we are investigating in our twins studies, examining those who generally remain out of hospital with Covid. We had already collected lots of information about their immune systems before Covid struck, so that put us in a very strong position for trying to identify biomarkers that predict who will do badly after Covid infection. We can look at the cytokines they had circulating in their blood five to ten years ago, to see if any predict the long-term response to Covid.”

So for those with an interest in cancer-related fatigue, the big question now is whether the urgent need to better understand long-Covid will prompt broader efforts to join the dots on fatigue more generally.

It’s a possibility that there will now be a new impetus for wider research,” says Frances Williams. “But in the end it comes down to politics,” she says. “Large amounts of funding have been made available for post-Covid fatigue because it is uppermost in everybody’s minds, but it hasn’t been joined up with an overwhelming requirement to understand fatigue in general, which affects many people in different parts of the healthcare system.”

*This article was first published on the Cancer World website on 17 September 2021. To comment on or share the article go to [bit.ly/CW-LongCovid-CRF](https://bit.ly/CW-LongCovid-CRF).*

some radiotherapy patients, some chemotherapy patients, some post-viral patients, some inflammatory arthritis patients and some post-Covid patients and really study them in depth to find out whether there are similarities or differences and what the mechanisms in each of these conditions is. That requires very big scale funding, and we don’t have that at present. We do, however, have funding

to do some very Covid-specific work.”

One of the potentially common areas that certainly needs further investigation is the role of immune proteins such as cytokines. “Clearly one of the theories about cancer-related fatigue is that it isn’t necessarily the treatment that is causal, but a long-term cytokine response to treatment. I think it is highly plausible that this is at the



# TORONTO

MASCC/ISOO  
ANNUAL MEETING

2022

JUNE 23-25

SUPPORTIVE CANCER CARE

**REGISTER TODAY**

*Virtual Meeting Option Available \**

The MASCC/ISOO Annual Meeting is the foremost international and interdisciplinary conference on supportive cancer care. It covers the entire spectrum of problems experienced by patients as a result of their cancer and cancer treatment. At the 2022 Annual Meeting, you'll discover what's new and what's on the horizon in the diverse and exciting field of supportive care.

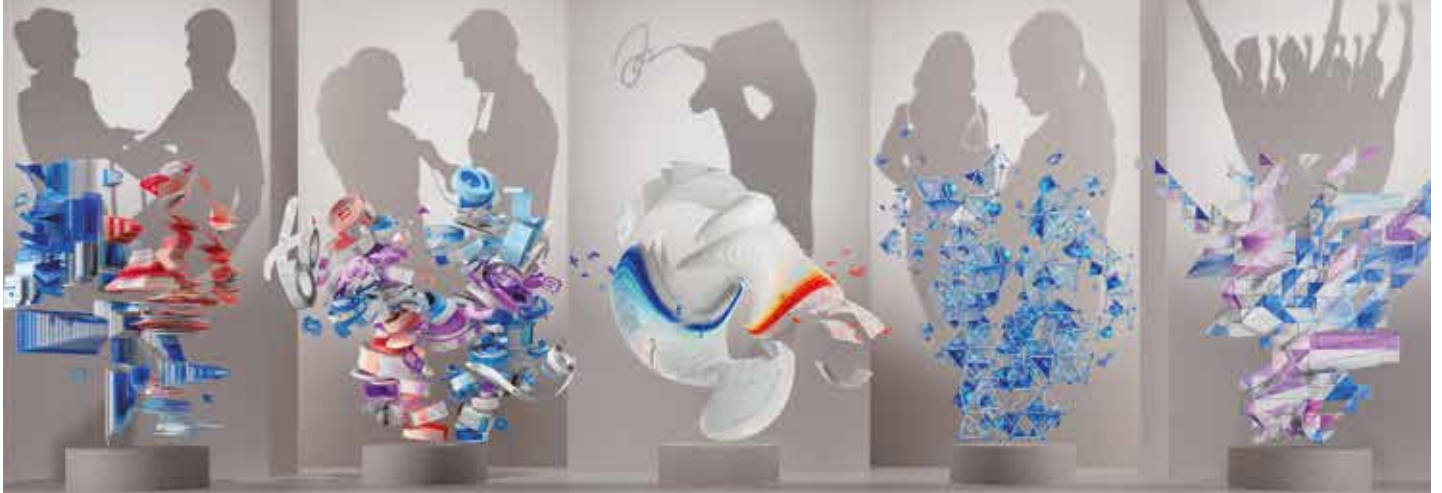
This year's meeting themes are:

- Supportive Care Post-COVID-19: Best Practices
- Disparities in Supportive Care: Solutions Needed
- Big Data and Predictive Analytics in Supportive Care
- Patient Empowerment & Self-Management Enhancement
- Burnout in Oncology (healthcare professionals & caregivers)
- Sessions on the Various MASCC Study Group Topics

**MASCC**  
MULTINATIONAL ASSOCIATION OF  
SUPPORTIVE CARE IN CANCER

**ISOO**  
INTERNATIONAL SOCIETY  
OF ORAL ONCOLOGY

\* Visit [www.mascc.org](http://www.mascc.org) for  
details & more information



*The Healthcare Journey,  
2021*

Mixed media sculptures:  
Various medical data

Understanding  
disease means  
facing an  
overwhelming  
amount of data.

No matter where you are in the healthcare journey, everyone can benefit from having less uncertainty.

Personalised Healthcare aims to give you greater clarity.

At Roche, we are collaborating with partners to create powerful tools for diagnostics and disease management to better cut through and integrate all the data available, so that everyone – from the doctors and hospital administrators, to the payers and policymakers, and the patients living with the condition – can give and receive more optimised care than ever before.

**Shining a light on the healthcare journey to give you greater clarity.  
That's Personalised Healthcare.**



# Evolution of the doctor– patient relationship *from ancient times to the personalised medicine era*

A doctor's ability to relate effectively to their patients has always been important to their therapeutic role. But never before has that relationship been so central to choosing the right option for the right patient at the right time. **Francesca Albini** and **Adriana Albini** look at how the doctor–patient relationship has evolved through history, and how it needs to evolve further to fulfil the promise of personalised medicine.

**T**he nature of the doctor–patient relationship has gone through various phases in history, based on the changing role of the physician in the community, as well as progress in medicine and increased choices of care, together with better-informed patients. Broadly speaking, the shift

in the dynamic between doctor and patient has been from an active–passive relationship towards guidance–co-operation, and more recently mutual participation.

Within Europe, cultural changes over many decades have seen a significant shift towards mutual partici-

pation, with an emphasis on informed patients and shared decision making. And with the recent rapid rise in the therapeutic options available to treat cancer, the quality of the discussion between doctor and patient has become increasingly important in ensuring that the treatment strategies

## Delivery of Care



A doctor pumps the stomach of his obese seated patient while another couple wait. One who has already undergone reduction examines his deflated countenance in a mirror.

Coloured etching by H. Heath, 1827. Credit: Wellcome Collection. Public Domain Mark

now available are used to best effect.

Yet while the nature of the relationship may have changed significantly throughout history, the quality of that relationship has always been central to quality care.

### Doctor–patient relations through the ages

A doctor figure has probably always existed in human communities. There are cave paintings representing healers that date as far back as fourteen thousand years ago. Before the secularisation of medicine brought in by the Hippocratic school in the 5th Century BCE, there were no clear-cut boundaries between medicine, magic and religion, and the doctor–patient relationship would have been an extension of the priest–supplicant, with an expected compliance from the patient, and less

personal responsibility on the part of the doctor, who was after all acting out the will of a god.

In medical literature, encounters between doctors and patients were usually described by doctors, and are thus limited to their observation and treatment of the patient, and their own professional and moral code. We might be told the outcome of a therapy, but the patient’s opinion remains unknown. The most conspicuous exception to the rule comes from the 2nd Century CE. The Greek orator Publius Aelius Aristides suffered long bouts of poor health (real or psychosomatic) and sought relief in the worship of Asclepius, the god of medicine. He spent much of his time as a patient at the Asclepeion of Pergamum, where his god-induced dreams were interpreted into cures. Eventually, Aristides wrote the *Sacred Tales*, six books in which he

records the revelations he received in dreams by the healing god. At the beginning of Book 1, in an entry dated winter 170 CE, we read, “I decided to submit truly to the God, as to a doctor, and do in silence whatever he wishes” – a dramatic example of passivity.

### Bedside manner

Before the relatively recent introduction of patient satisfaction questionnaires, and Aristides aside, to learn about the doctor–patient relationship from the patient’s perspective we must turn to fiction. Fictional characters can, of course, be somewhat biased, as they are intended to trigger a reaction in the reader. Nevertheless, it is fascinating to see how certain behaviours and deportments have been present – and contested – throughout history.

The first time the expression ‘bedside manner’ was recorded is in a famous cartoon published in the British magazine *Punch* in 1884: “Lady Visitor: ‘Oh that’s your doctor, is it? What sort of a doctor is he?’ Lady Resident: ‘I don’t know much about his ability, but he’s got a very good bedside manner.’” Rightly or wrongly, this was interpreted as meaning, “the manner that a physician assumes toward patients.”

One of the oldest human dilemmas for doctors is the delicate balance between expectations and reality – that is, how to protect the patient’s hope without lying. This is no easy task, not least because patients seem very skilled at recognising when their doctor is not being straight with them. In one of Aesop’s fables a sick man tells the doctor his dreadful symptoms, and every time the doctor comments, “That’s good”,

“That’s fine”. Finally, a friend asks the patient how he is feeling, and the patient replies, “I am dying of good signs.” The moral of the fable is: “A death-bed flattery is the worst of treacheries.”

One of the most enlightening collections of doctor–patient passages in literature is provided by Solomon Posen in his book *The Doctor in Literature* (2005). Posen was an endocrinologist and expert in bone and mineral diseases in Australia. He also had a deep knowledge of literature. One of the main purposes of his book was “to identify and analyse a number of themes that constantly recur in the portrayal of medical doctors, especially themes that seem unaffected by time, place, or clinical training.” He believes the basic relationship between patients and physicians remained essentially unchanged over two and a half millennia.

The experience of internist and rheumatologist Ed Rosenbaum, as described in his 1988 autobiography, *A Taste of My Own Medicine: When the Doctor Becomes the Patient*, would seem to bear this out. He practised as a doctor for fifty years before becoming a patient in the same hospital where he used to work. “It wasn’t until then that I learned that the physician and the patient are not on the same track,” he writes. “The view is entirely different when you are standing at the side of the bed from when you are lying in it.” The film *The Doctor*, which came out in 1991, was based on that autobiography. Both film and book show typical doctor–patient encounters that we can all relate to, and of which we see examples throughout literature. Why do doctors, like the one in Aesop’s fable, have to tell us what they think we want to hear? Why can’t they

be more straight with us, so we know where we stand and can make informed decisions? And why do they use such patronising language, as in: “How are *we* today?”, “Just a little prick”? Of course, a good doctor is preferable to a charlatan with a good bedside manner, and ultimately the physician and the patient’s goal is the same.

### From family doctor to guidelines and waiting rooms

Aside from basic remedies and surgical interventions, medicine that actually cures is a somewhat recent phenomenon in human history. The period from around the 15th to the 18th century saw a gentle upward curve of medical discoveries, which was followed by a steep rise in the 19th and 20th centuries, and then an astonishing exponential growth in the past few years, spurred by massive technological advances.

Until the past couple of decades, all patients were pretty much treated the same from the medical science perspective, with a few guidelines on adapting protocols according to co-morbidities, age, and allergies.

Most of that tailoring was done by the doctor, based on their general experience and personal acquaintance with the patient. “That big back of his has curved itself over sick beds until it has set in that shape. His face is of a walnut brown, and tells of long winter drives over bleak country roads, with the wind and the rain in his teeth.” This is how Arthur Conan Doyle describes Dr. James Winter, in the short story *Behind the Times* (1894). Those of us who are old enough should – but often don’t – remember doctors’ house calls. The patient, surrounded by family,

in their own environment, waits for the doctor with a mixture of fear and expectation. And, come rain or shine, the doctor arrives, often out of breath, carrying a bag of tools, ready to dedicate their entire soul and expertise to that one patient. The rest of the world can wait outside the front door. The doctor’s bedside manner and judgement might be poor or passable, but the dedication felt real.

But the axis has now shifted decisively from house calls to waiting rooms in doctors’ practices. In the clinic, the naturally skewed relationship between doctor and patient became more pronounced. On their own turf, doctors always seemed too busy with other patients, paperwork, interruptions by nurses and colleagues, to care about that one patient. But then things started to change.

### Putting the patient back at the centre

While healthcare was becoming technologically and scientifically ever more advanced toward the end of the 20th century, it was also becoming increasingly impersonal, which negatively reflected upon the outcome for patients, especially those with a chronic illness. Businessman and philanthropist Harvey Picker and his journalist wife Jean, who had a terminal condition, understood this, and decided to do something to improve the situation. In 1986 the couple founded the Picker Institute ([picker.org](http://picker.org)), a not-for-profit organisation dedicated to researching how healthcare systems can improve the experience of patients. Harvey Picker is widely credited with coining the term ‘person-centred care’. The institute set out the seven principles of person-centred care that are still at

### Principles of patient-centred care

The seven principles of person-centred care, originally established by the Picker Institute, are:

- Fast access to reliable healthcare advice
- Effective treatment delivered by trusted professionals
- Continuity of care and smooth transitions
- Involvement and support for family and carers
- Clear information, communication, and support for self-care
- Involvement in decisions and respect for preferences
- Emotional support, empathy and respect
- Attention to physical and environmental needs

the core of high-quality care delivery.

