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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.



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'Cancer treatment is for life'
by Sara Corsi

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Cancer World is an online magazine that publishes weekly news reports and features. It has also been published in print since 2004. This issue will be the final printed issue.

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Cancer Efficiency Metrics Study

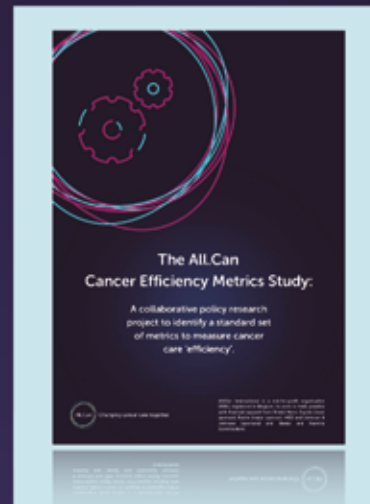


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Changing cancer care together



Leave no-one behind

Matti Aapro – SPCC President

Cancer World is moving online, which means this will be the last printed version. We're all sad to see the end of a physical magazine, which gave our readers real pages to turn, and the chance to take time away from the screens that now dominate our lives. But having been online-first for a few years now, we've come to appreciate the opportunities the humble hyperlink gives us to present not just our own coverage, but also to link readers directly to the wealth of organisations and published material that we come across during our research.

Since 2004, under the editorship of Kathy Redmond, then Alberto Costa, and now Adriana Albini, *Cancer World's* team of journalists has been covering evolving stories in cancer care, to spread information and promote discussion on how to *reduce the unacceptable number of deaths from cancer that are caused by late diagnosis and inadequate cancer care* – the goal of the European School of Oncology, which launched the magazine. Since 2019, *Cancer World* has been supported by the Swiss-based not-for-profit entity Sharing Progress in Cancer Care (SPCC.net), but the goal remains the same.

We know that you, our readers, are busy people and that it's up to us to earn the right to your time and attention. We try to do this by providing you with unique and timely coverage of the issues that matter most to patient care and the professionals who provide it, and doing so in a way that is not only informative and critical, but also enjoyable and even entertaining to read.

We value your interest immensely, and hope you will continue to read Cancer World by signing up to our online magazine, if you have not already done so. You can do this at bit.ly/CW_Subscribe. We will then send you fortnightly email alerts to let you know of the

latest news and features published over the previous two weeks.

Ending our print issue will free up resources to further expand the scope and extent of our coverage. *Cancer World* is aiming to become truly universal, and for this purpose we are widening the international base of our team of journalists, bringing onboard some excellent reporters from North America, Poland and Romania, Brazil and Mexico, as well as Uganda, Turkey and India. While inequalities in access to all aspects of the fight against cancer exist even between regions of European countries, they are obviously lesser when one looks at other areas of the world. Thus, while highlighting and welcoming the progress made in cancer prevention, detection, treatment and social issues, *Cancer World* will continue our critical but constructive approach, focusing on ways to ensure every community reaps the benefits of that progress, with health spending prioritised and spent effectively.

Some of this coverage can be read in this issue, which carries a report from Poland about the challenges involved in delivering care to the influx of patients from Ukraine, a story from India about the progress that can be made when the Global North and South are able to learn from one another, and a report from Uganda on a new WHO toolkit to help countries integrate palliative care into their universal health coverage, as well as the latest thinking on the science of survivorship from the US.

But this issue also carries our usual mix of cutting-edge science, multidisciplinary clinical practice, prevention and screening, and personal perspectives from oncologists and the patient community. We hope you enjoy reading it and will continue to follow our coverage online: bit.ly/CW_Subscribe.

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Long-term health

Is it time to update the priorities of cancer research?

We have the technology to explore off-target organ effects of experimental therapies. We have the tools to gather and mine data about lasting and late effects of treatment and the priorities and care needs of survivors. Isn't it about time we start to use them? **Anna Wagstaff** reports from a lively discussion organised by the AACR Scientist ↔ Survivor Program.

“I was told that cancer was a temporary condition – just get through treatment and things will go back to normal. I quickly realised that this is not true.”

Gregory Aune was treated for Hodgkin's disease when he was

17. That treatment – eight chemotherapy agents and a heavy dose of radiation – saved his life and allowed him to pursue a successful career in medicine.

But the price he pays in long-term effects is quite sobering: hyperthyroidism; pulmonary fibro-

sis; infertility; aortic stenosis; 3-vessel coronary artery disease, all blocked by >95%; secondary skin cancers; stroke/transient ischaemic attack; diabetes; congestive heart failure; pulmonary hypertension/mitral valve disease.

Now in his mid-40s, and a pro-

fessor of paediatric medicine at San Antonio, Aune says he is not looking for sympathy. He is looking for recognition. Recognition of the scale of problems that many cancer survivors live with as a consequence of their disease and treatment. Recognition of the gap in planned and coordinated care for this large and growing population, and of the gap in reliable information about their needs. Recognition of the gap in research dedicated to understanding long-term and late effects, what causes them, and how they can be predicted, prevented or managed. And – a particular focus – recognition of the ethical imperative to change the way new cancer therapies are developed, so that potential late-effects are investigated at a preclinical stage, rather than letting them enter clinical practice and just waiting to see what might happen to patients like him, 10, 20, 30 years down the line.

“We must incorporate off-target organ effects into early development of new cancer therapies,” he says.

Aune was speaking at a session on the Science of Survivorship, organised in June 2022 by the American Association for Cancer Research, under the auspices of its ‘Scientist↔Survivor’ Program.

The headline statistics underpinning the session were ones that are familiar to many in the cancer community: In 1971, when President Nixon signed the National Cancer Act, there were around three million cancer survivors in the US. Today there are 18 million – that’s more than the entire population of the Netherlands. Almost 50% of people diagnosed with cancer in the US now live for at least 10 years.

These statistics tend to be cited as evidence of the progress made in treating cancer, and to galvanise efforts to extend survival times still further.

But in this session, the focus was on the 18 million survivors, and on the gaping hole in knowledge about how their lives – their health and psychological, social and economic wellbeing – have been impacted over the longer term by their cancer diagnosis and treatment. It was on the urgent need to fund a coherent research programme to understand the scale and nature of long-term problems, in order to better prevent, monitor and manage them. Crucially, it was also about the role for survivors themselves, in generating ‘real world evidence’, by reporting the issues they face, and defining their unmet needs for support and care, and their priorities for research.

“We must incorporate off-target organ effects into early development of new cancer therapies”

What it was not about was pitting the needs of people with better prognoses against those for whom survival remains the overriding issue, as Adam Hayden, an advocate with the AACR Scientist↔Survivor Program, made clear. Hayden was diagnosed almost seven years ago with an aggressive brain tumour that carries an average life expectancy of no more than two to three years. The need to develop durable therapies is hugely important, he says, “But sometimes

there is so much focus on the newly diagnosed or newly recurred, that people like me, who have lived with this for seven years, are forgotten about.”

‘See you next scan’

A researcher at the department of philosophy at Purdue University, Indianapolis, Hayden has found his analytical skills helpful in making sense of what he is going through. His description was a great illustration of the ‘real world’ insights that will be so important to improving care and support for survivors.

First up, the emotional/psychological whack that goes with a brain tumour diagnosis makes the offer of psychosocial support essential right at the start. It’s not just about the prognosis, it’s about what happens to your confidence and your identity when the body you took for granted starts behaving in unpredictable ways. Then just as you have greatest need for friends and family, those relationships get disrupted, which can bring an added burden. “After illness, all experience becomes cast in the shadow of illness. People behave differently. The emotional distress is an existential weight on the shoulders of survivors. You are no longer the person family and friends thought. You are that plus cancer.”

“I had to go and find a mental health professional,” said Hayden. “That should be automatic because all of our relationships have changed. Many cancer centres offer access to mental health counselling, but we don’t access it early enough. It should be right at the start.” (Hayden also points out that

a more constructive alternative to the question, “You do know you are going to die with this?” might have been used, at the point of diagnosis, if greater priority had been given to the quality of his survivorship, and to helping him find the best way to navigate the years ahead.)

Another pressing need for people in his position, says Hayden, is information and guidance about what is happening with his disease and what he can do to help his own health and wellbeing. “See you next scan,” is how he refers to this set of issues. At a general level, he’d like better coordination between the actors involved in different aspects of his care, and to feel that there is joined-up oversight across all the health and wellbeing aspects that matter to him.

“Am I in remission?

What do I plan for now?

We need an ongoing prognosis conversation to help with life planning”

He would like evidence-based advice, for instance, on how to supplement his health, that goes beyond the standard “eat a healthy balanced diet”. He’d like more evidence on the long-term toxic effects of the gadolinium injected into him as a contrast enhancer for his regular MRI scans. Having survived seven years now, he’s had more than 30 doses – is it still the best option for someone in his position?

Above all, anything that can throw light on how his disease is

likely to progress, about timelines, is a priority, and he finds it frustrating to get so little feedback after his scans. “Am I in remission? How do I plan? I would have planned differently if I knew I had six more years. What do I plan for now? We need an ongoing prognosis conversation to help with life planning.”

Turning experiences into evidence

For Patty Spears, a fellow patient advocate with the AACR Scientist↔Survivor Program, the testimony Hayden gave about the challenges he faces as a glioblastoma survivor, and of his priorities and unmet needs, provides essential building blocks in developing the science of survivorship.

Assembling those building blocks from across the full spectrum of patients and cancers, she believes, will require the integration of patient reported outcomes (PROMs) into routine clinical care. Not just during the treatment and follow-up period, but along the patient’s entire lifespan. And not restricted to a set of pre-selected symptoms, but capturing data on all health, psychological and socioeconomic issues. “We need to capture all long-term effects.”

More tailored and sophisticated apps are lightening the burden of such reporting, says Spears, who is herself a breast cancer survivor, and works as a Research Manager at the Patient Advocates for Research Council, at the University of North Carolina’s Lineberger Comprehensive Cancer Center. Conducted effectively, she argues, many patients see the benefits,

quite independent of their research value. “Patients question everything that happens after treatment. They fear what will happen once treatment ends,” she says. “PROMs are really useful to tell doctors about experiences, and PROMs conversations can help better manage side-effects.”

Questions about how it might be possible to mine such data to get a full picture – harmonisation, storage, security, access – are of course currently the focus of intense discussion across the medical research world. But you can’t mine what you don’t gather.

Her hopes are that the evidence gathered in this way could be quickly put to use to improve the care of survivors. If you can predict the sorts of issues any given patient is likely to face, that enables clinicians and patients to monitor the progress of side effects that persist beyond treatment, to watch out for late effects that might arise, sometimes long after treatment ends, and to plan for coordinated delivery of the right support and care.

Spears finds it frustrating that even the evidence currently available is not reaching the people who need it most. This year, 23 years after being diagnosed and treated for locally advanced breast cancer, Spears found out she had a primary liver cancer.

Despite her long involvement as a patient advocate with a number of cancer research councils and networks, this new diagnosis took her completely by surprise. For many weeks she assumed the pain she was feeling was probably a gallstone complaint – something that runs in the family. Only after an MRI scan revealed the liver cancer

did she learn that liver primaries 20 years after breast cancer treatment are not so unusual.

“Why did no one talk to me about long-term effects before, or even after treatment?” she asks. “The focus was all on acute effects. You are not really told what [long-term effects] to look for. This information is not given to patients. We need to say that is important to talk about. Even the basics are not being done.”

“Why did no one talk to me about long-term effects before, or even after treatment?”

She would also like to see much greater efforts to understand the causes, as a step towards preventing – or at least predicting – this late effect. “We should make an effort to ask the question: Where did this liver cancer come from? Is it my genes? If you can learn from patients like me, you can predict at an early stage and you know what to look for.”

Doing the science

Finding answers to questions like that one, regarding the biological mechanisms behind clinically observed potentially life-threatening late effects, is a priority for Gregory Aune.

He can't see it happening on the scale that is needed, without a strategic policy decision to direct more support into survivorship research.

Having himself undergone

replacement of his aortic valve and triple bypass surgery at the age of 35 – “like going through cancer all over again” – he now focuses his own research work on exploring the mechanisms of cardiac toxicity associated with anthracycline treatment – the drug class that he says causes the most problems.

“Over half of paediatric patients treated with anthracycline get cardiotoxicity, often with a 20-year latent period. There is not much research into the mechanism.

We need to go back and reinvestigate how these old drugs do this damage,” he says. “Chemotherapy will be needed for a long time to come.”

The damage from “old drugs” he accepts is a legacy from the days when “regimens were decided by trial and error with no understanding about how they affected other organs.”

But as he points out, new tools are now available that make it possible to explore those effects during the early, preclinical stage of developing new therapies. He regards it as “almost unethical” not to use them.

“We need to go back and investigate how these old drugs do this damage”

New classes of drugs such as immune checkpoint blockade and antibody-drug conjugates are known to impact ‘off-target organs’, and yet they are being introduced, even in an adjuvant setting, without trying to under-

stand the mechanisms involved.

He also agrees with Spears on the vital importance of gathering long-term data, and has himself established a cohort of long-term survivors of paediatric cancer, for this very purpose.

The Scientist ↔ Survivors’ ask

The essence of AACR’s Scientist ↔ Survivor program is that, when survivors and scientists work together, they can help ensure a better life for millions of people living with and after cancer. But – and this is the headline ask – it will require those who shape the cancer research priorities and infrastructure, and allocate funding, to put survivorship much higher up the agenda.

It will require a national effort to establish cohorts for all cancer types to gather long-term clinical and PROMs data along the lines of the one that Aune has set up for paediatric cancers – and the political will to overcome all the legal, ethical and funding issues and barriers from vested interests that continue to hamper data sharing.

And it will require recognising how the challenge of cancer has changed since the National Cancer Act was signed more than 50 years ago. Finding ways to prevent and predict, and to monitor and manage, lasting and late effects of treatment must now become a research focus in its own right. A journal and an annual meeting dedicated to preclinical survivorship research, together with its own funding streams, and ideally its own institute – the 38th US National Institute of Health – is something Aune has been advo-

cating for the past decade.

Then there are questions about what, if anything, can be asked of pharmaceutical companies. They won't want anything that involves following up patients in the long term, was the feeling, but what about the preclinical work? Should regulators require preclinical data that might predict lasting or long-term impacts on off-target organs that might not become apparent during the course of the clinical trials? Should companies be obliged to share data that could be of concern for lasting or long-term effects?

And finally, the question of the bottom line – how do you convince the funders? Just do the sums, was the unanimous view of the panel. Preventing lasting and late effects in this huge and growing population, predicting them better,

It will require those who shape cancer research priorities and allocate funding to put survivorship much higher up the agenda

detecting them earlier, managing them more effectively makes economic sense. It saves healthcare costs, it enables survivors to stay economically active, and avoids carers having to leave work to care for dependents.

Factor in some of the more common lasting effects – pain, fatigue, impaired immune function, anxiety and other mental health issues – and the scale of the problem

becomes clear. Then remember the size of the population – larger than that of the Netherlands and rapidly growing, and that two in five are younger than 60, and that the risk of bankruptcy is 2.5 times higher among survivors than the general population.

Add that all together and the funding ask from the Scientist↔–Survivors' panel might begin to look quite reasonable... as might the demand that cancer research should integrate a long-term perspective into its investigations of new therapies.

This article was first published on the Cancer World website on 8 July 2022 (bit.ly/CW-Research-Longtermhealth).



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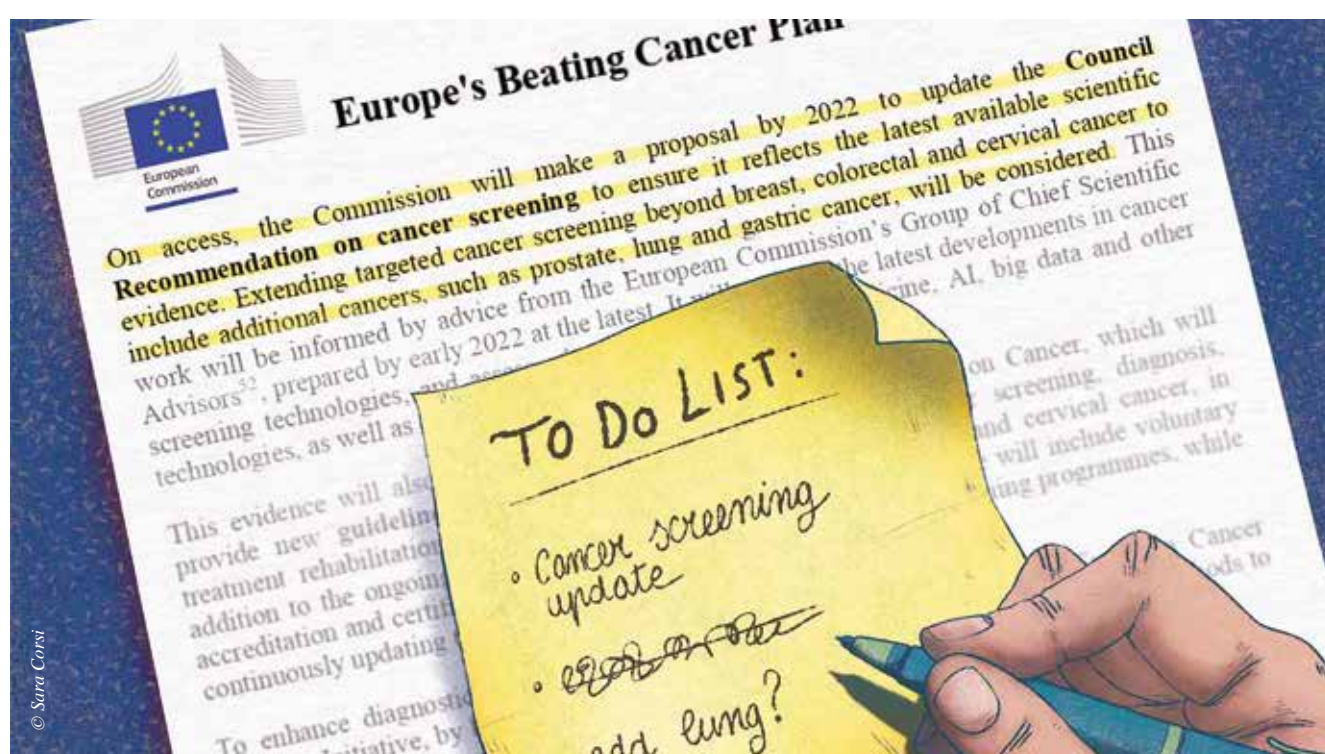




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Lung cancer screening

2022 could be a turning point for Europe

European member states are now advised to add lung cancer screening to their existing screening programmes, following an update to the European Commission's recommendations on cancer screening, issued in September 2022. Getting the implementation right will be crucial, but tricky, with challenges and solutions varying from country to country. **Janet Fricker** reports on the experiences of some countries that have already made a start.

If cancer screening policies were driven purely by mortality rates and curability, then lung cancer would have topped the priority list for population screening programmes long ago. Accounting for almost one in every four can-

cer deaths in men and almost one in seven for women, lung cancer kills more Europeans each year than any other cancer type. Early diagnosis could make a huge difference – when diagnosed at an early stage, five-year survival rates can

be higher than 60%, compared with around 5–7% for lung cancers diagnosed after they have spread. Given that symptoms suspicious for lung cancer are uncommon in early stages of the disease, the option of systematically screening people at particular

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risk of the disease would seem to make sense.

Yet the problem, as with all screening programmes, has been finding techniques and strategies that ensure the survival benefit to those whose lung cancers are detected early outweigh the risks of unnecessary radiation and potentially false-positive results run by the great majority of people screened who will not have cancer.

But the past two decades have seen important advances that are now feeding through to highly significant policy changes at national and European level. Key among these has been progress in low-dose CT lung screening techniques, which can make detailed images of the lungs with relatively low radiation exposure. In the early 2000s, researchers at Milan's European Institute of Oncology were at the forefront of developing low-dose CT protocols that were effective at picking up early-stage lung cancers, based on nodule doubling times.

Also important has been the development of protocols that reduce false-positives, and better ways to identify and engage with populations at high-risk for lung cancer.

Major trials – most recently the Dutch-Belgian NELSON trial – showing significant survival benefit, have now considerably strengthened the evidence base for setting up risk-stratified lung cancer screening programmes (see, for instance, bit.ly/CW-LungScreening-Evidence).

By the time the first iteration of Europe's Beating Cancer Plan was published in February 2021 (bit.ly/EUCancerPlan), the evidence was sufficiently convincing for the Plan to raise the prospect of extending existing European cancer screening

recommendations to include lung.

The Beating Cancer Plan committed the European Commission to “make a proposal by 2022 to update the Council Recommendation on cancer screening to ensure it reflects the latest available scientific evidence,” specifically naming lung as one of the cancers to be considered.