Many organisations have since been created worldwide to empower the patient, by providing them, their families and their carers with support, information and involvement, and patient-centred care now tops the agenda in the healthcare revolution.

The cultural shift to more patient-centred care has been reflected in challenges to the dominant terminology, for instance with the word ‘patient’ – which can be seen as denoting a passive role, where the doctor has all the agency – being substituted by ‘client’, where the doctors is seen as providing a service. Discussions within the medical community about appropriate terminology were stimulated by Julia Neuberger’s article: ‘Let’s do away with “patients”’ published in the *BMJ* in 1999 (vol 318, pp 1756–58), although no consensus has yet been reached.

### Patient-centred care in precision oncology

With its high-tech and complex diagnostics and treatment, involvement of multiple specialists in hospital and community settings, and its heavy physical and psychological

burden, cancer is a challenging – but most rewarding – disease area to implement patient-centred care.

The emergence of personalised, precision approaches to treating the disease is in a sense moving the science itself towards patient-centred medicine, in which the precise molecular biology of their disease and their own body become central to the clinical decision making. Genome sequencing, microbiomes, concepts like artificial intelligence and ‘big data’, projects like the Human Cell Atlas, all point in the direction of personalised medicine, and personalised medicine enables and requires patients to play a greater role.

And yet the progress this has brought to extending lives and improving the quality of life for many people with cancer is making the decision-making process considerably more demanding for both doctor and patient.

Until recently the scenario for cancer was pretty much black and white: there were patients with limited disease, who were curable, and patients with disseminated disease, who were treatable but incurable. Breaking and receiving bad news about a terminal condition was obviously very pain-

ful, but, in a sense, clear-cut.

Today, by contrast, there is a sort of limbo between the two conditions, where a cure remains unlikely, but where a growing number of options, associated with side-effects of varying severity, have been shown with different degrees of certainty, in specific patient populations, to hold back the disease and add varying degrees of benefit in both survival and quality of life.

The challenge for doctors is to help patients in this limbo make sense of their own situation, and the options available, so they can reach an informed decision on how far they are willing to go in risking the short- and long-term side effects, disruptions to daily life, and sometimes also expense, involved in pursuing particular treatment options for what likelihood of gaining additional months or years – or even being cured.

From an historical perspective, therefore, the ideal doctor for the era of personalised/precision oncology is one who combines the close personal relationship of the traditional family doctor, on the one hand, with the scientific precision of the most up to date high-tech diagnostics and analytics, on the other ... and then a ‘bedside manner’ that facilitates the informed discussion that is so key to working out the right treatment for the right patients at the right time.

*Opening image credit: ‘The Doctor’s Surprise’. Oil painting after JG Vibert. Wellcome collection. Public Domain Mark*

*This article was published on the Cancer World website on 30 December 2021. To comment on or share the article go to [bit.ly/CW-Doctor-Patient](http://bit.ly/CW-Doctor-Patient).*

oncotypeDX<sup>®</sup>  
Breast Recurrence Score

It's never  
been as clear™

Predicting chemotherapy benefit<sup>a,1-8</sup>

TAILORx  
and RxPONDER  
establish the  
Oncotype DX<sup>®</sup> test  
as standard  
of care<sup>1-8</sup>



**NO**  
CHEMOTHERAPY

**YES**  
CHEMOTHERAPY

<sup>a</sup> Prediction of chemotherapy benefit was established for NO patients based on NSABP B-20 study<sup>1,2</sup>, and for N1 post-menopausal patients based on SWOG-8814 study<sup>3</sup>. TAILORx and RxPONDER refined the chemotherapy benefit estimates for patients with Recurrence Score<sup>®</sup> results 11-25 and Recurrence Score<sup>®</sup> results 0-25 respectively.<sup>7,8</sup>

**References:**

1. Sparano et al. *N Engl J Med*. 2015.
2. Sparano et al. *N Engl J Med*. 2018.
3. Sparano et al. *ASCO* 2018.
4. Paik et al. *J Clin Oncol*. 2006.
5. Geyer et al. *njy Breast Cancer*. 2018.
6. Albain et al. *Lancet Oncol*. 2010.
7. Kalinsky et al. *N Engl J Med*. 2021.
8. Kalinsky et al. *SABCS* 2021.

HR+ = hormone receptor positive; HER2- = human epidermal growth factor receptor 2 negative; N0 = node-negative; N1 = node-positive (up to 3 positive nodes); TAILORx = Trial Assigning Individualized Options for Treatment (Rx); RxPONDER = a clinical trial Rx for P0sitive NoDe, Endocrine Responsive breast cancer.

It's never been as clear. Oncotype DX Breast Recurrence Score and Oncotype DX are registered trademarks of Genomic Health, Inc. Exact Sciences is a registered trademark of Exact Sciences Corporation. © 2022 Genomic Health, Inc. All rights reserved. EXS12587\_0122\_EN\_INT

oncotypeDX<sup>®</sup>  
Breast Recurrence Score

**EXACT  
SCIENCES**

# Bridging the Age Gap in Breast Cancer

## *A treatment selection tool for the over-70s*



Undertreating or overtreating? Given that older patients are heavily under-represented in clinical trials, it can be hard to know. A major UK study was set up in 2012 to generate evidence and tools to improve decision making and outcomes specifically in elderly breast cancer patients. **Alberto Costa** asked **Lynda Wyld**, Chief Investigator of the 'Bridging the Age Gap' study, about what they found, and the implications for clinical practice.

**Q.** *Surgery tends to be a bigger issue for older people, and physicians need reliable guidance on who is likely to benefit and who could be harmed. You looked at selection practices and outcomes at 56 breast units across the UK. What did you find?*

**A.** The Bridging the Age Gap in Breast Cancer study [*Br J Cancer* 2021, 125:209–219] recruited nearly 3,500 women over the age of 70, who were newly diagnosed with operable breast cancer. We wanted to collect very detailed data about their level of baseline fitness so we could understand treatment selection and age- and health-stratified outcomes. We therefore organised a prospective observational study, planning to adjust for bias by use of propensity score matching.

A key area of enquiry concerned elucidating the factors associated

with selecting patients in the age group either for surgery or for primary endocrine treatment, and the related outcomes. Of 2,854 women with oestrogen receptor positive (ER+) breast cancer, 82% had surgery and 18% had primary endocrine therapy. We found that women receiving primary endocrine treatment were older and less fit than those treated with surgery.

In terms of outcomes, with a median follow up of 52 months, an unadjusted analysis showed that all-cause mortality and mortality from breast cancer were both lower in women having surgery (HR=0.27, 95%CI 0.23–0.33,  $P<0.001$ ; and HR=0.41, 95%CI 0.29–0.58,  $P<0.001$ , respectively). However, when we performed very specific propensity score matching for age, tumour characteristics and health status, whilst all-cause mortality was still slightly better with surgery (denoting imperfect match-

ing) (HR=0.72, 95%CI 0.53–0.98,  $P=0.04$ ), breast cancer specific mortality was no longer significantly different (HR=0.74, 95%CI 0.40–1.37,  $P=0.34$ ).

We also looked in detail at chemotherapy outcomes in these women, using the same methodology. Chemotherapy was given to almost 28% (306/1,100) of fit patients who had a high breast cancer recurrence risk. Comparison of chemotherapy versus no chemotherapy demonstrated reduced metastatic recurrence risk in high-risk patients, when comparing unmatched patients (HR=0.36, 95%CI 0.19–0.68) and also when comparing propensity-score-matched patients (adjusted HR 0.43, 95%CI 0.20–0.92). However, no benefit to overall survival or breast-cancer-specific survival was found in either group. Unplanned subgroup analysis found that chemotherapy improved overall and breast-can-



cer-specific survival in women with ER-negative cancer (HR=0.20, 95%CI 0.08–0.49, and HR=0.12, 95%CI 0.03–0.44, respectively).

In both the surgery and the chemotherapy analyses, we also looked at the quality of life. In both, more aggressive treatment had negative impacts on quality of life, but these changes were transient and largely resolved after two years of follow up.

*Q. What are the key messages from the Bridging the Age Gap study?*

**A.** We concluded that surgery should be advised for the majority of women aged over 70, but in women over the age of 85–90, especially for those in poor health, consideration of primary endocrine therapy may be appropriate. For the chemotherapy analysis, we concluded that chemotherapy was associated with reduced risk of metastatic recurrence, but survival benefits were only seen in patients with ER-negative cancer. Quality-of-life impacts were significant but transient. This should be taken into account when discussing treatment options with older women.

*Q. Part of the study involved developing an online decision support tool to help reach the best decisions on treatment options. Can you tell us about that?*

**A.** The Age Gap decision tool is a decision aid for use with women who have been offered surgery or primary endocrine therapy, or women who have had surgery and are now facing a decision about whether to have chemotherapy. The online tool can be used to calculate potential outcomes from different options, stratified for age, cancer (grade, size nodal status)

and fitness. The tool was carefully developed with input from older women to ensure it met their informational needs and was designed to meet their preferred options for data display and terminology.

The tool was embedded into the second half of the Age Gap project as a cluster randomised trial, and we found that use of the tool modified treatment selection and improved patient knowledge. We were surprised that use of the tool tended to make women more likely to choose a more conservative option – presumably when they saw that survival rates differed by only relatively small amounts.

The online tool was released for wider use in the Spring of 2020, and, in its first year, was accessed over 10,000 times in more than 70 countries. We have had interest from groups in France and Canada to validate the tool for use in their own populations. We are currently developing the tool to add quality of life and adverse event data outputs alongside the survival outputs it already contains. The data from the Age Gap study will be used to develop age and health stratified outcome models for these metrics. We hope this will go live at the end of 2022.

*Q. What were the key motivations behind launching the study?*

**A.** We knew that some centres in the UK were offering surgery to women who were very frail and unfit, who were unlikely to benefit, while at other centres, relatively fit older women were being denied surgery, even though they would undoubtedly develop progression within their expected lifetime. So

we wanted to try to develop advisory thresholds for older women who might not benefit from aggressive primary treatment due to their age, frailty, comorbidity and disease biology, to help minimise over- and under-treatment in this age group. Existing guidelines such as those by the International Society for Geriatric Oncology are rather imprecise, so we needed detailed health and fitness data at baseline so we could perform stratified analysis. The Age Gap dataset then helped us to develop the online tool which can assist in this decision making process.

We also wanted to explore these differences in rates of surgery versus primary endocrine therapy and differences in rates of chemotherapy across the UK. We analysed the data from the study and confirmed that rates do vary more than can be explained by case mix. We went on to study the reasons for this variation by conducting some qualitative research and a wider questionnaire study of UK breast professionals to explore the reasons for this variation. The questionnaire included a discrete choice instrument, which presents people with a set of clinical scenarios with five variables and looks at how these sway treatment choices. These studies clearly showed that clinicians have different thresholds for how they allocate women to treatments, with age being a significant factor.

*Q. It is not easy to enrol nearly 3,500 patients in a study, and it is rarely attempted in that age group. How did you do it?*

**A.** We had previously tried to recruit to randomised trials in this age group to look at both the surgery versus primary endocrine

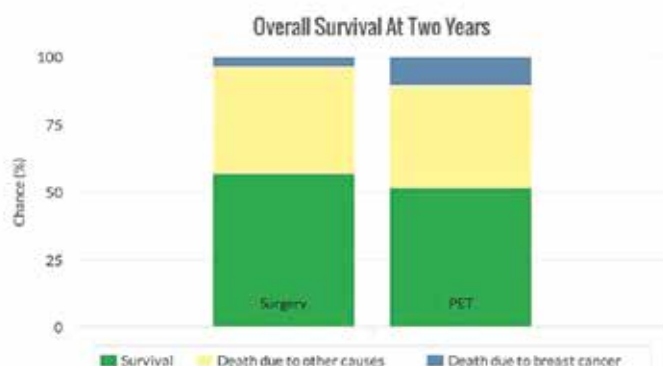
## Interview with the expert

### Age Gap Decision Tool: Surgery v PET

Age	Tumour grade	Tumour size	Disease node positive?	Comorbidities
87	3	15mm	No	Diabetes Mellitus (no complications)

Based on the details above, research suggests that the potential outcomes of surgery and Primary Endocrine Therapy (PET) are as described in the charts and diagrams below.

Age	Tumour grade	Tumour size	Disease node positive?	Comorbidities	Frailty
87	3	15mm	No	Diabetes Mellitus (no complications)	ADL Stage 1



Screenshot of the Age Gap Decision Tool comparing survival estimates between surgery and primary endocrine therapy (PET) for a patient aged 87 years, with a node-negative, grade 3 breast cancer measuring 15 mm, also diagnosed with diabetes mellitus without complications. Image captured 2 March 2021 ([agegap.shef.ac.uk/](http://agegap.shef.ac.uk/))

therapy question (ESTEEM trial) and the use of adjuvant chemotherapy (ACTION trial). Neither randomised trial was successful due

to poor recruitment, which is often felt to be an issue in this age group.