The scientific advice commissioned to inform that proposal, published in March 2022, concluded that “there is a strong scientific basis for introducing lung screening for current and ex-smokers using the latest technologies, such as low-dose CT scanning,” and that this should be “combined with ongoing programmes to help people give up smoking” (bit.ly/EU-Screening-ScientificAdvice).

In September 2022, the Commission acted on that advice. The updated screening recommendations now include lung cancer screening for current and former heavy smokers between the ages of 50 and 75 (bit.ly/EC_ScreeningUpdate).

A few European countries didn't wait for the update, and have already started lung cancer screening programmes or pilots of their own. Here, we highlight three such initiatives, being undertaken in Croatia, England and France.

Croatia – Europe's first population lung screening programme

Croatia, where a national lung cancer population screening programme was launched in October 2020, is the only country in Europe to have fully implemented targeted screening so far. “As we already have results from the NELSON study showing that screening works,

“We decided something urgently had to be done, because the incidence of lung cancer was so high in Croatia”

we didn't see the point in running a pilot,” says Ante Marušić, from the University Medical Centre, Zagreb, in Croatia.

Goals of the programme include saving more than 500 lives annually by reducing lung cancer mortality by 20% over the coming 5–10 years, achieving a 50% response rate to screening invitations and raising five-year survival rates for people with lung cancer from 10% to 15%. Such ambitions are especially important in Croatia, a country where in 2014 one in four adults were daily smokers – above the EU average of one in five. “We decided something urgently had to be done, because the incidence of lung cancer was so high in Croatia,” says Marušić. The screening programme is financed by the Croatian Health Insurance Fund, which covers all public sector health services.

Eligibility and referral

Family doctors are central to the scheme's organisation. They are responsible for identifying patients, during routine visits, who are eligible for referral – a task made easier by databases already available on their patients' smoking habits relating to other conditions such as COPD and heart disease. “Everyone in Croatia has a dedicated GP, with around 90% of the population visiting their GP at least once a year,” says Marušić.

Eligibility for lung cancer screening is restricted to those aged 50 to 75 years, with a smoking history of 30 pack-years (equivalent to smoking 20 cigarettes per day for 30 years), who are either current smokers or quit smoking within the previous 15 years.

When a GP identifies one of their patients as fitting these criteria, they use a national IT platform to make appointments at one of 16 public sector hospitals around the country. “GPs make the appointment while the patient is still with them in the office, so there’s no getting away,” says Marušić. The additional work involved in motivating patients to take part is recognised with a special payment to GPs.

Screening centres: training and equipment

Screening centres are located such that no-one in Croatia has to travel further than 50 kilometres. To qualify as a low-dose CT scanning centre, hospitals need to be equipped with a 128-slice CT scanner as a minimal technical requirement, and aim for less than 1m SV irradiation. The radiologists who operate the scanners are required to have undertaken a minimum of 300 thoracic CTs per year and to have attended two special training courses. The scan additionally provides quantitative and prognostic information on coronary artery calcification and emphysema. For around 5% of scans, quality control is provided by a centralised radiologist in Zagreb, using computer-aided diagnosis.

Early diagnosis pathway

Regarding results, an important consideration is whether the images are baseline or repeat scans. For

those lung nodules where consecutive scans are available, doubling times are used to identify potential tumours. The Croatian service has defined a doubling time of 400 days for a positive diagnosis of a potential tumour; 400–600 days for an indeterminate diagnosis, and more than 600 days for a benign diagnosis. In patients undergoing a baseline scan, for whom no previous scans are available, the focus is on the volume, with a volume greater than 2,000 mm³ defined as a positive (i.e. suspicious) result. For people with ‘normal’ baseline scans, repeat scans are offered after a year, and then every two years until the age of 75.

Any suspicious findings are referred to one of six nodule clinics, where patients have access to a multidisciplinary team which provides a full work-up that includes full-dose contrast CT, PET scan, bronchoscopy, and transthoracic biopsy.

In the first year the Croatian programme performed 4,500 low-dose CT scans (on 4,000 participants), with a recall rate of 11%, resulting in the detection of at least 30 cancers (including one breast cancer).

The infrastructure is expected to evolve. An international multidisciplinary quality control committee has been appointed to identify ways to improve the programme. “At the moment we’re keeping things simple, but in future we hope to encourage GPs to play a bigger role in offering smoking cessation services. We are also considering introducing specific risk assessment models for our population, going beyond age and pack-years,” says Marušić. “We especially want to be able to take into consideration the increased risks of our war veterans.”

England: a stepwise pilot approach

England has taken the approach of introducing pilot lung cancer screening programmes, which are being rolled out across England’s National Health Service (NHS) in three distinct phases. The idea of the phased approach is to provide early insights into potential challenges and pitfalls, allowing the programme to evolve as it goes along.

The first phase of the Targeted Lung Health Check programme was launched in February 2019 at 10 locations, the second phase added a further 13 locations, with an additional 20 locations added in April 2022, bringing the final number of lung cancer screening locations across England to 43. “We’re carrying out continuous evaluation of the projects already running to review their effectiveness and to inform a successful national roll out,” says Richard Lee, the Joint Clinical Lead for the NHS England Targeted Lung Health Check pilot. The hope and expectation, he says, is that the pilots will eventually grow into a national lung cancer screening programme.

The concept for the pilots came from the NHS Long Term Plan, launched in January 2019, which set out priorities for NHS reform over the following 10 years. The plan stated the ambition that 55,000 more

The hope and expectation is that the pilots will eventually grow into a national lung cancer screening programme

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people would survive their cancer, and that to achieve this aspiration it was necessary to increase the number of cancers diagnosed at an early stage.

The first 10 lung cancer screening pilots were situated in areas in England that were selected for having the highest lung cancer mortality. However, with the third expansion, it is planned that every Cancer Alliance (regional clinical/managerial partnerships that coordinate local cancer pathways) will have at least one project in place. “This will allow existing projects to slowly expand their population coverage, and move into neighbouring areas, until the programme is offered across England,” explains Lee, who is also a consultant respiratory physician at the Royal Marsden NHS Foundation Trust.

Eligibility and referral

In the English pilots, everyone aged over 55 but under 75 who has ever smoked is being invited for the lung health check. GP records are used to identify those eligible, with local advertising also employed to encourage people to take up the offer, and self-refer if they have somehow fallen through the net. The check uses two separate risk calculators – the Liverpool Lung Project risk prediction model and the Prostate, Lung, Colorectal, and Ovarian programme – which take into consideration factors such as smoking history, overall lung health, lifestyle, and family and medical history to calculate a person’s risk of developing lung cancer. Only those considered at high risk are referred on for a low-dose CT scan. Smoking cessation is considered a core part of the lung

health check, with current smokers who want to quit being offered brief advice and then referred to a local smoking cessation service.

Screening centres: training and equipment

Each project must follow the Quality Assurance Standards and Standard Protocol, set out by NHS England, which specify the main building blocks required before projects can start to invite participants.

The majority of the projects use mobile CT scanners that are sited in easy-to-reach locations, such as supermarket car parks

The protocol includes the minimum specification for the CT scanner (16-channel multi-detector), and the required workforce. Key roles include the clinical director of the programme, who takes overall responsibility for the safety of patients involved in the programme; the assessor, responsible for selecting and assessing individual referrals for entry; the radiologist, responsible for the low-dose CT; and the clinician, who manages referrals of suspicious scan results to the rapid-access lung clinic. Requirements for both individual professional training and continuing professional development are included in the document.

The majority of the projects use mobile CT scanners that are sited in easy-to-reach locations,

such as supermarket car parks. This change came in the wake of the landmark Manchester ‘Lung Health Check’ pilot, which showed that providing local low-dose CT scanning services close to where people live increased the lung cancer detection rate above any international clinical trial, with one lung cancer detected for every 33 people undergoing a low-dose CT lung scan. “Taking the programme closer to the people we’re trying to reach has been a critical part of our strategy,” says Lee.

Early diagnosis pathway

Results of the initial scan determine the frequency of future scans. Participants with negative baseline scans are reassessed at 24 months; participants with indeterminate findings after 12 months; and participants with significant findings after 3 months. Participants are offered repeat scans until they reach the top end of the eligible age range (75 years).

Even the Covid-19 pandemic did not stall the roll-out for long. At the start of the pandemic all projects were initially paused whilst the risk of Covid-19 was assessed. Adaptations were then made to the way in which the checks were carried out, which involved moving to a virtual model for the initial consultation, which took place over the telephone.

As the Targeted Lung Health Check becomes more established, the organisers hope to offer research opportunities to the different pilots, allowing them to assess whether use of different artificial intelligence programmes and biomarkers will improve the early detection of lung cancer.

The Department of Health estimates that by 2024–2025, around 1.5 million people in England will have been invited for a lung health check, with a predicted 7,700 cases of lung cancer found at an earlier stage than they would otherwise have been.

France: an exploratory implementation pilot

In France, the CASCADE lung cancer screening pilot has taken the bold decision to focus screening solely on female smokers. The reason for this choice, explains Marie-Pierre Revel, Head of Radiology at Cochin Hospital, University of Paris, is to explore the gender differences revealed in the NELSON lung cancer screening study. The results at 10 years showed that, while screening led to a 24% reduction in lung cancer mortality among men, a reduction of 33% occurred among women. “From CASCADE we hope to find out more about why screening benefits are so much higher in women,” explains Revel, who is leading the CASCADE study.

“We want to evaluate whether our strategy is reproducible in everyday real-life clinical settings”

The pilot is designed to shape any future lung cancer screening programme in France through evaluating the most effective strategies. “Our aim is to be practical. There’s no need to demonstrate mortality reductions from lung screening, as this has already been shown conclu-

sively in NELSON. What we want to evaluate is whether our strategy is reproducible in everyday real-life clinical settings,” says Revel, a radiologist from Cochin University Hospital, Paris.

In France, the decision was taken in 2016 by the Haute Autorité de Santé (National Authority for Health) that they would not introduce organised lung cancer screening due to the high number of false-positives. However, results from the NELSON study transformed the screening landscape. “As well as showing reductions in mortality, NELSON also showed that screening strategies using nodule volume doubling time had few false-positives,” explains Revel.

Eligibility and referral

The CASCADE pilot, which started recruiting in March 2022, aims to enrol 2,400 asymptomatic women, aged between 50 and 74 years, with 25 pack-year smoking histories (equivalent to smoking 20 cigarettes per day for 25 years). To be eligible, women also have to be either current smokers or to have quit smoking within the previous 15 years. The pilot, funded by the Ministry of Health and the Institut National de Cancer (INCa), with a budget of €1.8 million, is focusing efforts on Paris, Rennes, Béthune and Grenoble, four cities that were selected for their diverse socio-economic profiles.