So we were pleasantly surprised that our older women were

very positive about taking part in the Bridging the Age Gap study. We started recruitment in 2013 and completed it in 2018, recruiting at 56 sites across the UK.

The trial had been specially designed to be user-friendly for older women. The study was observational, with treatment as normal, but women were asked to complete quite a lot of questionnaires, which took time to do. We allowed women to elect whether they wished to complete the quality of life questionnaires, to keep the burden of participation as low as possible. We also permitted many of the follow up visits to be done by telephone and could post the questionnaires out. We also wanted to recruit women with dementia, so we designed the trial such that a proxy could consent on behalf of women who lacked capacity to consent for themselves.

Overall, the ratio of women screened for the trial to those recruited was about 50%, which is very good. Retention rates were also excellent, with very few women withdrawing. We did notice that we slightly over-recruited the younger end of the over-70 age range, and slightly under-recruited at the older end, but our oldest recruit was 102, so we are very pleased with what we achieved.

**Q.** *The trial is exclusively a UK study. Do you expect its results to have an impact on other countries? Did you receive enquiries from other centres?*

**A.** We only recruited in the UK, as a key aim was to explore the dif-

ferences in rates of surgery versus primary endocrine therapy and differences in rates of chemotherapy across the UK, which have long been a cause for concern. We have had interest in the study from France, Canada, the Netherlands and the USA, and are collaborating with the group from Leiden, to compare our data with their own similar dataset (the CLIMB study) to see where practice and outcomes differ between the UK and the Netherlands.

**Q.** Was surgery in this elderly population mainly mastectomy or conservative procedures?

**A.** Data on the type of surgery undergone by the women in the study have been published. Of 2,854 surgical procedures, 40% underwent mastectomy and 60% breast conservation. Increasing age, tumour size, and nodal status were all significantly associated with receipt of mastectomy. This is likely to be linked to the lack of screening and reduced breast awareness in older women, resulting in larger tumours with a higher risk of node positivity.

Very few women underwent reconstruction in this over-70 age group – only 2.8% had post-mastectomy reconstruction, compared with a rate of 20% recorded in published series in the UK across all ages. Outcomes were good, with no deaths directly attributable to surgery, although the risk of adverse events was moderate.

Excluding seromas, which we regard as inevitable after breast surgery, there were 761 complications after 551/2,854 procedures. The vast majority were local complications and not classed as severe. Only 59/2,854 procedures (2.1%)

had systemic complications such as stroke, cardiorespiratory problems or deep vein thrombosis. Complications were more likely after major surgery (mastectomy or axillary clearance compared with breast conserving surgery or sentinel lymph node biopsy). This suggests that, for the majority of older women, surgery is safe and well tolerated.

However we also measured quality of life after surgery and found that it does have a negative impact on some domains of quality of life. Of particular note, compared with sentinel lymph node biopsy, axillary clearance caused a 6-point reduction in the global health score of the EORTC QLQ C30 tool, as well as greater arm symptoms. Similarly, mastectomy had a greater negative impact than breast conserving surgery. In the early post-operative period, mean role function declined by 5.2 points for women treated with primary endocrine therapy, compared with 16 points for surgery.

Pain scores increased by 1.8 for primary endocrine therapy compared with 7.1 for surgery plus endocrine therapy, and breast symptoms increased by 0.7 points for primary endocrine therapy compared to 12.7 for surgery followed by endocrine therapy.

The overall burden of illness increased by 4 points in the primary endocrine therapy group compared to 10.1 for surgery plus endocrine therapy. By 24 months many of these differences were largely back to baseline levels, but with several domains treatment had a more lasting negative impact. Changes were more notable when comparing major surgery (mastectomy or axillary clearance) with

primary endocrine therapy.

We conclude that surgery is generally safe and well tolerated, but it does have a – largely transient – negative impact on quality of life, and for the frailest older women may not be needed. Selection for treatment may be supported by use of the Age Gap decision tool.

*The Bridging the Age Gap study was funded by a programme grant from the UK National Institute for Health Research (NIHR).*

### About Lynda Wyld

Lynda Wyld, Professor of Surgical Oncology at the University of Sheffield and Honorary Consultant Surgeon at the Jasmine Breast Centre, Doncaster, England, is Chief Investigator of the Bridging the Age Gap study. She has served as President of the British Association for Surgical Oncology, Board Member of the European Society of Mastology (EUSOMA), Chair of the Education and Training Committee of the European Society of Surgical Oncology (ESSO), and Chair of the European Union of Medical Specialists (UEMS) Surgical Oncology exam board. She has published extensively on managing breast cancer in older women.

*This article was published on the Cancer World website on 2 March 2021. To comment on or share the article go to [bit.ly/CW-AgeGap](http://bit.ly/CW-AgeGap)*



# Tackling drug resistance

## *How our commensal bacteria can hinder or help*

From immunotherapies and antimetabolites to endocrine therapies, evidence is emerging about how our gut microbes can influence our response to cancer treatments. **Rachel Brazil** hears from leading researchers about how this new knowledge might be used to improve the impact of current treatments, and about why oncologists need to be more aware of the influence of the microbiome on the treatments they prescribe.

**R**esponse to therapeutics can differ widely from patient to patient, with some gaining highly significant survival benefits from a therapy that in others elicits no response at all. Patients who respond initially often develop resistance or

relapse over time. Not all of this can be explained by tumour genetics. Another factor that is increasingly recognised to play a key role in therapy response is our microbiome – the community of bacteria and other microbes that are our fellow travel-

lers through life. There is emerging evidence that it plays a crucial role in cancer drug response, and that in some cases there is a correlation between the microbiome and resistance to treatment.

The largest microbial commu-

nities in animals are found in the digestive tract; they include a complex ecosystem of approximately 300–500 bacterial species. In general they are considered to exist symbiotically, assisting with the breakdown of food and synthesis of certain vitamins and amino acids.

This means they also interact with the drugs we take orally. “Bacteria are able to produce enzymes that can break down or metabolise drugs,” explains pharmacologist Niall Hyland, from University College Cork, Ireland. “The enzymes that are produced by the microbes could perhaps inactivate that drug, which could have a negative impact, or in some cases it could activate the drug, which could be beneficial.” Even when drugs are not given via an oral route, they may be broken down by the liver and their metabolites secreted into bile and subsequently released into the small intestines, where interaction with the microbiome becomes possible.

More surprisingly, perhaps, we are learning that the field of interactions involving the microbiome is not limited to the gut. “It has become clear in the last decade that bacteria [are] basically everywhere,” says Godefridus Peters, a professor of pharmacology of cytostatics at the Vrije Universiteit, Amsterdam. There is surprising evidence that bacteria are present inside tumours, with the potential to impact drug performance (*Science* 2017, 358:1443–48). The extremely low numbers have made this difficult to study, but results published in 2017, by Susan Bullman, from Harvard Medical School in Boston, Massachusetts, showed that the *Fusobacterium nucleatum* gut bacteria, found to be prevalent in colorectal

tumour sites, was also found in distant liver metastases from colorectal primaries.

What is now very clear, says Giorgio Trinchieri from the US National Cancer Institute in Maryland, is that for many drugs, how a patient responds is linked to their gut microbiome. “Certain bacteria species are associated with a good response and certain with a bad response,” he says. The intravenously-administered chemotherapy, gemcitabine – commonly used to treat pancreatic ductal adenocarcinoma, and as an adjunct treatment for certain types of ovarian cancer, non-small-cell lung carcinoma, and metastatic breast cancer – is an example of such a drug.

### The emerging evidence

Gemcitabine (2',2'-difluorodeoxycytidine) is a nucleoside metabolic inhibitor, whose incorporation into cells prevents their division. Peters first became aware of the problem when a cancer cell line in his lab developed a resistance to this cytotoxic. After some investigation, he says, “it appeared that this was due to mycoplasma infection, which would degrade the drug.” Mycoplasma are bacteria with no cell wall, and they are capable of converting gemcitabine into an inactive metabolite (2',2'-difluorodeoxyuridine). A similar result was published in 2017, but in this case the culprit was gamma-proteobacteria – a diverse class of gram-negative microbes. The common factor was their expression of an enzyme cytidine deaminase, which the research team hypothesised was being expressed by intra-tumoural bacteria. They found 76% of pancreatic ductal adenocarcino-

mas tested for bacteria were positive – mainly for gamma-proteobacteria (*Science* 2017, 357:1156–60). Peters has also collaborated on a study to investigate similar resistance patterns with EGFR inhibitors such as osimertinib, a third-generation tyrosine kinase inhibitor used to treat lung cancer (*J Can Res Clin Oncol* 2021, 147:3135–37).

## The emergence of endocrine resistance in mice can be delayed by treating them with antibiotic therapy

Another very important result, published in October 2021, has shown how the microbiome may be an important factor in the onset of castration-resistant prostate cancer (*Science* 2021, 374:216–24). In many patients prostate cancer can be controlled by reducing androgen production, but resistance to this treatment can occur, where the treatment is no longer able to lower the patient's testosterone levels, rendering the cancer much harder to treat. “This inevitably occurs in 10–15% of patients affected by prostate cancer,” says oncologist Andrea Alimonti, from the IOR Institute of Oncology Research in Bellinzona, Switzerland. Research he carried out as part of an international consortium of researchers, which included analysing the gut microbiomes of 74 resistant and non-resistant patients, together with studies in mice, found an expansion of “peculiar bacterial microflora,” associated with endocrine resistance.

The study identified non-response with the bacterial species *Ruminococcus gnavus*. “We have shown that this species of bacteria can actually start to produce androgen from [the] precursor [pregnenolone], which is available in the intestine,” explains Alimonti. Pregnenolone, produced in the pituitary gland, reaches the gut via the liver, and when it gets there is metabolised by *Ruminococcus* bacteria. “This was really very exciting, because we proved by several experiments that [the *Ruminococcus* bacteria] can uptake pregnenolone and convert it through into testosterone.” Alimonti was able to show that the emergence of resistance in mice can be delayed by treating them with an antibiotic therapy, whilst a faecal transplant of bacteria from resistant mice can lead non-resistant mice to develop resistance. They now hope to understand whether a specific microbiome signature can predict prostate cancer survival.

Response to immunotherapy has also been linked to the composition of the gut microbiome. Several international studies looking at response to anti-PD1 treatment in patients with melanoma and epithelial cancer have shown an association (*Science* 2017, 359:91–97). A 2018 study of 112 melanoma patients, conducted by Jennifer Wargo from the University of Texas MD Anderson Cancer Center and others, showed significant differences in the diversity and composition of patient microbiomes, with responders having a relative abundance of bacteria of the *Ruminococcaceae* family (*Science* 2017, 359:97–103). Similar links have been found for anti-CTLA4 immunotherapies. There is also some evidence to show that antibiotics given

before or soon after immunotherapy may cause patients to relapse quicker and decrease overall survival. A recently published study has, however, found that taking antibiotics prior to anti-PD1 treatment does not negatively impact outcomes in patients with advanced melanoma (*J Natl Cancer Inst* 2022, djac019).

### **“Sometimes even patients with a hot tumour will not respond... that may be caused by the microbiota, particularly gram-negative bacteria”**

For a patient to respond to immunotherapy, the tumour must be ‘hot’ – meaning it shows signs of inflammation and infiltration by the T cells that are needed to kill cancerous cells. But sometimes, says Trinchieri, “even patients with a hot tumour will not respond, and we think that may well be caused by the microbiota, particularly by gram-negative bacteria.” These types of bacteria produce large lipopolysaccharide molecules on their outer membrane, and elevated levels of lipopolysaccharide are linked with a number of unfavourable changes in human health.

### **Mechanisms of action**

Research into the link between response to cancer drugs and the microbiome is making some headway but, so far, the mechanisms involved seem to be different for each drug. “[While] they’re clearly not generalisable, they’re probably all true, but that doesn’t mean [the

mechanism] is effective in every patient,” says Trinchieri. Alimonti does suggest, however, that the mechanisms he and others have investigated in prostate cancer may also be apparent in breast cancer, which can be promoted by the hormone oestrogen – but the evidence has not yet been collected.

Part of the difficulty in interpreting the evidence stems from the extent to which microbiomes differ from patient to patient. “The gut microbiota can be extremely variable according to the race, sex or geographic location of a specific patient,” says Alimonti. And as Trinchieri points out, the type of microbes present in a person’s gut do not change much over time: “Once the bacterial species are present in the individual, this is more or less fixed for life, although the relative proportion can still change dramatically,” he says. This has meant that studies carried out in different locations often highlight different bacteria as the culprits behind – or indeed the solution to – drug resistance.