To recruit women, the team took the decision to avoid going through family doctors. “People who go to GPs are those with health problems. We wanted to reach asymptomatic populations,” says Revel. Instead, they are evaluating different advertising strategies including using bill boards and TV, radio, and newspa-

per ads. “We’ll also be looking at whether recruitment is helped by sending out personalised invitations.”

Before undergoing screening, women have an initial appointment with a pneumonologist, who checks whether they meet programme eligibility criteria, and explains the risk/benefits of undergoing lung cancer screening to those who are eligible. Women are warned that screening can reveal additional health information, including calcium scores (indicating cardiovascular disease) and signs of other lung conditions, such as COPD and emphysema.

“People who go to GPs are those with health problems. We wanted to reach asymptomatic populations”

The pilot will also explore potential negative psychological effects of undergoing screening, recognising that distress relates not only to receiving positive or indeterminate results, but also includes the patient’s experience prior to screening, during the examination, and while waiting for the results.

Training

A shortage of expert thoracic radiologists to read low-dose CT scans is predicted to be a major problem if lung cancer screening becomes widespread. Investigators are therefore planning to assess whether it is possible to take general radiologists and train them to perform low-dose CT. They are using a programme developed by

Delivery of Care

the European Society of Thoracic Imaging, known as the Lung Cancer Screening Certification Project, which involves webinars, e-learning and workshops. The team plan to assess whether it is feasible for the first reading to be performed by a radiologist who has undertaken the training programme and the second reading to use computer-assisted diagnosis. “In NELSON, double reading from expert radiologists was used, which isn’t practical outside a clinical study,” says Revel.

As the pilot develops, the team plan to introduce smoking cessation and combine lung cancer screening with other forms of low-dose CT appropriate for women in the age range 50–74 years, including screening for breast cancer and osteoporosis.

“We hope our focus will have the

additional benefit of highlighting the increase of lung cancer in the female population. This is of vital importance, since lung cancer is now the first cause of cancer death among women in France,” says Revel.

Next steps for Europe

With lung cancer still the single biggest cancer killer in Europe, the question of whether – and how – to implement lung cancer screening is likely to shoot up national policy agendas, now that the European Commission is recommending in favour.

The practical experiences and lessons learned from the lung screening programmes and pilots already running in countries such as the Croatia, the UK and France could now prove valuable resources

in helping other countries develop their own programmes.

The most important lesson of all may be that there are many different ways to implement these programmes, and that success comes from tailoring programmes to the priorities, resources, systems and cultures of each country, applying quality control to every aspect, and monitoring and learning as you go along.

This article was published on the Cancer World website on 14 January 2022 (bit.ly/CW-Lung-Cancer-TurningPoint)

It has been updated to reflect the SAPEA advice and the update to the EC screening recommendations



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INTERACT-EUROPE: Developing an Inter-specialty Cancer Training Programme



The European Commission has launched new funding calls for EU4Health and Horizon Europe – another sign of its commitment to Europe's Beating Cancer Plan and Cancer Mission. With the valuable support of the cancer community, the European Cancer Organisation (ECO) is proud to answer some of these latest calls. We were privileged to be awarded the coordination of our first EU4Health project (INTERACT-EUROPE) earlier this year. Our assignment is to develop an inter-specialty cancer training programme (ISCTP) across the European region.

Our approach in everything we do is profoundly holistic. We have long maintained that multidisciplinary and multiprofessional teams, working collaboratively, are the only way to provide the highest quality of care to patients, many of whom have complex medical needs. It is why we are gathering professionals from all oncology disciplines to craft a comprehensive training programme, providing oncologists with a broader understanding of the tasks and responsibilities of their colleagues.

This is only possible through our unique consortium of 33 partner organisations from 17 countries, including the European School of Oncology who have vast experience in this area. The consortium brings together a diverse mix

of expertise to set the standard for inter-specialty cancer training in Europe.

As coordinators of this 18-month project, we organised its launch on 27 and 28 June at an in-person kick-off meeting in Brussels, with many of our INTERACT-EUROPE partners in attendance. We also had an opportunity to meet and discuss informally during an event at the European Parliament with Tomislav Sokol MEP, to whom we are grateful for his consistent support.

The INTERACT-EUROPE website (interact-europe.org) is now up and running, providing you with details on project deliverables, publications, and newsletters. We encourage you to follow the project's progress and to be part of this much-needed upgrade in cancer care training.

More recently, the European Commission has asked the ECO to co-ordinate two additional projects: PROTECT-EUROPE, which addresses the need for a national, gender-neutral, HPV vaccination programme in EU Member States; and smartCARE, to develop a 'Cancer Survivor Smart Card'. We are now busy finalising details so we can hopefully launch both projects next year.

On behalf of our member societies, the ECO is dedicated to supporting the Beating Cancer Plan in any way possible with the resources we have available. We are now contributing to a variety of other EU projects through our communication efforts. If you are leading a consortium and interested in having us contribute, please contact us.

We believe that we cannot leave change to chance. We cannot simply react to current circumstances. Instead, we must act – and interact – to meet the growing needs of European cancer patients for years to come.





Liver cancer: how Europe can halt the rising death toll

Liver cancer is among the most deadly, and rates are steadily rising across Europe due to its association with obesity as well as alcohol. We know the risk factors, we can detect and monitor liver cirrhosis – the most common precursor condition – and treatment is curative if caught early. **Marc Beishon** reports on the chorus of voices now campaigning for urgent action on a cancer that has been neglected for far too long.

When the cancer community in Europe talks of neglected cancers it usually means relatively rare or uncommon types, of which there are many. But conspicuous in the list are two digestive cancers that are both deadly, not uncommon and increasing in impact – liver and pancreatic. The Innovative Partnership for Action Against Cancer (iPAAC) – an EU Joint Action that ran from 2018 to 2021 – addressed

neglected cancers, in particular with work on new care and treatment indicators for pancreatic cancer (bit.ly/CRC-Pancreatic-Indicators). Yet although primary liver cancer is also classed as neglected it has received less attention. Pressure for much more action is now growing.

That pressure was much in evidence as the iPAAC work drew to a close, with multiple events and publications presented during October – liver cancer awareness month –

that aimed to fill gaps in awareness of the disease and in delivering the standard of care. Among them was an urgent call by Digestive Cancers Europe (DiCE) and the European Liver Patients Association (ELPA), which pooled their respective strengths in treatment and prevention to highlight the message that Europe is losing the fight against liver cancer.

Rates of risk factors such as hepatitis C infection, alcohol consump-

Not all liver cancers are the same

There are two main types of liver cancer: hepatocellular carcinoma (HCC), which arises in the liver cells, and accounts for around 85% of cases, and intrahepatic cholangiocarcinoma (ICC), which concerns bile duct cells and accounts for most other liver cancer diagnoses. Both tend to be grouped under the 'liver cancer' heading in the statistics, but they have different risk and treatment profiles. There is also a combined HCC-ICC subtype.

tion, and obesity are rising, leading to 78,000 deaths in Europe each year from an incidence of 87,000.

The International Agency for Research on Cancer (IARC) predicts that, by 2040, the death rate in Europe will rise above 101,000 with an incidence of 109,000. It is the major countries that account for by far the highest numbers, current and future – France, Italy, Russia, Germany, the UK and Spain, in descending order. New cases of liver cancer are expected to rise by almost 35% in France, and 40% in Spain, by 2040. Smaller countries may see even higher rises, albeit from a lower baseline.

While these numbers are still lower than for pancreatic cancer – which is projected to take the lives of 168,000 people a year in Europe by 2040, putting it on track to become the third leading cause of cancer-related deaths in the EU countries – the rise in estimated liver cases in Europe is certainly troubling.

Deadly but preventable

There are similar percentage rises in mortality and incidence for pancreatic cancer in Europe, and both liver and pancreatic have something else in common: they are mostly detected only at

advanced stages, and have among the lowest survival rates of all cancers. In most countries, fewer than 15% of people diagnosed with liver cancer survive for five years.

Liver cancer differs significantly from pancreatic cancer in one important aspect, however: it is amenable to prevention and screening, owing to its risk factors. In that respect, it has more in common with the biggest killer, lung cancer, which for many years was viewed fatalistically by healthcare systems, also owing to its late detection and poor outlook, but of course has the preventable risk factor of smoking and now the possibility of low-dose CT screening.

There's another factor in common with lung, which is new treatment options. While surgery is the preferred curative strategy, this can be carried out only in a small minority of patients. Liver cancer is also one of the few tumours for which cytotoxic chemotherapy has little effect, at least in HCC, the most common type, which has no doubt contributed to its status as a neglected disease (see box).

But for about a decade there has been an effective targeted therapy in advanced disease, and now there are several targeted agents and also an immunotherapy in play. Responses remain highly variable,

however, and much remains to be done in trials and in optimising sequencing of drugs. There are also a number of interventional radiological and radiotherapy techniques, and even liver transplantation, and techniques used on the liver cross over into the treatment of liver metastases from other cancers, principally colorectal, which are much more common than primary disease.

Liver disease comes first

Two virtual events staged during the last liver cancer awareness month presented a stark picture of the worsening situation across Europe, but also highlighted many opportunities to improve it. One was the launch of a white paper at a masterclass by DiCE and ELPA, *Liver cancer, no patient left behind*, which covers all aspects of care (bit.ly/LiverCancer-WhitePaper); the other was a meeting held by the European Association for the Study of the Liver (EASL), 'Beating liver cancer in Europe', which focused mainly on prevention and early detection (bit.ly/EASL-1, bit.ly/EASL-2), and benefited from parliamentary support from Slovenia, which currently holds the EU presidency and has a track record in promoting high-level European cancer policy.

A key point highlighted in these and other recent events is that liver cancer occurs mainly because the liver first suffers from other diseases, and all such liver conditions including cancer are a substantial burden in Europe. A *Lancet* commission on the UK, for example (*The Lancet* 2015, 386:2098–111), reported that mortality attributable

to liver diseases has risen four-fold between 1980 and 2013, with liver disease likely to overtake heart disease as the leading cause of years of working life lost. (See also a final paper about ‘unacceptable failures’ to tackle liver disease in the UK – *The Lancet* 2020, 395:226–239.)

Looking at Europe, a *Lancet*-EASL commission has noted that, while alcohol-related liver disease is the major cause of cirrhosis in many European countries, there is also an increasing incidence of non-alcoholic fatty liver disease related to a rise in obesity, diabetes and high blood pressure, which has become both a cause of cancer and also an indication for transplantation (*The Lancet* 2018, 392:621–622). There is also a synergy between obesity and alcohol – a high body mass index can increase toxicity of alcohol on the liver (*BMJ* 2010, 340:c1240).

Hepatitis B and C infections are also significant in Europe; the hepatitis C virus, which has been more prevalent in EU member states than Hep B, causes chronic hepatitis in 60–70% of infected people, of whom 5–20% will develop cirrhosis and 1–5% will contract HCC, although this typically takes up to 30 years. The good news is that hepatitis C is now curable in most people. The European Network for Hepatitis B and C Surveillance (ecdc.europa.eu) is the key source on prevalence.

As Abid Suddle, a hepatologist at King’s College Hospital, London, noted at a British Liver Trust event (bit.ly/LiverCancerWebinar), it is non-alcoholic fatty liver disease that is set to be a leading cause of liver cancer in the West, and the perception of cirrhosis as mainly

associated with alcohol is far from accurate. A major difficulty, he noted, is that liver disease tends to develop silently with no symptoms over a long time, and without abnormalities in blood tests that may be ordered by GPs and others checking on other conditions. So the challenge is two-fold: detecting liver disease that may develop into cancer, and detecting cancer itself.

The DiCE/ELPA white paper cites evidence that Europe has the biggest liver disease burden globally, which may indicate that the projections for increased cancer incidence in the region are based on solid ground. There is much to consider in public health to reduce liver disease and also cancer with alcohol policies (such as pricing), tackling the pandemic of obesity among Europeans, and viral hepatitis vaccination and treatments. But alcohol policies are lagging those in smoking, which have finally turned the tide on male smoking rates at least, while there is little progress in reducing the numbers of overweight children and adults through measures such as a tax on sugar (and the Covid-19 pandemic may have exacerbated unhealthy eating). The potential for stigmatising patients owing to drinking or weight is also clear.

Hepatologists push for screening

As liver cancer patients usually have two diseases – cancer and the condition that caused it – the physicians with particular responsibility for, and interest in, treatment are hepatologists (liver specialists), and many are playing a leading role in multidisciplinary cancer

Lack of early detection of cancer in the context of liver disease is the universal frustration for hepatologists and others in the MDT

teams (MDTs) and in stepping up calls for better policies. It’s similar to the way that respiratory physicians have taken on much of the heavy-lifting in quality initiatives in lung cancer.

Lack of early detection of cancer in the context of liver disease is the universal frustration for hepatologists and others in the MDT, especially as there is good evidence of better outcomes for those undergoing surveillance by ultrasound, which is the current tool used to detect tumours and can be coupled with a blood test for a tumour emitting alpha-fetoprotein (AFP).

The recommended screening interval is six months for those with cirrhosis and also those with hepatitis B infections without cirrhosis. There is also work on monitoring earlier fibrosis before it develops into the more serious scarring in cirrhosis (see the LiverScreen project at liverscreen.eu).

So screening is important in patients with high-risk liver disease, but Europe is way behind countries such as Japan and Taiwan in using surveillance, as reflected in a big gap in median survival – 60 months in Japan, for example, compared with just 24 months in Europe, in figures cited by Pierre Nahon, a hepatologist at Jean Verdier Hospital in Paris (bit.ly/EASL-2). In France about 75% of

patients are diagnosed at advanced stages, with less than two years survival. Many liver cancers are only picked up when they become symptomatic at an emergency stage – about 30% in the UK, for example, noted Suddle. Surveillance programmes have been in place in countries such as Japan for some time, but they do have higher rates of HCC and higher risk.

Nahon notes that surveillance is

**Median survival is
60 months in Japan
compared with just 24
months in Europe**

recommended in a number of guidelines, including from ESMO and EASL, so it should be a standard of care. But comparing screening in clinical trials against what happens in routine care in hospitals in Belgium and France has also shown that adherence to recommendations may be low in Europe, he said. In a study with 100% screening, 61% of HCC patients were eligible for curative treatment, but 20% screening in ‘real life’ led to only 24% being picked up at a curative stage. The standard in all the guidelines is six-monthly surveillance of cirrhosis patients with ultrasound with or without the alpha-fetoprotein blood test; diagnosis is usually made with further imaging with CT or MRI, and also biopsy.

Liver specialists want to raise the profile of surveillance to improve compliance and early detection through education of patients and their healthcare providers. Identifying those who have liver conditions

such as non-alcoholic fatty disease who are on course to develop cirrhosis and possibly HCC is certainly a major challenge. As Nahon points out, up to 30% of Europeans have this type of condition, so this is a huge population, but there are algorithms that primary care providers can use to identify people who may have cirrhosis and need to be referred to a liver clinic for surveillance. EASL has issued updated guidelines on non-invasive tests for evaluating liver disease, which includes a proposed algorithm for primary care (*J Hepatol* 2021, 75:659–689).

They also recognise that better tools are needed to improve the sensitivity of the current ultrasound/blood test regime, which misses up to half of early cancers. Other imaging methods and new biomarkers are under research, as are ways to personalise screening so it is more cost effective. One such trial in France is Fastrak (ClinicalTrials.gov identifier NCT05095714), which is comparing six-monthly ultrasound with ultrasound+MRI to detect smaller tumours. Nahon also points out that the level of evidence for current screening is low as, understandably, patients with cirrhosis won’t agree to be randomised into a no-surveillance arm, but there is consensus that it remains a strong recommendation, despite the usual drawbacks of screening, such as false-positives.

Complex and multidisciplinary

Treating liver cancer is complex and demands an expert MDT that assesses the cancer stage, liver function – this is a particularly critical indicator emphasised by MDT

members – and fitness to undergo treatments. Such MDTs, which may be part of a hepato-pancreato-biliary unit, are starting to find their voice as an essential approach to care. (See, for instance, a US liver cancer tumour board discussion hosted by the Global Liver Institute, which can be viewed at bit.ly/LiverCancer-TumourBoard, and papers on the importance of MDTs in managing liver cancer, such as *J Multidisc Healthcare* 2017, 10:95–100 and *Clin Liver Dis* 2020, 24:771–787).

But, as with other common cancers, there is no doubt large variability around Europe in the MDT approach (which DiCE/ELPA agree is likely in their white paper). A research-oriented MDT at Hammersmith Hospital in London, which is led jointly by a hepatologist and a medical oncologist, could be seen as a ‘gold standard’, and is claimed to be the UK’s only specialised service providing such joint expertise at the head of the team (bit.ly/LiverCancer-HammersmithHospital).

ESMO updated its treatment guidelines in 2021, listing the wide variety of options now considered to be the standard of care (*Ann Oncol* 2021, 32:801–805). In early stages, according to the Barcelona Clinic Liver Cancer (BCLC) staging system, and also with liver function assessed with the Child-Pugh system, apart from surgery there can be a choice of transplantation, thermal ablation and transarterial chemoembolisation (TACE). Alternatives to the standard of care can also include radiotherapy (external and brachytherapy), and selective internal radiotherapy (SIRT – which uses radioactive beads).

Medicine

In the non-curative setting, ESMO has given the highest score in its Magnitude of Clinical Benefit Scale to the combination of the immunotherapy drug atezolizumab together with bevacizumab (approved in 2020) for a significant improvement in survival in HCC compared with the targeted inhibitor sorafenib (*N Engl J Med* 2020, 382:1894–1905), which had been the only option for some time, but has also been joined by other inhibitors. But for BCLC stage D, where the liver has severe damage, or performance status is too poor, there is only best supportive care.

Given the complexities of liver disease and its diagnosis and subsequent treatment it is not surprising that survival rates differ widely among countries (see the Concord-3 study, *The Lancet* 2018, 391:1023–75) and most patients are unlikely to have access to the full range of current treatment options, such as SIRT, outside of expert centres.

It isn't just doctors who are vital MDT members – one important professional who spoke at the British Liver Trust event was Sarah Selemani, a clinical nurse specialist who has expertise in guiding patients through the journey with liver cancer; such nurses still aren't in place in many countries.

The policy backdrop

The uptick in pressure to increase awareness of and treatments for liver cancer no doubt also correlates with the launch of the EU's Beating Cancer Plan, as there is huge ambition in elements of the plan. There is an emphasis on prevention such as encouraging

healthy lifestyles, which is particularly relevant for liver cancer.

The plan also includes commitments on ensuring access to hepatitis B vaccination and to treatments to prevent liver and gastric cancers associated with hepatitis C, and the 2022 roadmap on the plan does include actions on the viruses (bit.ly/EU-CancerPlan-Roadmap).

Liver cancer advocates will be happy to see the roadmap also includes the promised inequalities registry and upgrading of comprehensive cancer centre infrastructure – the latter being one of the more ambitious moves.

Taking stock of the latest round

The latest round of liver cancer initiatives reveal a lot of ambition, but also concern

of liver cancer initiatives reveals a lot of ambition, but also concern. The DiCE/ELPA white paper is the most thorough of the crop, covering all bases in optimising knowledge, prevention, early diagnosis, treatment and patient involvement.

It references the Beating Cancer Plan, EASL and ESMO guidelines and also an action plan for five types of viral hepatitis in the WHO European region, said to be the first plan of its kind, with the aim of eliminating it as a threat by 2030.

In addition to well-referenced sections on lifestyle, screening and treatment, the paper includes important points on data, noting there is a lack of good quality comparative data among Euro-

pean countries in registries, and that there are common miscoding issues such as recording liver metastases as primary cancers, underestimation of liver cancer incidence due to lack of diagnostic capability, and under-reporting of liver cancer on death certificates.

It also notes evidence that a multidisciplinary approach is associated with improved survival in HCC (*PLoS ONE* 2019, 14:e0210730), and that the complexity of liver cancer is a challenge to health literacy – common language should be used around Europe.

The white paper's recommendations are complemented by 10 'asks' from EASL to improve liver cancer care and prevention, which invites people to sign an open letter aimed at European policymakers (easl.eu/10asks). Also included is a short report by the International Liver Cancer Network that reinforces calls for action (bit.ly/ILCN-WhitePaper).

There are other organisations, especially in the liver field, active in raising awareness about cancer. But there is a formidable set of issues that needs to be tackled to reverse the projected rise in incidence, not least the challenge on the prevention side in promoting an active, healthy population in diverse nations and where pronounced inequalities are evident.

This article was first published on the Cancer World website on 26 November 2021 (bit.ly/CW-Halting-LiverCancer-DeathToll)

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What can we expect from mRNA cancer vaccines?