Trinchieri’s team recently made a major effort to bring together all the data currently available, which they expect to publish soon. Using data from the American Gut Project ([microsetta.ucsd.edu](http://microsetta.ucsd.edu)), involving 20,000 faecal donors, they have found regional microbiome clusters distributed geographically across the US, and have used this to understand differences observed in cancer drug response data. “You can actually start to get a much more consistent picture. It’s not perfect... it’s not always the same bacterial species, but at least when you [look at] groups of species and so on, you find this consistent among the different studies,” Trinchieri explains. This

should start to help with the first step in dealing with the issue – stratifying patients into those who are likely or unlikely to become resistant to a treatment.

Adding a further layer of complexity, the pharmacologist Hyland adds that we do have to bear in mind that the disease itself may also create changes in the microbiome. “The microbiome can be different at different points during the tumorigenic process,” he says, “and that of course could then inform how a person might respond to a particular drug. Then maybe we need to be going beyond just looking at a single-point-in-time analysis and really better understand how the microbiome is changing.”

### **Tackling microbiome-driven resistance**

So far, there have been a variety of approaches to dealing with drug resistance. In Alimonti’s prostate cancer study, patients were given antibiotics on top of their standard therapy to prevent the expansion of the resistance-causing bacteria. His team are now undertaking further trials in Switzerland and at the Royal Marsden Hospital in England, with a cocktail of four antibiotics. “We are going to see whether, by doing this, we can achieve a more

**“Antibiotics can alter the microbiome in a negative way... oncologists need to clearly record when treating patients for infections”**

durable response in patients and we can impact on the circulating levels of testosterone.”

But evidence from other studies shows that antibiotics can also alter the microbiome in a negative way. Pharmacologist Peters says this is something that oncologists now need to think about and clearly record, when treating cancer patients for infections. “Oncologists sometimes just mention antibiotics, and do not really specify which type of antibiotic.” Understanding exactly how antibiotics are used is now an imperative, he adds. “There needs to be awareness that the microbiome is playing a role in the treatment of cancer.”

Another treatment option is using probiotics – providing bacteria identified with a positive drug response. In prostate cancer, Alimonti’s team identified several ‘good’ species of *Prevotella* bacteria associated with non-resistant patients. “We have cultured one of these (*Prevotella stercorea*) and we have seen that, if you supplement the mouse with this *Prevotella*, essentially you prevent the expansion of the bad bacteria.” They also showed *Prevotella* was able to inhibit tumour growth in culture. Alimonti is looking to generate a probiotic that could be used to prevent the onset of castration-resistant prostate cancer, or alternatively a ‘postbiotic’, which would not contain the bacteria itself, but a mixture of the enzymes secreted into culture by the bacteria.

The probiotics approach has not always been successful in other areas, however; for example, a 2008 study of probiotics to treat pancreatitis showed increased risk of mortality (*The Lancet* 2008, 371:651–659). As Trinchieri points

out, when you add one species, “you don’t know exactly how you’re going to alter the ecology.” An alternative approach could be faecal microbiota transplantation, which involves administering a solution of faecal matter from a donor into the intestinal tract of a recipient. “You’re basically replacing one type of ecology with a different type of ecology,” explains Trinchieri. The treatment is currently used to treat persistent *Clostridium difficile* infections.

**“If we continue to supplement them with this faecal microbiome, we delay the occurrence of resistance for a very long time”**

Alimonti showed this approach was successful in mice, using transplants from patients or mice sensitive to the hormone therapy. “The mouse never developed castration-resistant prostate cancer. So, if we continue to supplement them with this faecal microbiome, essentially we delay the occurrence of the resistance to standard of therapy for a very long time.” Trinchieri also used this approach for two groups of 25 patients on anti-PD1 immunotherapies. Whilst it was not a controlled study, he says, “the results are dramatic enough to believe in the protocols.” But he does concede, “It’s not obviously [an] ideal type of treatment.” There is of course the concern that pathogens could be transferred inadvertently to a possibly already immunocompromised patient. “The other problem is that

we cannot really yet say for sure, ‘use this donor and the patient will respond’,” he adds.

In the long term, there may be solutions in new or improved pharmaceuticals than can counter the negative effects of the microbiome. Trinchieri suggests that, once we have a better understanding of the mechanisms involved in microbiome-mediated drug resistance, “the same pathway could be targeted by small molecules.” Peters says we may be able to take advantage of the difference between human cells, which have a permeable membrane, and the bacterial cell wall. “With a bacterium, the uptake is different... [so] you can design your drug in such a way that it can bypass this.”

### The implications for dietary advice

The other important consideration is diet, and the advice patients should be given to try to preserve a healthy microbiome. It probably won’t come as a surprise that high-fibre diets seem to be protective. In December 2021, Trinchieri, in collaboration with several research teams including Jennifer Wargo at MD Anderson, published a study showing that a high-fibre diet was associated with significant improvements in progression-free survival among melanoma patients taking anti-PD-1 immunotherapy (*Science* 2021, 374:1632–40). “The amount of fibre in the diet has a clear-cut effect on the response of the patient,” he says.

In mice they demonstrated an impaired response to the drug when given a low-fibre diet or probiotics containing commercially available bacteria, *Bifidobacterium longum* or *Lactobacillus rhamnosus*. The pos-

itive benefits of a high-fibre diet are of course not limited to impacts on drug resistance, says Hyland. “Fibre that can be converted into short-chain fatty acids tend to have a beneficial effect, and that’s also the case in cancer prevention strategies.”

### “There may be multiple bacteria that, in the future, could be discovered to impact prostate or another type of cancer”

Another interesting dietary strategy could be eating fermented food, which can alter the microbiome balance. Recent evidence shows these foods can increase microbiota diversity and decrease inflammatory markers, but so far there is no data on its impact on drug metabolism. “In general, a good diversity of foods in your diet as well is going to help promote the healthy microbiome state that we want to achieve,” says Gerard Clarke, a neuropharmacologist from University College Cork, in Ireland.

Clarke has been studying the bidirectional communication between the brain and intestinal functions, which seems to be influenced by the gut microbiota.

He has looked at interactions involved with antipsychotic drugs, but has now also started to consider whether there may be similar impacts involving cancer therapies, given that the occurrence of such side-effects also vary greatly from patient to patient. “We’re really just at the tip of the iceberg,” he believes. Clarke has hypothe-

sised that the typical neurological effects, sometime characterised as ‘brain fog’, can be related to the microbiome. “It’s very plausible to us that the microbiota could play a role there,” says Clarke, who has started investigating the symptoms in immunotherapies.

There is still much to learn about the microbiome and its influence on the treatment of cancer. Alimonti acknowledges the complexity of the microbiome will make it difficult to pin down some of the precise mechanisms causing drug resistance. “There may be multiple bacteria that, in the future, could be discovered [to] impact prostate or another type of cancer,” he says.

While the microbiome is only one among many mechanisms known to play a role in the development of resistance to anti-cancer therapies, its contribution can no longer be ignored. “We probably need to open our minds a bit more,” says Hyland. “We think we know how drugs work, we think they’re affecting DNA synthesis, or our protein metabolism, but actually, there might be an unknown mechanism of action, which involves the microbiome, which is either contributing to drug efficacy or contributing to drug toxicity. We need to take that into consideration.”

*This article was first published on the Cancer World website on 7 January 2022 ([bit.ly/CW-resistance-microbiome](https://bit.ly/CW-resistance-microbiome)). It has been updated to reflect the latest evidence on the impact of antibiotics taken before anti-PD1 treatment of advanced melanoma.*





## **60 Years of the European Organisation for Research and Treatment of Cancer**

### ***Celebrating the Past, Inspiring the Future***

The European Organisation for Research and Treatment of Cancer (EORTC) will celebrate its 60<sup>th</sup> Anniversary on September 30<sup>th</sup>, 2022 bringing together our members, partners, patient advocates and other key stakeholders in cancer research.

Beyond celebrating EORTC's past through revisiting this organisation's remarkable achievements, this important event will also look to the future, as the EORTC adapts to a changing landscape. Key experts will give insights on **how clinical cancer research has evolved**, and **what the future should look like** for the EORTC. There will be discussions with policymakers on how clinical research can help shape European policies and how EU institutions can facilitate a comprehensive European agenda for clinical cancer research.

Find out more about our programme and the inspiring **sessions** we are preparing:

- Reflect on the Past to build the Future
- Multidisciplinary clinical cancer research in 21<sup>st</sup> Century
- An alliance for independent clinical cancer research: creating opportunities
- Clinical cancer research: a European vision

#### **EORTC – A history of changing practice**

EORTC's 1400+ studies have helped make significant impact in the treatment and management of cancer, evaluating new molecules, refining existing treatment regimens, identifying biomarkers, and assessing patients' quality of life – resulting in practice-changing

treatments and the establishment of new standards of care for cancer patients.

#### **An evolving organisation, with multidisciplinary as a mantra**

*'We have revamped EORTC's governance to make it truly competitive in today's clinical research environment'*, says Prof. Bertrand Tombal, EORTC Immediate Past-President.

As more people are affected by cancer, there is a critical need for better understanding this multifaceted disease – through research and **collaboration**. Collaboration is part of EORTC's DNA: we **join forces** with partners across disciplines, borders, and across tumours, **to overcome global cancer challenges**.

*'EORTC has always been and will be the place for cancer scientists from all over Europe collaborating to improve the outcome of our patients. We can't do that in silos'*, says Prof. Winette Van der Graaf, EORTC President *'Clinical research is teamwork'*.

EORTC's 60<sup>th</sup> Anniversary celebration is an opportunity to welcome clinical research groups from across the world to foster better alliances, reducing inefficiencies and striving for the best care for cancer patients, to ultimately improve their survival and quality of life.

Join us in Brussels to celebrate the 60<sup>th</sup> Anniversary of this truly unique organisation.

For more information visit: [www.eortc.org/60anniversary](http://www.eortc.org/60anniversary)



Sharing Progress  
in Cancer Care

# IMPROVING CANCER OUTCOMES AND LEADERSHIP COURSE: AN ESO, ECO & SPCC EUROPEAN INITIATIVE



Warsaw, Poland

**7-9 JULY 2022**

**HYBRID COURSE**  
*online + in-person event*

Further details and application  
via [www.eso.net](http://www.eso.net) (Future Events) or email [chall@eso.net](mailto:chall@eso.net)



# Preventing alcohol-related cancers in Europe

## *Lessons from three countries*

Europe has the highest drinking levels in the world, and cancers resulting from drinking alcohol end more lives in Europe than any other alcohol-related cause of death. Europe's Beating Cancer Plan has set a target of reducing harmful use of alcohol by 10% by 2025. **Esperanza Escribano** looks at what the experiences of three member states can tell us about how this target might be reached.

**A**lcohol can be bad for your health. Most people know that. But what many people have yet to grasp is that – like smoking tobacco – drinking alcohol can significantly raise their risk of developing and dying from a wide range of cancers. According to the World Health Organization, in the

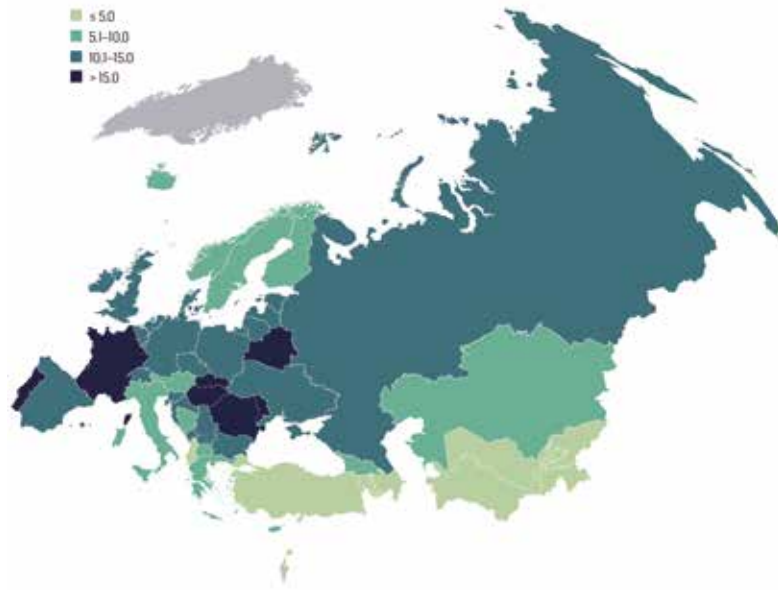
EU+ countries, cancer was the main cause of deaths due to alcohol in 2016, accounting for almost 3 in 10 alcohol-attributable deaths, followed by liver cirrhosis, cardiovascular disease and injury.

Getting that message across, and changing behaviours, is a particular issue for cancer control in Europe,

which leads the world in alcohol consumption.

The World Health Organization estimates per capita consumption in its European region (2016 data) to be 50% higher than the global average (9.98 vs 6.4 litres/adult/year). Estimates from the International Agency for Research on Cancer (IARC) indi-

## Comparative map of cancer cases caused by alcohol



Age standardised rates of cancer cases in the WHO European region caused by alcohol, per 100,000 (2018)

Source: WHO Regional Office for Europe (2020) *Alcohol and cancer in the WHO European Region: an appeal for better prevention*. WHO Regional Office for Europe, Copenhagen

cate that, of the 4.2 million cancers diagnosed in the WHO European region in 2018, 4.3% – i.e. almost 1 in 20, or 180,000 in all – could be attributed to alcohol. Those figures vary significantly between countries; in Turkey for instance, fewer than two per 100,000 people are diagnosed with a cancer attributed to alcohol, while in Hungary and Romania that figure rises ten-fold to almost 20 per 100,000.