The mRNA vaccine technologies that proved their value against Covid were originally developed to help cancer patients mount an effective immune response against their disease. With a number of mRNA cancer vaccines now in trials, **Sophie Fessler** asks what mRNA vaccines might be able to add to existing therapeutic strategies.

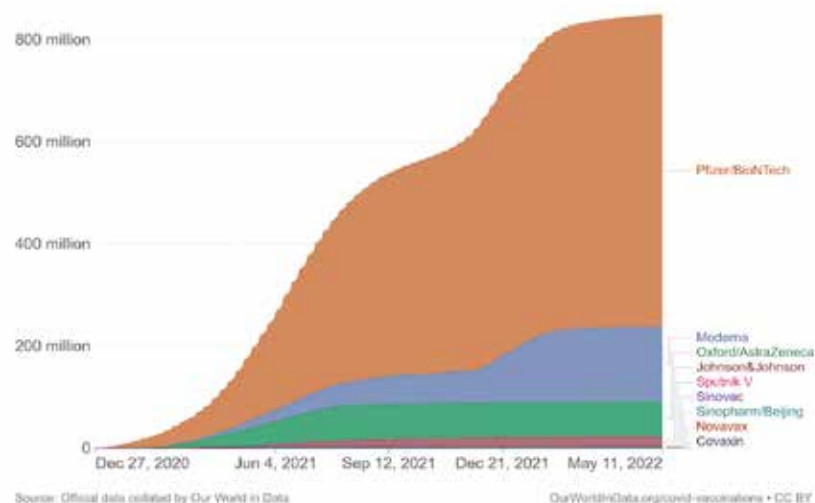
Messenger RNA vaccines turned around Europe's fight against the Covid pandemic. Less than a year after the first lockdowns were declared, mRNA vaccines got regulatory approval for emergency use, first in people at high-risk from Covid, and later in the broader population. By April 2022, more than 600 million doses of Pfizer/BioNTech's mRNA-based Covid vaccine and nearly 150 million doses of Mod-

erna's vaccine had been administered in the European Union. But while this novel approach to vaccines came into its own during the pandemic, mRNA vaccine technology had initially been developed for use against cancer, with the aim of boosting the ability of the patient's own immune system to recognise and attack tumour cells.

Before the pandemic, CureVac, founded in Tübingen, Germany, in

2000 – the first of the 'big three' mRNA companies – was testing an mRNA vaccine, combined with local radiation, in patients with non-small-cell lung cancer (*J Immunother Cancer* 2019, 7:38). BioNTech – a company based in Mainz, Germany, which started operations in 2008 – had been focused on developing therapies for melanoma, triple-negative breast cancer, head and neck cancer, lung cancer and KRAS-mutated solid

Covid-19 vaccine doses administered in the EU



mRNA vaccines accounted for the vast majority of coronavirus vaccines administered across the EU. Having proved so safe and effective in that setting, the cancer community is now waiting to see what they can do against cancer – the disease for which mRNA vaccine technologies had originally been developed

Source: Official data collated by Our World in Data, downloaded on 12 May 2022 from <https://our-worldindata.org/grapher/covid-vaccine-doses-by-manufacturer?country=~European+Union>. Republished under a creative commons licence

tumours. Moderna – the third big player, established in Cambridge, Massachusetts in 2010 – was also investigating the use of mRNA vaccines in an oncological setting. “Back then, all of them tried to develop vaccines against cancer,” says Peter Brossart, Head of Haematology and Oncology at Bonn University Clinic, who was himself involved in some of the earliest clinical trials of mRNA vaccines in cancer patients, starting in 2003 (*OncolImmunol* 2016, 5:e1108511).

Then came Covid, and the rush to develop vaccines at speed and at scale that could offer reliable protection. All three companies turned their attention to developing mRNA vaccines against the SARS-CoV-2 virus. The performance of the Pfizer/BioNTech and Moderna vaccines showed what the new

virus technology could do, in terms of efficacy, safety and speed of development. It also delivered huge commercial success – the first for mRNA vaccines – that could give a major boost to efforts to develop its use as a cancer therapy. “The companies have now the financial resources to develop and conduct vaccination studies again, to treat patients with malignant diseases,” says Brossart.

“The principle of using vaccines against cancer is to train the immune system to recognise tumour antigens and target them”

mRNA cancer vaccine therapy: principles and history

The principle of using vaccines against cancer is to train the immune system to recognise tumour antigens and target them. The strategy has relevance in treating active disease as well as for adjuvant treatment, says Dirk Arnold, a gastrointestinal cancer specialist, and head of the Asklepios Tumour Centre in Hamburg, who is currently involved in a phase II trial of a BioNTech colon cancer vaccine (CancerTrials.gov identifier NCT04486378).

“At the moment, mRNA vaccines [in oncology] are clinically developed for two fields: to shrink existing lesions in highly immunogenic tumours and to prevent a relapse in minimal residual disease. In this adjuvant situation, the principle is similar to how Covid vaccines worked: a virus enters but the immune system is prepared and can kill it. In the oncologic situation, the disease recurs but now the vaccine strikes – it has trained the immune system for this situation and the tumour cells can be attacked.”

As Arnold points out, mRNA technology is a relative newcomer to the cancer vaccine scene. “Tumour vaccines have been studied a long time, especially with immunogenic tumours,” he says. The BCG vaccine, which is used primarily to prevent tuberculosis, also acts as immunotherapy for early-stage bladder cancer, where it has been approved and studied for decades. The first vaccine specifically developed as a therapeutic cancer vaccine, Provenge, was

approved in 2010 to treat patients with prostate cancer.

To train the immune system to detect cancerous cells with Provenge, dendritic cells and antigen presenting cells are collected from the patient. Outside of the patient, these cells are exposed to a protein intended to stimulate and direct them against prostate cancer cells. Finally, the immune cells are returned to the patient and should now be able to detect and fight cancer cells. “However, this can be made more effective with mRNA, which can show target structures to the immune systems more efficiently,” says Arnold.

The concept behind mRNA vaccines is (deceptively) simple. During protein production in normal cells, mRNA is the messenger – hence its ‘m’. It ferries genetic messages that contain instructions for the building of various proteins which carry out all the functions necessary for life. To achieve this, mRNA is copied from DNA in the nucleus and delivered to ribosomes in the cytosol, where the protein is built.

mRNA vaccines can make use of this process by introducing mRNA that contains instructions to build proteins that code, for instance, for the production of the SARS-CoV-2 spike protein, or proteins expressed by cancer cells. When such ‘therapeutic’ mRNA is injected into the body, cells take up the nucleic acid. The cells are then coaxed into producing the desired protein or peptide from the introduced mRNA script. Among the cells likely to take up mRNA are dendritic and other antigen-presenting cells, which produce the encoded peptide and present it to

immune cells, starting the adaptive immune response. mRNA vaccines can induce both an antibody-mediated response and T-cell responses. Unlike DNA, this mRNA doesn’t have to enter the nucleus to be transcribed, but instead goes directly to ribosomes for translation.

“There is a huge difference between inducing an effective immune response against a virus and doing the same against cancer cells”

Simple as it may sound, as Brossart emphasises, there is a huge difference between inducing an effective immune response against a virus and doing the same against cancer cells. Pathogens carry antigens that are foreign to the human body, and the immune system has evolved over millions of years to identify and eliminate them rapidly. Tumour cells, on the other hand, grow over a longer time, and have evolved mechanisms to evade the immune system. “It is more difficult to induce an immune response as the tumour cells’ milieu is often very immune-suppressive,” he says.

To induce an immune response at all, the vaccine needs to contain the right antigen to train the immune system. In earlier trials, vaccines used antigens that are selectively expressed or overexpressed in tumour cells but not in healthy cells. “Their advantage is that they are off-the-shelf vac-

cines,” says Brossart. “However, high-affinity T-cells recognising self-antigens will be eliminated more in the thymus.”

Most cancer vaccines currently tested instead follow a completely individual approach, where the vaccine is tailor made for each patient. A patient’s tumour is sequenced to find neoantigens – a new protein that forms on cancer cells when certain mutations occur in tumour DNA, and is not expressed on healthy cells. The advantage of this approach, explains Brossart, is that neoantigen-specific T-cells will not be eliminated in the thymus. As the antigens are novel and foreign to the immune system, the response will also be stronger,” explains Brossart. “However, finding mutations and peptides to direct the immune response against is time-intensive.”

Arnold believes a middle ground is likely to be found between these two approaches. “One option is a vaccine targeting one feature, which can be given to a subgroup of patients. The other is a combined vaccine containing several target structures, with which a large intersection of patients can be treated.”

A rocky road

The ‘tangled history of mRNA vaccines’ was traced in an article in *Nature* in 2021 (vol 597, pp 318–324). Brossart points to the seminal role played in the mid-1990s by Eli Gilboa and the team at the Center for Genetic and Cellular Therapies at Duke’s University, in Durham, North Carolina. They were among the first to investigate the potential

for using mRNA that coded for proteins expressed by specific tumour cells to train the immune system to attack those same cells.

Their approach involved taking immune cells from the blood, then coaxing them, *in vitro*, to take up synthetic mRNA that encoded tumour proteins, after which they would be injected back into the body to marshal the immune system to attack cells expressing those proteins. Success in animal studies was followed by clinical trials using the same approach. But despite early signs of promise, they came to nothing.

The Eureka moment fell to a PhD student at the University of Tübingen, in Germany, by the name of Ingmar Hoerr. Having learned about the work of Gilboa, he experimented with injecting mRNA directly into mice intradermally – initially as a control. Surprisingly, the mRNA remained active in the cells for at least a little while – enough to produce the antigen to raise an immune response against the protein.

Unlike others, who had observed similar phenomena but then abandoned the line of research, Hoerr decided to pursue the mRNA approach further. In 2000, together with colleagues from his laboratory, Hoerr founded the company CureVac.

Based on these findings, Brossart, then a consultant in oncology and haematology at the University of Tübingen ran a trial using *in vitro* transcribed mRNA coding for several tumour-associated antigens to vaccinate patients with kidney cancer (*OncolImmunol* 2016, 5:e1108511). That started in 2003 – almost 20 years ago. “We injected

RNA intradermally into patients. It worked partly and we observed clinically relevant remissions in some patients – but partly not,” Brossart recalls. He and his group collaborated with CureVac, who produced the mRNA without any of the modifications and stabilising procedures that have since been developed. “Already then we could see an immune response from patients against the vaccination. In several patients, symptoms improved and the tumours shrank in size,” says Brossart.