It was no surprise therefore to see alcohol control feature in the European Commission’s Europe’s Beating Cancer Plan, which was launched February 2021. The Commission has set a target to achieve a relative reduction of at least 10% in the harmful use of alcohol by 2025. To get there, the Commission says it will “increase support for the

Member States and stakeholders to implement best practices and capacity-building activities to reduce it”. In addition, it will review EU legislation on the taxation of alcohol and cross-border purchases of alcohol by private individuals. This article will have a look at the alcohol policies of three EU countries with different experiences in alcohol regulation.

### Alcohol and cancer

IARC classifies alcohol consumption as a human carcinogen in the oral cavity, pharynx, larynx, oesophagus, colorectal, liver and female breast cancers.

### Biology

The mechanisms by which alcohol exerts its carcinogenic effect have

not been defined, because alcoholic beverages are complex mixtures, but ethanol is known to be the predominant agent responsible for carcinogenesis. A population study of the ‘Global burden of cancer in 2020 attributable to alcohol consumption’, published in *The Lancet* (vol 22, pp 1071–80), notes several biological pathways by which the consumption of alcohol, such as ethanol, can lead to cancer, including “DNA, protein, and lipid alterations or damage by acetaldehyde, the carcinogenic metabolite of ethanol; oxidative stress; and alterations to the regulation of hormones such as oestrogens and androgens.”

### Epidemiology

The risks vary by cancer type: the proportion of deaths accounted for by alcohol is higher for cancers of the head and neck than for any other type of cancer, but in terms of overall deaths, the biggest toll is in breast cancer.

As the WHO points out in its 2020 briefing on *Alcohol and cancer in the WHO European region*: “all types of alcoholic beverages, including beer, wine and spirits, are linked to cancer, regardless of their quality and price,” with the risks of developing cancer increasing “substantially” the more alcohol is consumed ([bit.ly/WHO-Alcohol-Cancer](https://bit.ly/WHO-Alcohol-Cancer)). No level of consumption is entirely safe, it emphasises, with the equivalent of just a single glass of wine a day estimated to have accounted for more than 4,600 breast cancer cases in women in the WHO European Region in 2018.

According to the *Lancet* Global burden study, of almost 750,000 alcohol-attributed cases of cancer diagnosed worldwide in 2020, ‘mod-

erate' alcohol consumption (less than 20g per day) accounted for 103,100 cases (14%), 'risky' consumption (between 20 and 60g per day) accounted for almost 291,800 cases (40%) and 'heavy' consumption (more than 60g per day) accounted for around 346,400 (47%).

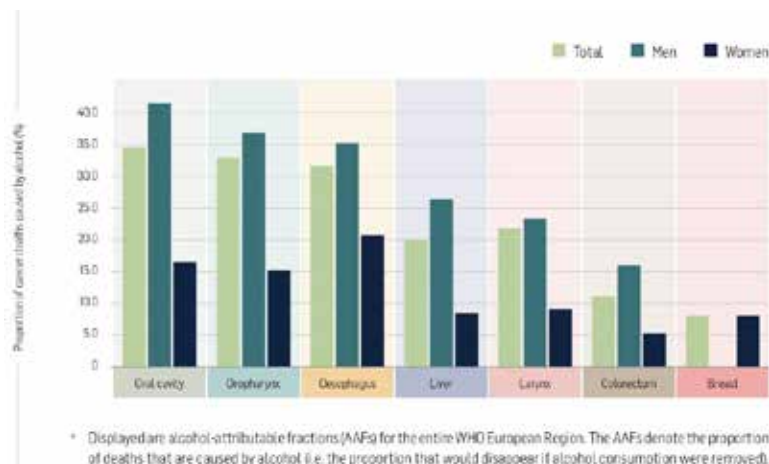
### Alcohol and Europe – different cultures, different policies

What we drink, how much we drink, and drinking patterns vary across Europe, as do policies and regulations designed to control the use of alcohol. In general, for instance, 'binge drinking' episodes (heavy episodic drinking) are more common in Northern European countries, while Mediterranean countries drink more wine with their meals. Different countries make different use of various policy options for controlling alcohol consumption, such as excise tax, restrictions on advertising, age limits, limits on where or when alcohol can be purchased, and drink driving legislation.

If EU member states are to achieve the goal set down in Europe's Beating Cancer Plan to reduce harmful use of alcohol by at least 10%, they will need to assess and build on their existing policies and work out the most effective way to change existing drinking cultures for the better.

While there can be no 'one-size-fits-all' solution, member states can certainly learn from each other's experiences – both bad and good. Below, we look at the experience of three countries: Lithuania, the country with the highest per capita consumption in the EU, Slovakia, where alcohol consumption is around average for the EU, and

## Proportion of cancer deaths attributable to alcohol



Proportion of cancer deaths, per cancer type, that are attributable to alcohol (alcohol-attributable fractions), by sex, 2018

Source: WHO Regional Office for Europe (2020) *Alcohol and cancer in the WHO European Region: an appeal for better prevention*. WHO Regional Office for Europe, Copenhagen

Italy, which per capita drinks less than any other EU member state.

Notable differences between the countries, as documented in the comprehensive WHO *Global status report on alcohol and health 2018*, include what is drunk, and patterns of drinking ([bit.ly/WHO-global-alcohol-health](https://bit.ly/WHO-global-alcohol-health)). In Italy, wine accounts for 65% of all alcohol consumed, while in Lithuania it accounts for a mere 7% and in Slovakia 21%. Spirits, by contrast, account for only 10% of alcohol consumption in Italy, compared with 37% in Lithuania and 42% in Slovakia.

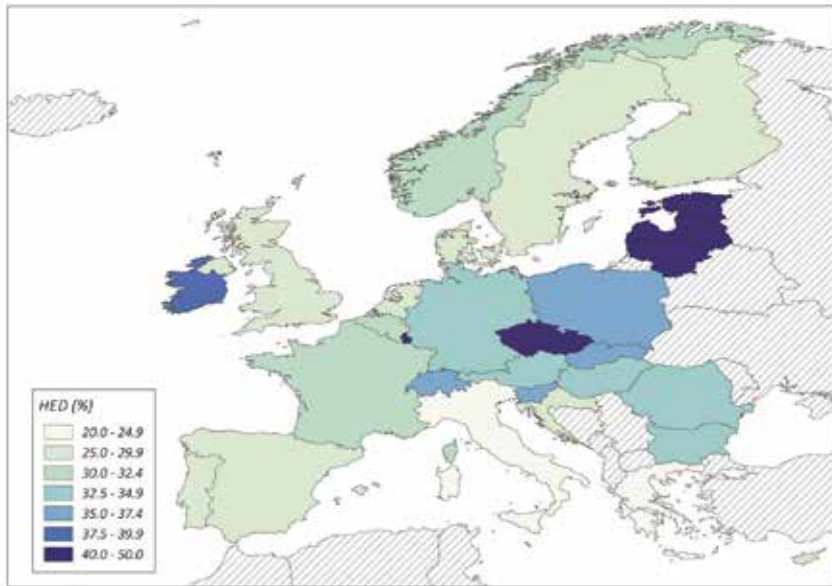
Episodes of binge drinking are also more rare in Italy, where, in 2016, 37% of men and 8% of women reported drinking the equivalent of at least 60 grams of pure alcohol "on at least one occasion in the past 30 days". This compared with 71% for men and 32% for women in Lithuania and 56% of men and 18% of women in Slovakia.

### Lithuania: a roller coaster ride

Lithuania is not only one of the countries with the highest alcohol consumption, but also a country where the benefits associated with controlling alcohol consumption can best be observed. Consumption indicators have undergone dramatic changes with changes in its policies since Lithuania gained independence from the USSR.

Alcohol consumption was relatively low during Soviet times, due to a very restrictive anti-alcohol campaign launched in 1985. In 1990, when Lithuania declared its independence from the USSR, all foreign laws were banned. Accession to the European Union in 2004 resulted in a rise in disposable income, and this, combined with the very weak alcohol control policies, is seen as a major factor contributing to the rapid rise in alcohol consumption, which

Prevalence of ‘heavy episodic drinking’ (HED)



Percentage of adults with at least one occasion of a minimum intake of 60g pure alcohol ‘in past 30 days’ in EU+ countries, 2016

Source: WHO Regional Office for Europe (2019) *Status Report on Alcohol Consumption, Harm and Policy Responses in 30 European Countries 2019*, Figure 4. © WHO 2019

almost tripled from 5.56 litres of pure alcohol per person 1990 to 15.4 litres in 2010.

That rise was reflected in growing death rates from alcohol-attributed cancers, which by 2016 accounted for 280 deaths per 100,000 men and almost 135 per 100,000 among women ([bit.ly/WHO-global-alcohol-health](https://bit.ly/WHO-global-alcohol-health)).

In the last three decades, alcohol control policies have undergone a roller coaster in which there have been cycles of stricter control and stages in which consumption has been liberalised.

During the early '90s, nearly all the alcohol control laws vanished. There was no regulation of production, import or sale of alcohol until 1995. The Alcohol Control Law, the main policy document, was adopted

that year. But 63 amendments came into effect between 1995 and 2020, making it the most frequently reformed act in Lithuanian democratic history.

“Let’s say alcohol consumption was a well-developed culture,” says Mindaugas Štelemekas, from the Health Research Institute of the Lithuanian University of Health Sciences. “The very first law prohibited home-brewed alcohol beverages, but not those naturally fermented below 18% [alcohol by volume] and 9.5% in the case of beer,” he says.

Sales were restricted to people over 18 years old and were forbidden for intoxicated people and uniformed officers. Sales of alcoholic drinks were also banned in healthcare, education or sports facilities, shops selling stuff for children, petrol stations

and vending machines.

The foundation of all future changes in alcohol policy came with a norm criminalising drink-driving in 2000, says Štelemekas. But a year after, an amendment came into effect allowing alcohol to be sold in petrol stations. It was not banned again until 2016, when Lithuania renewed its commitment to alcohol control, with the establishment of the State Fund for Public Health Promotion.

Alcohol consumption in that year was 15 litres per capita – almost triple the level for 1995 – and accounted for approximately 7.6% of total deaths in Lithuania. This was the first time community action toward alcohol prevention harm was publicly supported, says Štelemekas.

The first real demonstration of political commitment to alcohol control had come almost a decade earlier, in 2008, which was declared the ‘Year of Sobriety’. But it wasn’t until the end of 2018 that the country adopted its National Programme for Drug, Tobacco, and Alcohol Control and Prevention 2018–2028, which for the first time developed a public health response, with the perspective of a decade.

The legal minimum age to purchase alcohol was increased to 20 years and retail hours were reduced from 10 am until 8 pm on Mondays

**“The main problem is that the alcohol control policy in Lithuania focuses on laws, rather than documents developed by experts”**

to Saturdays, and from 10 am to 3 pm on Sundays, “[though] we still have a huge problem with people going drunk to work on Monday morning,” Štelemekas comments.

Štelemekas contributed to an expert review of the Lithuanian Alcohol Control Legislation between 1990 and 2020, which was published in 2020, with the aim of informing effective policies going forward (*Int J Environ Res Public Health* 2020, 17:3454).

“The development of alcohol control policy in Lithuania reflects the complexity confronting decision-makers in balancing the economic and public health interests,” he says, and he argues strongly in favour of investing in and listening to expert advice to inform policy making. “The main problem is that the alcohol control policy in Lithuania focuses on laws, rather than documents developed by experts,” he says.

There are signs that this approach may now be changing. The most recent amendments to alcohol control laws came about through a transparent and democratic parliamentary process, which Štelemekas sees as a welcome sign that his country is going in the right direction.

### Slovakia: targeting adolescent drinking

Slovakia has a mix of two diverse cultures regarding alcohol consumption. It has many vine growing areas, where wine is part of daily life, as it is in Mediterranean countries. But at the same time, the consumption of spirits is quite high, and often results in intoxication, according to a 2011 study on alcohol-related mortality in regions in Slovakia (*Health*

## Reducing harmful use of alcohol: how policies compare across EU member states (#1)

	Written national policy (adopted /revised)	National action plan	Excise tax			National legal minimum age for off-premise sales of alcoholic beverages			National legal minimum age for on-premise sales of alcoholic beverages		
			On beer	On wine	On spirits	Beer	Wine	Spirits	Beer	Wine	Spirits
Austria	Yes (2016/-)	No	Yes	No	Yes	Subnational			Subnational		
Belgium	No	—	Yes	Yes	Yes	16	16	18	16	16	18
Bulgaria	Yes (1973/2016)	No	Yes	No	Yes	18	18	18	18	18	18
Croatia	Yes (2010/-)	No	Yes	No	Yes	18	18	18	18	18	18
Cyprus	Yes (2004/2013)	Yes	Yes	No	Yes	17	17	17	17	17	17
Czechia	Yes (2003/2016)	Yes	Yes	Yes	Yes	18	18	18	18	18	18
Denmark	Subnational	—	Yes	Yes	Yes	16	16	18	18	18	18
Estonia	Yes (2014/-)	Yes	Yes	Yes	Yes	18	18	18	18	18	18
Finland	Yes (2003/2015)	Yes	Yes	Yes	Yes	18	18	20	18	18	18
France	Yes (2008/2013)	No	Yes	Yes	Yes	18	18	18	18	18	18
Germany	Yes (2003/2012)	No	Yes	No	Yes	16	16	18	16	16	18
Greece	No	—	Yes	Yes	Yes	18	18	18	18	18	18
Hungary	No	—	Yes	No	Yes	18	18	18	18	18	18
Ireland	Yes (1996/2013)	No	Yes	Yes	Yes	18	18	18	18	18	18
Italy	Yes (2001/2007)	Yes	Yes	No	Yes	18	18	18	18	18	18
Latvia	Yes (2005/2012)	Yes	Yes	Yes	Yes	18	18	18	18	18	18
Lithuania	Yes (1998/2016)	Yes	Yes	Yes	Yes	18	18	18	18	18	18
Luxembourg	No	No	Yes	No	Yes	16	16	16	16	16	16
Malta	No	—	Yes	Yes	Yes	17	17	17	17	17	17
Netherlands	Yes (2007/2016)	No	Yes	Yes	Yes	18	18	18	18	18	18
Norway	Yes (1998/2012)	No	Yes	Yes	Yes	18	18	20	18	18	20
Poland	Yes (1996/2016)	No	Yes	Yes	Yes	18	18	18	18	18	18
Portugal	Yes (2009/2015)	Yes	Yes	No	Yes	18	18	18	18	18	18
Romania	No	—	Yes	Yes	Yes	18	18	18	18	18	18
Slovakia	Yes (1993/2016)	Yes	Yes	Yes	Yes	18	18	18	18	18	18
Slovenia	Yes (2009/2016)	No	Yes	No	Yes	18	18	18	18	18	18
Spain	Yes (1998/2009)	Yes	Yes	No	Yes	18	18	18	18	18	18
Sweden	Yes (2001/2016)	No	Yes	Yes	Yes	18	20	20	18	18	18
UK	Subnational	—	Yes	Yes	Yes	18	18	18	18	18	18

Source: World Health Organization (2018) Global status report on alcohol and health 2018. World Health Organization, Geneva

*Place* 2011, 17:701–709).

In contrast to Lithuania, alcohol consumption in the country has been slowly decreasing since the ‘Velvet Revolution’ took the country (then part of Czechoslovakia) out of the USSR in 1989. It remains relatively high, however, at 10.4 litres per capita per year in 2016 ([bit.ly/WHO-global-alcohol-health](http://bit.ly/WHO-global-alcohol-health)) – (compared with 13.8 in Lithuania, and 7.1 in Italy, the same year. The incidence of alcohol-related cancer deaths is the highest of the three countries, with 305.9 deaths per 100,000 men, and 155.8 for women (*op cit*).

Studies agree that the rate of unemployment has a lot to do with the high rates of alcohol consump-

tion and the related mortality. Until 1989 the unemployment rate was almost zero, but it rose to a peak of 16% in 1998, before dropping back to around 8% in 2007, and then rising again to almost 13% in the wake of the global financial crisis.

In 2008 the Slovakian parliament passed the Act on the Protection from Alcohol Abuse and Establishment and Operation of Detoxification Centres. This was reinforced the following year, to strengthen provisions on under-age drinking, with measures banning people aged under 15 from public places that serve alcoholic drinks after 9 pm, unless accompanied by their legal guardians.

## Reducing harmful use of alcohol: how policies compare across EU member states (#2)

	Restrictions for on-/off-premise sales of alcoholic beverages (any)		Restrictions for on-/off-premise sales of alcoholic beverages			National maximum legal blood alcohol concentration when driving a vehicle (%)			Legally binding regulations (any) on		Legally binding regulations (any) on		Legally required health warning labels (any) on		National government support for community action (any)	National monitoring system(s) (any)
	Hours, days	Places, density	Specific events	Intoxicated persons	Petrol stations	General	Young	Professional	alcohol advertising	product placement	alcohol sponsorship	sales promotion	alcohol adverts	containers		
Austria	Yes, Yes	Yes, No	No	Yes	No	0.05	0.01	0.01	Yes	Yes	Yes	Yes	No	No	Yes	Yes
Belgium	No, No	No, No	Yes	Yes	Yes	0.05	0.05	0.02	Yes	No	No	Yes	No	No	Yes	Yes
Bulgaria	No, Yes	Yes, No	Yes	Yes	No	0.05	0.05	0.05	Yes	Yes	No	No	No	No	Yes	Yes
Croatia	No, No	Yes, No	Yes	Yes	No	0.05	0.00	0.00	Yes	Yes	No	No	No	No	Yes	Yes
Cyprus	Yes, Yes	Yes, Yes	Yes	Yes	Yes	0.05	0.02	0.02	Yes	No	No	No	No	No	Yes	Yes
Czechia	No, No	Yes, No	Yes	Yes	No	Zero tolerance			Yes	Yes	No	No	No	No	Yes	No
Denmark	No, No	No, No	No	Yes	No	0.05	0.05	0.05	Yes	Yes	Yes	No	No	No	Yes	Yes
Estonia	Yes, No	Yes, No	No	Yes	No	0.02	0.02	0.02	Yes	No	No	Yes	Yes	No	Yes	Yes
Finland	Yes, Yes	Yes, Yes	Yes	Yes	Yes	0.05	0.05	0.05	Yes	Yes	Yes	Yes	No	No	Yes	Yes
France	Yes, No	Yes, Yes	Yes	Yes	Yes	0.05	0.02	0.02	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Germany	No, No	No, No	No	Yes	No	0.05	0.00	0.00	Yes	Yes	No	Yes	No	No	Yes	Yes
Greece	No, No	No, No	Yes	No	No	0.05	0.02	0.02	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Hungary	No, No	Yes, No	Yes	Yes	No	Zero tolerance			Yes	No	No	No	No	No	Yes	Yes
Ireland	Yes, Yes	Yes, Yes	Yes	Yes	Yes	0.05	0.02	0.02	Yes	Yes	No	Yes	No	No	Yes	No
Italy	Yes, No	Yes, No	No	Yes	Yes	0.05	0.00	0.00	Yes	Yes	Yes	Yes	No	No	Yes	Yes
Latvia	Yes, No	Yes, No	Yes	No	No	0.05	0.02	0.02	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Lithuania	Yes, No	Yes, No	Yes	Yes	Yes	0.04	0.00	0.00	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Luxembourg	Yes, No	No, Yes	No	Yes	No	0.05	0.02	0.02	Yes	No	No	No	No	No	Yes	No
Malta	Yes, No	No, No	Yes	Yes	Yes	0.08	0.08	0.08	Yes	Yes	Yes	Yes	No	No	Yes	No
Netherlands	No, No	Yes, No	Yes	Yes	Yes	0.05	0.02	0.05	Yes	Yes	No	No	No	No	Yes	Yes
Norway	Yes, Yes	Yes, No	No	Yes	Yes	0.02	0.02	0.02	Yes	Yes	Yes	Yes	No	No	Yes	Yes
Poland	No, No	Yes, No	Yes	Yes	No	0.02	0.02	0.02	Yes	No	Yes	Yes	Yes	No	Yes	No
Portugal	Yes, No	Yes, No	Yes	Yes	Yes	0.05	0.02	0.02	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Romania	No, No	Yes, No	Yes	Yes	No	Zero tolerance			Yes	Yes	Yes	Yes	Yes	No	Yes	No
Slovakia	No, No	Yes, No	Yes	Yes	Yes	Zero tolerance			Yes	Yes	No	No	No	No	Yes	Yes
Slovenia	Yes, No	Yes, No	Yes	Yes	No	0.05	0.00	0.00	Yes	Yes	No	No	Yes	No	Yes	Yes
Spain	Yes, No	Yes, No	Yes	No	No	0.05	0.03	0.03	Yes	No	Yes	Yes	No	No	Yes	Yes
Sweden	Yes, Yes	Yes, Yes	Yes	Yes	Yes	0.02	0.02	0.02	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
UK	Sub-national		Sub-national			Sub-national			No	No	No	Yes	No	No	Yes	Yes

Source: World Health Organization (2018) Global status report on alcohol and health 2018. World Health Organization, Geneva

The effectiveness of this approach was questioned in a 2011 study conducted by public health experts from Slovakia, Belgium and the Netherlands (*Health Place* 2011, 17:701–709). “In the Slovak Republic, unlike the legislative steps taken in recent years leading to a restriction on smoking in public and to a health protection of non-smokers, the field of alcohol consumption still lacks effective actions which would have a positive impact on the health of inhabitants,” wrote the authors. They recommended greater use of price deterrents: “as alcohol is cheaper than soft drinks, politicians

should consider the tax instrument to be used in the fight against avoidable alcohol-related mortality.”

In 2013, local municipalities were given powers to add places where the selling of alcohol was prohibited to those defined at the national level, such as healthcare premises or education centres.

This was the year that Slovakia first approved an official alcohol control policy based on the approach recommended by the WHO, which sees it as a public health priority. The policy aimed to promote activities to reduce social tolerance toward alcohol consumption, espe-

cially among younger people.

A further significant amendment, in 2018, explicitly banned drinking under the age of 18, strengthening existing regulations that banned selling to and serving this age group. This was an important step, because access to alcohol among adolescents was, and remains, a significant issue, according to a 2021 study that looked specifically at ‘Alcohol Use and Its Affordability in Adolescents in Slovakia between 2010 and 2018’ (*Int J Environ Res Public Health* 2021, 18:5047).

The study found that, among 15-year-old schoolchildren, more



than one in five boys and more than one in ten girls admitted to having drunk alcohol at least once a week in 2017/2018. In an echo of the findings of the Lithuanian review, however, the authors, with backgrounds in medicine, healthcare and social work, flag up the limitations of relying too heavily on legislation to control alcohol consumption.

They note that, while control measures focused on adolescents play a crucial role in preventing the health and social impact of excessive alcohol use, “their impact is significantly mediated by an overall social environment, namely prevalence of drinking among the general adult population, together with culturally/historically based drinking patterns, family influences, and peer pressure.” Nowadays, they conclude, preventive measures still have a “relatively weak effect”.

### **Italy: changing the drinking culture**

Mediterranean countries have done well in reducing alcohol consumption over the past three decades. The success has been particularly marked in Italy, where per capita consumption decreased from 12.4 litres in 1990 to 7.6 litres in 2014. It is reflected in rates of death from alcohol-attributed cancers that are one-third lower than the equivalent rates in Slovakia for men, at just over 190 cases per 100,000, and around a quarter lower for women, at around 120 per 100,000 (2016 data, [bit.ly/WHO-global-alcohol-health](http://bit.ly/WHO-global-alcohol-health)).

The key to the country’s relative success in reducing alcohol consumption compared to the rest of the European Union is widely seen to lie in early adoption of a paradigm shift

towards treating alcohol as a central issue in the national health strategy.

Prevention has been at the core of every programme linked to alcohol abuse in Italy since 1998. By 2000 it had reached its two main targets: to reduce by 20% the prevalence of male and female drinkers consuming respectively more than 40g and 20g alcohol a day, and to reduce by 30% the prevalence of drinkers consuming alcohol between meals. The fact that wine is the most widely preferred drink for Italians is a sign that they drink alcohol mainly while eating.

### **The key to the Italy’s success lies in its early paradigm shift towards treating alcohol as a central issue in the national health strategy**

Italy followed recommendations from international institutions, such as the WHO’s European alcohol action plan to reduce harmful use of alcohol ([bit.ly/WHO-plan](http://bit.ly/WHO-plan)) and the WHO Declaration on Young People and Alcohol ([bit.ly/WHO-declaration](http://bit.ly/WHO-declaration)) in drawing up its National Health Plans – national public health plans agreed with regional authorities every three years, which were first introduced in 1994. The approach is multidimensional – a combination of actions in different areas such as information, drink driving, legislation or advertising. Crucially, it includes monitoring, reporting and dissemination in its core strategies.

To monitor success in meeting health targets, in 2000 Italy defined

key indicators. Experts advised that ‘per capita’ alcohol consumption was a poor metric, because it reflects overall alcohol sales, and does not identify the distribution of consumption among individuals and the related patterns of consumption. The ‘per capita’ metric was therefore substituted by ‘prevalence and trends’ in daily alcohol consumption, alcoholic beverages consumption between meals, and crude quantities.

This enabled the system to better identify people who were exposed to alcohol as a risk factor. Monitoring trends with year-on-year data also helped to put alcohol consumption on the political and public agenda. Public awareness campaigns have been running since 2001, when Italy designated April as Alcohol Awareness Month. The Ministry of Health supports a coordinated effort that brings together national, regional and local governments along with NGOs, media, and civil society.