“We received no more funding for our study, because no one believed that immune therapy could work against cancer”

It was a good start, but there were clearly many technical challenges ahead, on top of which, the whole enterprise suffered from a severe lack of commercial confidence around immunology approaches to treating cancer, which had taken a knock following a series of disappointments. “There came a time during which people stopped believing in immune therapy,” Brossart recalls. “We received no more funding for our study, because no one believed that immune therapy could work against cancer.”

It took the success of checkpoint inhibitors to rebuild that confidence. The immune system was once again seen as an ally in combatting cancer, says Brossart. “Checkpoint inhibitors revitalised

and revolutionised this field.” He adds, though, that the success of checkpoint blockade somewhat overshadowed the potential value of cancer vaccines. “People asked: what role would mRNA-based vaccines play? But not all patients respond to checkpoint inhibitors, many relapse. There are many reasons for this, and cancer vaccines could provide an additional tool to stimulate an anti-cancer mediated immunity in these patients.”

Before that could happen, however, there were a number of technical problems to be solved. Key among them lay in the nature of RNA itself. RNA is unstable and rapidly degraded by the ubiquitous RNase. Not only that, as soon as mRNA is injected into the body, it is easily destroyed. During evolution, immune systems have learned that foreign mRNA only belongs to viruses and other pathogens, so our bodies immediately attack mRNA molecules.

In the years between the very partial responses that Brossart and colleagues were able to show in kidney cancer patients, using unstabilised, unmodified mRNA, and the success shown by the mRNA vaccines during the Covid pandemic, a lot of work was done to develop clever ways to smuggle mRNA into cells, and coaxing cells into producing significant amounts of peptide.

Optimising mRNA

First of all, mRNA needs to be brought into cells – which isn’t that easy. Naked mRNA is unstable and quickly degraded, so mRNA is now protected on its way to cells by formulating it into ‘delivery vehicles’,

Biology Basics

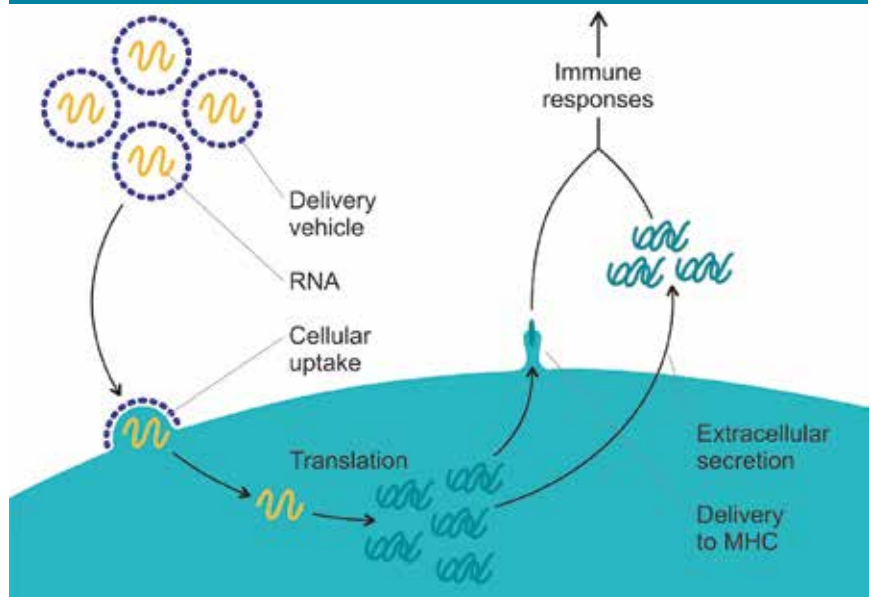
including lipid nanoparticles and polymers, that protect the mRNA until it reaches its site of action. Lipid nanoparticles were used to deliver both the BioNTech/Pfizer and the Moderna vaccines against Covid.

mRNA is also immunogenic, as it is recognised by a variety of pattern recognition receptors, which have evolved to detect single- and double-stranded RNA molecules from microbes and block mRNA translation. Pattern recognition receptors also activate the interferon-related pathway and elicit innate immunity, which inhibits antigen expression and dampens the immune response.

To reduce this inflammatory response, researchers have tinkered with the mRNA itself. Biochemist Katalin Karikó and immunologist Drew Weissmann, both at the University of Pennsylvania in Philadelphia, found that mRNA could be altered to reduce its immunogenicity, by replacing the nucleotide uridine with an alternative nucleotide, pseudouridine (*Mol Ther* 2008, 16:1833–40). Pseudouridine is similar to uridine, but contains a modification. Using pseudouridine not only decreases the anti-RNA immune response, but also enhances RNA stability. This technology is licensed by both BioNTech and Moderna

A lot of work was done to develop clever ways to smuggle mRNA into cells, and coaxing cells into producing significant amounts of peptide

How mRNA vaccines work



and found its way into their Covid vaccines. CureVac, on the other hand, does not replace uridine with pseudouridine. Instead, it alters the mRNA sequence so that the protein it codes for doesn't change, but minimises the amount of uridine used.

Lipid nanoparticles, pseudouridine and other modifications all contributed to the success that was seen in the mRNA-based Covid vaccines, which is generating huge interest in what the technology may be able to achieve with the various cancer vaccines that are currently in trials.

mRNA cancer vaccines: current strategies

Much remains to be clarified about where cancer vaccines can find their most effective place within therapeutic strategies, and the right choice of target. In the phase II trial of BioNTech's vaccine BNT-122, the vaccine is administered to patients who have

received surgery and chemotherapy for colon cancer, but test positive for circulating tumour DNA (cell-free tumour DNA), which points to minimal residual disease, and a high risk of relapse.

"If patients present with cell-free tumour DNA despite surgery and chemotherapy, there is likely an occult tumour, which will be targeted by the vaccine," says Arnold, the GI cancer specialist who heads up one of the many participating cancer centres, in Hamburg. Currently, he says, the first patients are still receiving chemotherapy, after which the mRNA vaccine will be given to those showing signs of minimal residual disease.

The BioNTech vaccine will be tailor-made based on the specific neoantigen expressed by each patient's individual tumour.

Findings from that individualised approach can inform such future approaches, says Arnold. "We will not only see which target structures

are there, but also whether they are suitable for targeting by vaccines.” For example, relapses might occur less frequently in patients in whom one antigen was targeted, while other antigens might mutate and evade targeting. “We will need to find stable, robust features, which don’t change rapidly.”

An alternative approach is being taken with the vaccine for HER-2-positive breast cancers pioneered by Herbert Lyerly, at Duke University. According to reporting by *Science Focus*, the vaccine will be administered to patients while they are receiving treatment with Herceptin, and rather than being tailor made for each patient, it will target four known mutations that arise in patients with HER2-positive breast cancer, in which the tumours have evolved mutations resistant to Herceptin ([bit.ly/BBC-ScienceFocus-mRNA](https://www.bbc.com/science/healthcare-56184444)).

In a study to be started in 2022, patients with advanced HER2-positive breast cancer who are not yet resistant to Herceptin will receive the same vaccine targeting these four mutations, which they are expected to develop in the course of treatment. “We’ll effectively be vaccinating people against mutations that their cancer doesn’t yet have,” Lyerly tells *Science Focus*. When cancer cells harbouring these mutations do appear, the immune system is expected to recognise and destroy the mutant cells. In this case, the tumours will remain sensitive to Herceptin and patients can continue to be treated with the drug.

That pre-emptive approach may foreshadow a time when cancer vaccines are even developed for a preventive setting, for people deemed to

be at high risk. Though that may still be a long way off, Arnold argues that prophylaxis for heritable tumours is something “very conceivable” and is eagerly anticipated. “If we have clear, unique target structures, it is imaginable that we can reduce risk of disease.”

“With less immunogenic tumours like colon cancer, the goal is to keep recurrence or minimal residual disease in check”

How much can realistically be expected of mRNA vaccines, he adds, will depend on the tumour. For highly immunogenic tumours, like renal cell cancer and melanoma, Arnold expects that existing tumours might be shrunk or controlled using a vaccine. “With less immunogenic tumours like colon cancer, the goal is to keep recurrence or minimal residual disease in check,” he says.

And as Brossart adds, though currently trialled as monotherapies, cancer vaccines may well also be combined with other therapies “Combinations with checkpoint inhibitors are one possibility, which could enhance the immune system’s function. Some data indicate that this might be the case.”

Looking ahead

These are exciting times in the cancer vaccine space, but Brossart warns that side effects, long term effects and efficacy of mRNA-

based cancer vaccines will have to be established, particularly before testing in a prophylactic setting. That said, as a result of their use in the pandemic, we now have copious and robust data on the side effects of mRNA vaccines, and – especially in the context of cancer – the data look good, says Arnold. “From the many millions of mRNA vaccinations to prevent Covid, we know the side effect profile: flu-like symptoms with very rare endocrine side effects and myocarditis.

These will also occur when treating tumours, but measured against the advantage, these side effects are in line with the benefits to be expected.”

Despite mRNA’s success in the Covid pandemic, it might still take some time until mRNA becomes a standard therapeutic molecule in oncology. “Studies in which a tumour is present and its size is reduced through vaccination – such as in melanoma or renal cell – this might be rapid, as one should be able to quickly judge success,” says Arnold. “In the adjuvant setting, we have to show that relapses don’t occur or occur more rarely. Just waiting for this endpoint means that the studies will take longer.”

Such trials recruiting now will have definitive results in three to four years, Arnold estimates. The results are eagerly awaited.

This article was published on the Cancer World website on 13 May 2022 ([bit.ly/CW-mRNA-CancerVaccines](https://www.cancerworld.com/news/2022/05/13/cw-mrna-cancer-vaccines))



The past, present and future of the European Code against Cancer (ECAC)

It seems that hardly a week goes by without some media outlet reporting anxiously on the latest thing that has been linked to cancer. The average person would be forgiven for thinking that everything can cause cancer. Thankfully, far-sighted experts brought together by the European Commission four decades ago developed a **framework to inform the public of the key things they needed to know to prevent cancer.**

The **European Code against Cancer (ECAC)** informs people about actions they can take to reduce their cancer risk (bit.ly/EuropeanCancerCode). An initiative of the European Commission, the scientific basis for the ECAC is provided by the International Agency for Research on Cancer (WHO/IARC), marking it out as **the definitive tool for cancer prevention in Europe.**

The Past

Right from the start, **cancer leagues** have been the **early adopters** and **primary promoters** of the ECAC.

Leagues have used it to inform targeted communication to specific groups, develop health promotion interventions, and support policy recommendations at the governmental level. At the Association of European Cancer Leagues (ECL), all of **our cancer prevention work has been based on the evidence provided by each edition of ECAC.**

Since 2014, ECL has acted as ECAC's **custodian**, having invested considerable resources to support member leagues to use ECAC and apply its evidence to promote cancer prevention at the national and local levels. We have also empowered and trained dozens of Youth Ambassadors to disseminate ECAC amongst their peers and the wider public.