Having done the right things early, Italy is now ahead of the game. Emanuele Scafato, Director of the WHO’s Centre for Research and Health Promotion on Alcohol-Related Issues, and part of the Italian National Institute of Health, says, “In the last years, we got to the next step: a change of behaviour. Even the industry understood that drinking less was an important target to reach. And the consumers moved, and especially the younger generation, to a healthier lifestyle.” Marketing communication evolved towards depicting drinking behaviours that project moderation and responsibility. The most recent Commercial Communication on Self Regulation, from 2017, strengthened the stipulation that marketing must not encourage uncontrolled consumption. Guidelines specify,

among other things, that marketing messages may not depict alcohol as a solution to personal problems or as a means to promote clear thinking or enhance sexual performance. Any implication that not consuming alcohol indicates social inferiority is also counter to the guidelines.

In contrast to Lithuania and Slovakia, the Italian approach is not heavily reliant on regulation, though policy measures do include a minimum purchase age of 18 years and vending regulations that prohibit shops from selling alcoholic drinks between 9pm and 2am in most municipalities. “I will never tell someone not to drink, but I want to provide all the arguments so people can choose with valid information. And health is a choice,” says Scafato.

### How can Europe do better?

As the recent *Lancet* ‘Global burden of cancer in 2020 attributable to alcohol consumption’ study concludes, “alcohol use causes a substantial burden of cancer, a burden that could potentially be avoided through cost-effective policy and interventions to increase awareness of the risk of alcohol and decrease overall alcohol consumption.” The authors recommend strategies such as those included in the WHO’s ‘best buys’ for the prevention and control of noncommunicable diseases ([bit.ly/WHO-BestBuys](https://bit.ly/WHO-BestBuys)): reduction of availability, increase in price via taxation, and a ban on marketing.

Speaking to *Cancer World*, a spokesperson for the European Commission stresses that alcohol-related harm is a major public health concern in the EU. “This is why we are including a clear target to achieve a relative reduction of at least 10% in

the harmful use of alcohol by 2025, a target also supported by the WHO.”

**“I want to provide all the arguments so people can choose with valid information... Health is a choice”**

Given that, between 2010 and 2016, the European Union achieved only a 1.5% reduction in total alcohol consumption, the target of a 10% reduction in harmful use over five years might be seen as a suitably ambitious one. Nonetheless, it would still stop woefully short of achieving average per capita alcohol consumption rates in line with the 20g/day used in the *Lancet* study, for instance, to define ‘moderate’ as opposed to ‘risky’ or ‘heavy’ drinking.

Using the WHO 2016 figures for the average per capita consumption among drinkers in 30 EU+ countries of 15.7 litres of pure alcohol a year – which translates to approximately 33g a day – a 10% decrease would reduce average consumption to 29.7g/day.

That average, however, disguises major gender disparities, with the average per capita daily consumption among male drinkers estimated closer to 22 litres per year, or 47g per day. A 10% drop would only reduce this to 42.3g/day, more than twice the limit defined as ‘risky’ in the *Lancet* study. It also disguises major disparities between member states. While male drinkers in Italy average 16.5 litres a year (35 g/day), the equivalent figure for Lithuania is 27.9 litres/year or 60g/day, which with a 10% reduc-

tion would fall to 56g/day.

Asked about strategies to reach that 10% target, the European Commission spokesperson acknowledged that policies to tackle harmful alcohol consumption “are complex and require trade-offs.” She stressed the value of learning from past experiences across the EU, building on the work done by the Steering Group on Health Promotion and Prevention – a Committee with representatives from health ministries of the different member states which, in 2020, identified 16 best practices. “One of them specifically targets alcohol consumption, while others promote a generally healthy lifestyle and so indirectly prevent addictions too.” Some of these best practices, “selected with the involvement of the Steering Group,” will be co-funded under the new EU4Health Programme, she says.

Emanuele Scafato believes member states could do well to follow the lead of Italy, with a strong focus on educating and convincing populations to change the whole culture around drinking. All EU health ministries are aware that alcohol is related to cancer, but there is no such awareness among citizens, he says. He argues for much greater urgency in collecting data to understand perceptions and consumption patterns, and then developing and applying the best communications strategy tailored to each situation.

*This article was first published on the Cancer World website on 30 July 2021. To comment on or share the article please go to [bit.ly/CW-Alcohol-cancer](https://bit.ly/CW-Alcohol-cancer).*

UNITED EUROPEAN  
GASTROENTEROLOGY

**ueg** week

# 30<sup>th</sup> United European Gastroenterology Week

In Vienna and Online

October 8–11, 2022

In a hybrid world,  
engage as one  
connected community.

[ueg.eu/week](https://ueg.eu/week)





# Decolonising cancer research

## *Why it matters, what can be done*

If the purpose of cancer research is to improve survival and quality of life, then focusing on the needs of communities that have high cancer burdens and low access to affordable diagnosis and treatment options makes sense. **Swagata Yadavar** explores why this doesn't happen, and asks what has to change to ensure a more effective distribution of research funding and capacity.

**W**hen cancer epidemiologist and medical doctor Nirmala Bhoo-Pathy returned to Malaysia in 2011 after completing her PhD in cancer epidemiology in the Netherlands, she hadn't expected the move to negatively affect her research prospects.

As it turns out, she was wrong. Getting funding for cancer research and getting those results published, she soon discovered, was much harder for researchers based in Malaysia than in the Netherlands.

There were several hurdles: domestic funding was scarce for

epidemiological research; grants available for researchers in low-income countries were not an option, as Malaysia is classed as an upper-middle-income country; and international funding for low- and middle-income countries (LMICs) is anyway predominately for infec-

tious diseases, not for cancer. Funding opportunities that she might have been eligible for came with the caveat that she would need to collaborate with a researcher in a western country to be eligible.

“At that time, we didn’t know any [western researcher] who worked in the same area, and when we wrote emails, they weren’t replied to and we didn’t get the collaborators,” says Bhoo-Pathy. So while a postdoc in a western country typically gets published and recognised quite quickly, she says, it took her ten years to overcome all the hurdles and reach a level when getting published became easier.

Bhoo-Pathy is now an Associate Professor of Clinical Epidemiology, in the faculty of medicine at the University of Malaya, and a recognised name in cancer research, with countless publications to her name that contribute vital evidence to discussions about how to make the best use of available resources to optimise cancer outcomes in the region.

But her many years of battling discrimination and misogyny to get to where she now is have not been easy, and she says she’s been “angry for a long time”.

Bhoo-Pathy’s experience is not unique. Many cancer researchers from developing countries face additional hurdles in their work because cancer research is still dominated by researchers in the Global North and reflects the perspectives and priorities of high-income countries. Researchers from Asian and African countries remain largely dependent on western institutions for expertise and funding, which frequently ties them to working on western research agendas, often at the cost of doing research that could

help address the very great needs of their own communities.

A growing awareness of this issue, in recent times, has led to calls to ‘decolonise healthcare research’. *Cancer World* spoke to leading cancer experts from both sides of the global divide about why this matters, and what can be done to ensure that resource capacity is shared out more fairly.

### **Greatest burden, least research**

Logic might dictate that cancer research efforts should focus on the areas of the world that face the heaviest burden. In reality, the opposite is the case.

Over the next two decades, the World Health Organization estimates that more than 80% of new cancer cases will occur in low- and middle-income countries, where survival rates are currently the lowest. Yet only a tiny fraction of almost US\$30 billion spent on cancer research every year goes towards research that could help countries that need it most to develop evidence on solutions that would work for their populations.

Looking specifically at randomised controlled trials – the most rigorous research methodology – a study showed that, between 2014 and 2017, fewer than 1 in 10 randomised controlled trials in cancer were led by researchers in low- and middle-income countries (*JAMA Oncol* 2021, 7:379–85).

### **High impact research, low impact-factor journal**

Along with structural issues like funding, which limit opportunities to conduct high quality research,

researchers from low- and middle-income countries face a variety of additional obstacles to getting published in high impact factor journals. The *JAMA Oncology* study found that trials from low- and middle-income countries are more likely to identify effective therapies and have a larger effect size than trials from high-income countries, yet they were published in low impact-factor journals. “There is a funding and publication bias against trials led by LMICs,” the study said.

### **“Reviewers often comment that the research is not ‘novel’... but our setting and our challenges are unique”**

This is illustrated by Bhoo-Pathy’s experience. She works in clinical epidemiology and implementation research, focussed on clinical and patient-centred cancer outcomes, and says she often finds unjustified resistance from journals she approaches. Reviewers often comment that the research is not ‘novel’, and ‘nothing new’, on the grounds that the topics have already been researched in high-income settings.

“But what is different is that our setting and our challenges are unique,” says Bhoo-Pathy. “Amid scarcity of health resources, what we are aiming to do is to share research findings and, importantly, local solutions that may work. And if we don’t get to publish this, there is no recognition of the science and we cannot share our best practices with other [countries with] similar settings.”

In a survey of African oncology

professionals conducted by the medical journal, *ecancer*, in 2019, almost 8 in 10 respondents reported facing barriers to getting their research published. Most of them cited a lack of funding, inadequate research techniques, geographical bias and linguistic difficulties to be the reasons. A lack of available data relevant to their regional or racial context was also a problem.

Research from low- and middle-income countries often gets shunted away from mainstream journals to global health ‘open access’ journals. But while these are free to access they charge up to US \$5,000 in article processing charges, which researchers in less developed countries cannot afford.

The *ecancer* survey also showed 85% of African oncology professionals had faced problems accessing the latest research and guidelines relevant to inform their patient care, citing cost as the biggest obstacle.

As the *ecancer* paper concluded, “This results in ‘lost science’ in the form of information which is either not published or simply not made freely accessible to all. This leads to doctors being unaware of specific data and best practices which would make a difference to outcomes for their patients.”

There is now a growing recognition among editors of some medical journals that things have to change.

In 2019, the Lancet Group adopted a diversity pledge that committed them to increasing the representation of women and colleagues from low- and middle-income countries among their editorial advisers, peer reviewers, and authors ([thelancet.com/diversity](http://thelancet.com/diversity)). In an editorial comment they noted that, “Editors generally use reviewers who are

recognised experts in the field and, given the pressure of time and volume of submissions, often rely upon tried and tested networks,” and pledged that, “With our renewed recognition and commitment to gender and diversity, expanding and diversifying our reviewer pool is now a priority.”

They set targets of increasing the proportion of reviewers at *The Lancet* by 25%, with local reviewers mandatory for all global health content and with a ‘strengthened preference’ for at least 50% Global South contributors for Series and Commissions (*The Lancet* 2019, 393:508–10).

More recently, the *Lancet Global Health*, in its February 2021 editorial (vol 9, ppe99) commented on the role journals play in maintaining and perpetuating the status quo, and called for readers to share their expertise and experiences on their frustration with global health research and what needs to change.

### **Implementation research: high impact, low priority**

Much of the research done in high-income countries is not relevant in the rest of the world. A lot of the funding for cancer research in these countries comes from industry and relates to development of new drugs like immunotherapies and precision medicine approaches which are out of reach for most cancer patients, including many public health systems in Europe. CAR-T cell therapy, for instance, where a patient’s T cells are modified in the laboratory to enable them to identify and kill cancer cells, costs around US \$500,000 in the US, and can go up to US \$700,000 or US \$1 million, with administration

and hospitalisation costs included ([bit.ly/CAR-T\\_Costs](http://bit.ly/CAR-T_Costs)).

CS Pramesh, Director and Head of Thoracic Surgery at the Tata Memorial Hospital, Mumbai, points out that funding research on how best to implement interventions that are known and proven to be effective in the community, can have a much greater impact in terms of lives saved and improved.

**“What we are trying to do with all of these is to bring the cost of cancer care down and provide effective and practical alternatives to expensive interventions”**

Many of these interventions are low-cost and provide solutions for low-resource settings, and Tata Memorial Hospital, India’s foremost tertiary care cancer centre, excels in doing cost-effective, implementable and scalable interventions for cancer control.

One good example is their study on cervical cancer screening, which showed that visual inspection with acetic acid, done by trained primary care workers, is a viable alternative to pap smears and resulted in 30% reductions in deaths from cervical cancer (*JCO* 2013, 31:18\_suppl 2-2).

The hospital is currently involved in trials using repurposed drugs for treating cancer, says Pramesh. The hospital is partnering with the Medical Research Council of the UK in a study on the use of aspirin as an adjunct after curative treatment of com-

mon cancers such as breast, prostate, colorectal, oesophageal and gastric. “What we are trying to do with all of these is to bring the cost of cancer care down and provide effective and practical alternatives to expensive interventions which have been developed in the West, because from a practical viewpoint, [they are] not implementable in the Indian situation,” he said.

### Studies in resource-poor countries have a global relevance

If good quality studies focussed on community needs in low- and middle-income countries find funding and support from local and international partners, the evidence generated can also benefit countries with greater resources.

For example, in a landmark study of breast cancer screening, whose 20-year follow-up results were published in 2021 (*BMJ* 2021, 372:n256), a team of researchers led by Indraneel Mitra, a surgical oncologist and professor emeritus at the Tata Memorial Hospital, showed that clinical breast examination conducted every two years by primary healthcare workers led to a relative reduction in deaths from breast cancer of almost 30% among women aged 50 and over.

That trial was supported by the US National Institutes of Health and by grants from the Indian Department of Atomic Energy, and the philanthropic Tata Trusts. It led to a recommendation that clinical breast examination should be considered for breast cancer screening in low- and middle-income countries, where screening programmes using mammography are not sustainable

because of the cost of equipment and trained radiologists. A mammography machine in India, for example, costs US \$400,000 and the price per mammograph is US \$26 which is more than the entire annual per capita spend on public health, which stands at just \$19.

The randomised controlled trial followed more than 151,000 women between 35 and 64 years for 20 years. In addition to demonstrating the significant drop in mortality among women aged 50 or more, the trial showed this affordable approach to breast screening resulted in a significant reduction in the proportion of women diagnosed with stage III or IV disease (37% v 47%,  $P=0.001$ ), and in more breast cancers being picked up at a younger age (55.18 v 56.50;  $P=0.01$ ).

The findings are particularly important because breast cancer remains one of the most common cancers across the world and the failure to diagnose the disease at an early stage accounts in large part for poorer survival rates in low- and middle-income countries. Some of the mortality-to-incidence ratios reported in Middle, Eastern, and West Africa, for instance, are as high as 0.55, compared with 0.16 in North America (*Clin Lab Med* 2018, 38:161–173).

The Indian study was the first to focus on the role of clinical breast examination alone, said Rajendra Badwe, surgical oncologist and now director of the Tata Memorial Centre, who co-authored the *BMJ* paper. Nineteen states in India have already trained their frontline health workers in clinical breast examination, and the Tata Memorial Hospital is in talks with health officials in Brazil who are interested in implementing

results of the study, he adds.

But the study also has a relevance in countries with much higher levels of resources, feeding evidence into evaluations of the risks versus benefits of mammography screening programmes. In 2014, 25-year follow-up results of a Canadian study of almost 90,000 women aged 40–59 showed that, in a setting where adjuvant therapy is freely available, annual mammography for breast cancer screening resulted in one woman being overdiagnosed for every 424 screened, yet mammography did not lead to a reduction in deaths as compared to screening by physical breast examination (*BMJ* 2014, 348:g366).

Anna Dare, Global Cancer Disparities Fellow at Memorial Sloan Kettering Cancer Center, argues that learning between countries at different levels of economic development should always be seen as something that occurs in both directions, where groups learn from each other’s clinical and research experiences and adopt and adapt them for their own contexts.

Dare’s own interest in health inequities stemmed from the realisation that life expectancy, including after a cancer diagnosis, on the Māori side of her family in New Zealand was much lower than for non-Māori, despite New Zealand being a high-income country.

“Global health is sometimes erroneously thought of as referring to geography. But it’s really about these common processes and structures and systems that create and maintain health inequity or promote equity,” says Dare, which is why it is important to consider inequities not only between countries but also within countries.

### Building local research capacity

Richard Sullivan, professor of Cancer and Global Health at King's College London and Director of the Institute of Cancer Policy, highlights the limitations of the current situation where so much global health research is still led by experts from the Global North, who are 'parachuted' into countries they are completely unfamiliar with.

It is a bit like being a travel writer, visiting a Greek island and still being confident enough to write a book on Greek culture, says Sullivan. "You have visited the country only once, you don't know the language, you've never lived there and haven't even talked to people there properly."

**"I suddenly saw that the narrative discourse was completely disconnected from the reality on the ground"**

He feels much global health research often overlooks important distinctions, such as those between countries where cancers are primarily related to infections and those where non-infectious related cancers predominate. These distinctions do not necessarily correlate closely with country income levels – low, lower-middle, upper-middle, high – which tend to be used to categorise countries for research purposes.

Sullivan has long been an ardent advocate of getting diverse voices in shaping global cancer policy. He says his outlook comes from his diverse

background – a Christian Lebanese father and Irish mother – and having spent his childhood in East Africa and the Middle East. Later, working in Zambia, India, Central African Republic DRC, he realised that the reality of the people in these countries was not reflected in papers coming out of western countries, "I suddenly saw that the narrative discourse was completely disconnected from the reality on the ground."

What makes it worse, he says, is when these researchers fail to give adequate credit and recognition to the local researchers they will have relied on, rendering their contribution invisible, making it harder for local researchers to attract their own research funding, and reaffirming perceptions that expertise resides only in the Global North.

Commitments like those made by the Lancet Group to increase the proportion of their contributors and reviewers from the Global South will hopefully help to end the worst of these practices. Journals such as *ecancermedicalscience*, published by the European Institute of Oncology, which focus specifically on under-resourced communities, also offer important platforms for research and researchers who face unfair barriers to getting published. Importantly, not only are the articles in the journal free to read and download, but authors who don't have funding for publication are not charged any processing fees. The *ecancer* website also offers a free platform for cancer research done across the world, along with educational resources.

Yet even dedicated journals like *ecancermedicalscience* – whose editor in chief, Eduardo Cazap, was founder and first President of the Latin American & Caribbean Soci-

ety of Medical Oncology (SLACOM) – can struggle to address the domination of western researches in the papers it publishes. Recognising the problem, the journal recently revised its submission criteria to only accept articles which feature at least one author from a low- or middle-income country, or which have a significant impact on under-resourced settings.

### Nurturing researchers – a local and global responsibility

Widening opportunities to get published, and incentivising researchers with greater funding access to collaborate with researchers in countries with fewer resources, are an important part of efforts to decolonise cancer research. But governments of developing countries need to back those efforts with investment, says Dorothy Lombe, clinical and radiation oncologist at the Cancer Diseases Hospital in Zambia. Only when governments invest in research and science through their national budgets will they have the agency to decide what kind of research they want to do and create trained personnel who can conduct it, she says.

After her training in Russia and South Africa, Lombe says she was lucky to return to Zambia at a time when cancer control had just started to be seriously discussed. The country launched its first National Cancer Control Programme in 2016 and is currently in the process of setting up a National Cancer Institute. Lombe is proud that her country has included HPV vaccination in its national healthcare programme, having adapted the WHO recommendations for HPV vaccination for girls between 9 and 14, to focus on girls



between 14-15, before they get sexually active, to fit the constraints on its budget.

**“Mentoring by seniors and domestic funding for research are essential to improve the situation”**

“Who would have thought that a country like Zambia [which is among the poorest in the world] will afford to vaccinate its girls against cervical cancer?” asks Lombe, who sees it as a sign that her country is going in the right direction.

Yet researchers from countries like Zambia still struggle with conducting research, because of high patient loads and poor support struc-

tures, says Lombe. She believes mentoring by seniors and domestic funding for research are essential to improve the situation.

Her views are echoed by Bhoo-Pathy, who says people like her who have been in the field for a long time need to ‘pass on the mic’; they need to groom younger researchers and give them the opportunity to lead.

Researchers, and research and funding bodies in high-income countries, for their part, need to be aware of the extent to which they dominate research partnerships, agendas and spaces, particularly through the flow of resources, and the impact this has on research priorities, says Dare from Memorial Sloan Kettering Cancer Center. “If we want to improve cancer control on a global level, we need to ensure the voices of those most affected by

cancer inequities are not only heard, but are setting the agenda.”

The time of reckoning may already be here, with the COVID-19 pandemic dramatically highlighting the dangers that global inequities pose even to higher-income countries. The growing social and political awareness about our interlinked world is opening opportunities to move decolonising cancer research up the agenda. For global health institutions and journals, it’s time to translate words into action.

*This article was first published on the Cancer World website on 16 July 2021. To comment on or share the article please go to [bit.ly/CW-Decolonising](https://bit.ly/CW-Decolonising).*



**A community in continuous dialogue**



- 7 Long-term projects
- 4 Online events
- 26 Webinars
- 50+ Hours online and on-demand education
- 100+ Cancer World articles with more than 35,000 readers on an annual basis (SPCC analytics data)
- 10,000+ Community members from 110+ Countries



**OncoCorner** is the e-learning platform of SPCC (SharingProgress in Cancer Care), which offers free access to webinars and online events that are led by globally recognized experts in oncology and CME accredited.

**OncoCorner** is a 'corner' of excellence for sharing knowledge, best practices, and innovation in the cancer field and to increase knowledge in the Cancer Care Continuum.

**OncoCorner** offers a space for independent and transparent dialogue between key stakeholders on major innovations and advances in the Cancer Care Continuum.

Scan the QR code to register to the platform.  
**It's free.**



[www.oncocorner.net](http://www.oncocorner.net)



*Oncocorner is the e-learning platform from*

**Sharing Progress  
in Cancer Care**





Sharing Progress  
in Cancer Care

Online Conference



# TELEMEDICINE IN CANCER CARE CONTINUUM: IMPLEMENTATION AND INTEGRATION

Live 06/07 May 2022

On-demand from 16 May 2022



Online Course

# PRECISION TESTING

EARLY AND LATER:  
A TOOL FOR DIAGNOSIS  
AND BETTER TREATMENT?

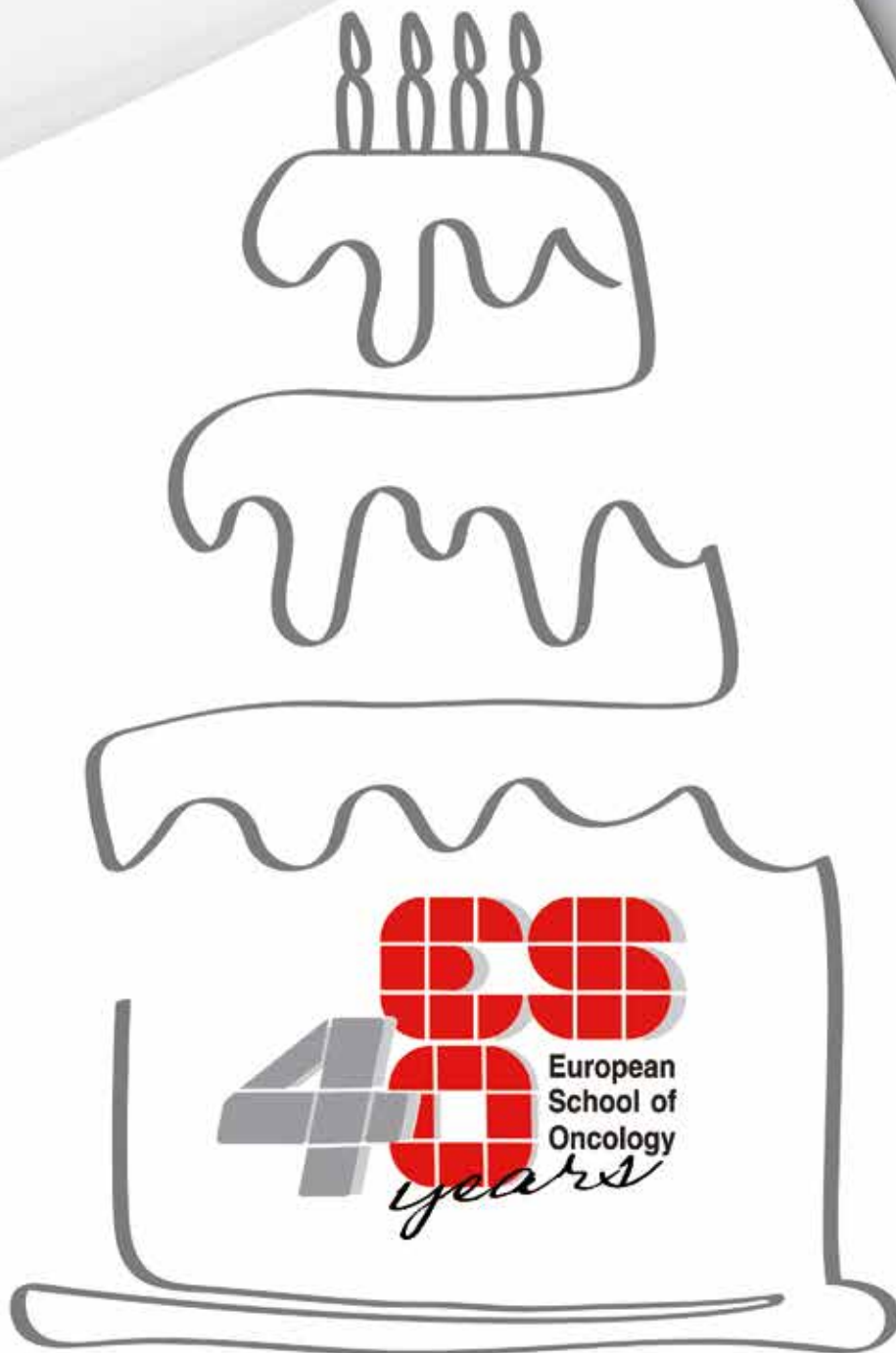
Live 20/21 May 2022

On-demand from 30 May 2022

*Register at*

[WWW.ONCOCORNER.NET](http://WWW.ONCOCORNER.NET)

1982  
2022



**40 years** of Learning to Care,  
a lot more to come, a lot more to Learn.

[www.ESO.net](http://www.ESO.net)