The Present

The current edition of ECAC consists of 12 **simple-to-understand messages** complemented by:

- **Fourteen scientific publications** describing the methodology to update ECAC and evidence for each message
- an extensive online **Q&A section**
- **Two sets** of self-paced, multilingual **e-learning modules** about ECAC (available in English and French and soon in German, Hungarian, Spanish and Polish)

We encourage everyone to make use of these free resources and complete the ECAC e-learning modules to **gain a certification as an ECAC promoter!**

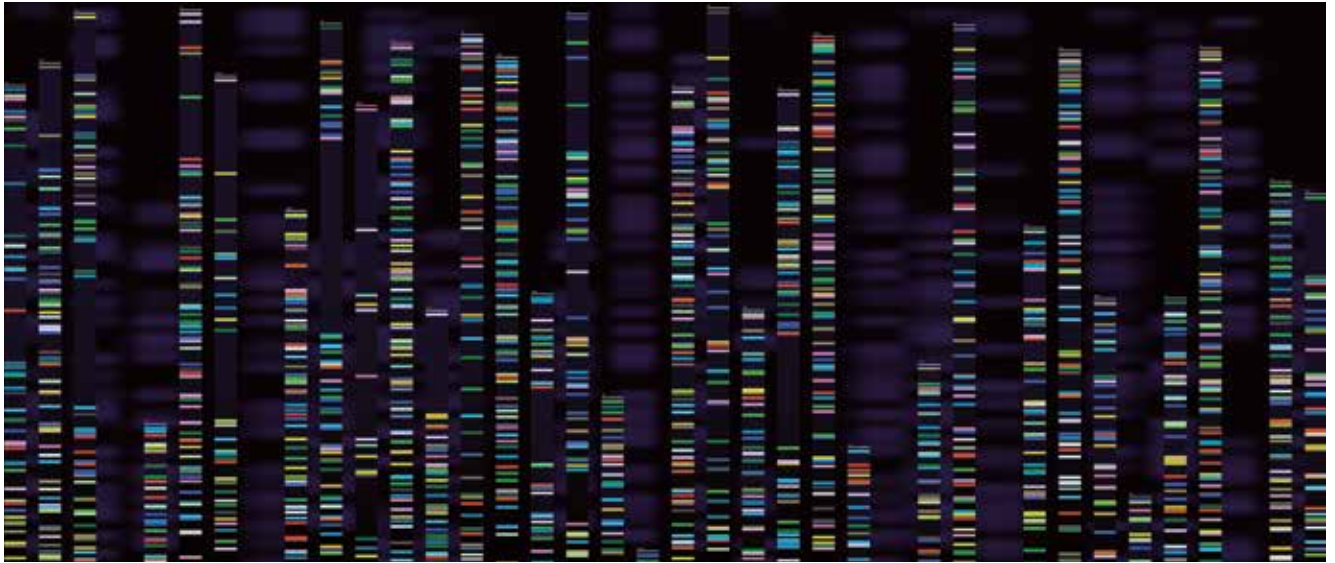
The Future

Europe's Beating Cancer Plan demonstrates the commitment of the European Union to diminishing the negative impact of cancer on society. A key priority of the plan is the **commitment to update the ECAC.**

The future **5th edition** represents a golden opportunity to build on past successes by expanding the scope of ECAC to incorporate new tools and materials to aid implementation and dissemination. To do so, **a permanent mechanism to update the ECAC in the long term is needed.**

ECL is appealing for the establishment of a **robust governance model** for the ECAC and calls on all stakeholders to become active promoters.

So why not join cancer leagues, WHO/IARC and the EU institutions in amplifying ECAC and, together, we can step-up cancer prevention in Europe!



Molecular diagnostics and NGS in the clinic

Where are we and where do we need to go?

Delivering precision medicine in everyday clinical practice requires addressing technical, logistical, bioinformatics and analytical challenges, not to mention challenges of collaboration and communication – all of that, while trying to stay focused on the patient and not just the biology of their disease. **Rachel Brazil** asks some of those driving change across Europe about where we are now, and what the future holds.

The development of next generation sequencing (NGS) has been a game changer for our understanding of genetics, and in turn for many aspects of biomedicine. This includes cancer, where it has led to greater understanding of the genetic changes that lie behind a cancer diagnosis, and enabled a precision approach to its treatment in some cases.

Its enhanced speed and affordability compared with previous sequencing techniques has made it feasible to introduce genetic sequencing into standard diagnostic practice. It may be used for sequencing single genes, such as screening for pathogenic BRCA mutations, which was its first use in a clinical setting. Or it can be used to sequence panels of genes known

to carry disease-causing mutations, or in some cases the whole exome – all the DNA known to code for proteins – and even mRNA, which reveals differential expression of proteins even in the absence of mutations.

But rolling out a molecular diagnostics approach based on NGS across Europe is not a simple endeavour. While some countries

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have made strides, others lag behind in developing systems with an infrastructure that can incorporate this approach into clinical practice.

The techniques used to identify biomarkers that can inform treatment are not restricted to the use of NGS. For example, the 30% of people with breast cancer who overexpress the *ERBB2* (*HER2*) proto-oncogene – and would benefit from a drug that inhibits that expression – can be identified using immunohistochemistry to detect the protein, or the fluorescent *in situ* hybridisation (FISH) method to detect the presence of the amplified gene.

“At the moment, the most extensive tumour testing done is relatively simple... it’s really not molecular diagnostics at all,” says Martijn Lolkema, a medical oncologist at the Erasmus MC Cancer Institute in Rotterdam, who has been involved in designing and building a national collaborative group to implement NGS for cancer patients. But as he adds, things are now starting to change, with the use of more extensive testing panels, “that is starting to be something that’s used in regular care.”

Some European countries were faster to spot the utility of NGS than others, explains Mark Lawler, an oncologist from Queens University Belfast, and Scientific Director of DATA-CAN, the UK Health Data Research Hub for Cancer. France provided some of the early evidence that the approach could be cost-effective in testing for pathogenic mutations in the epidermal growth factor receptor (EGFR) gene in cases of non-small-cell lung cancer, and providing inhibitors to those patients (*Econ Eval*

2020, 23:898–906). “They did a health economics analysis... and they showed up front that this will actually save money... That made it very easy for the French government to decide to introduce 28 laboratories,” says Lawler.

The power of such biomarker testing is now indisputable. A 2020 analysis of data from France of 1,213 patients with lung cancer, colorectal cancer, or melanoma showed that NGS testing done between 2013 and 2016 at one of seven certified biomolecular platforms led to identification of at least one genomic alteration in 75% of them; 53% of the alterations were actionable, leading to better survival outcomes after one year.

“Countries with centralised systems that permit infrastructure investment generally demonstrate greater uptake”

Access to molecular diagnostics is still patchy across Europe. “Germany, Denmark, Sweden, Finland, and the UK exhibit the highest uptake of NGS,” says Natacha Bolaños from the Lymphoma Coalition patient advocacy group, adding that countries with centralised systems that permit infrastructure investment generally demonstrate greater uptake than others.

A 2021 report from a consortium of policy, patient and industry groups, set up to identify barriers to biomarker testing in Europe, found that access to multi-biomarker tests

was even more restricted, with only Sweden, Denmark and Germany providing what they classed as ‘high access’ (bit.ly/BiomarkerTestingAccess). As might be expected, access was particularly low in eastern Europe.

Pathologist Claudio Luchini, from the University of Verona, acknowledges that it is currently impossible to sequence all tumours. “We have to have a tailored approach for selecting the right cases in the right patients for sequencing,” he says, which means focusing on sequencing the right tumours at the right time in the patients’ disease.

And indeed the number of biomarkers that can actually inform treatment remains quite limited. Lawler estimates only a quarter to a third of patients will currently have molecular abnormalities for which we can test, though he is confident that will increase: “We probably see 10–15 new molecular assays coming out every year to eighteen months... so I think we certainly will get to a stage where that pie chart will be much more highly represented with molecular markers that will then aid in [clinical] decision making.”

For many this means that NGS will be an approach of last resort, and used primarily in a metastatic setting, for instance in non-small-cell lung, prostate and ovarian cancer, and for those who do not respond to standard treatments. Luchini explains, for example, that although 90% of pancreatic malignancies will be pancreatic ductal adenocarcinoma, the remaining 10% will behave differently. “These should be analysed with next generation sequencing,” he says, which

will usually be done with targeted panels of genes. “The targeted panels, ranging from 100 to 300 genes, are already very good, because they can find more than 99% of the potential targets for molecular based therapies,” he says. What’s important, adds Luchini, is to “use the right molecular panel in the right moment.”

There are occasions where whole genome sequencing is being used outside a research setting. Lolkema gives the example of screening patients for early-phase clinical trials, “That has been very successful where we’re identifying patients that have actionable mutations,” he says. More extensive sequencing is also used for carcinoma of unknown primary origin (CUP). “We combine that at this moment with transcriptome sequencing [analysing which genes are being transcribed into proteins].” A combination of both is able to identify a primary tumour tissue of origin in up to 90% of cases, maybe even more,” says Lolkema. Treating CUP in line with the likely primary tumour tissue of origin can improve survival in some cancer types.

In the UK, whole genome sequencing is also available for sarcoma, paediatric cancers, haematological malignancies, and central nervous system tumours, according to Matthew Krebs, a medical oncologist at the Christie NHS Trust and the University of Manchester.

Molecular tumour boards

One approach to molecular diagnostics that has been adopted widely is the use of molecular tumour boards, pioneered by Michigan University. These are multi-

Training needs to catch up with the technology

As the use of NGS-based molecular diagnostics broadens, training for clinicians is becoming more crucial. A 2018 US survey conducted by the Harris Poll found that, while 75% of physicians believe that genomic testing improves patient outcomes, only 4% routinely ordered a molecular diagnostic test, only 50% of physicians felt confident in their ability to interpret molecular test results, and only 10% were confident in their ability to use test results as a guide for treatment (bit.ly/GenomicTestingSurvey).

Sufficient practical training and exposure to newer technologies is also critical for pathologists and molecular geneticists. An additional problem is a current shortage of pathologists in Europe, which is most acute in central and eastern Europe, in large part due to a brain drain to the West.

disciplinary meetings designed to identify and discuss potential therapeutic strategies based on molecular diagnostic results and other factors, such as a patients’ comorbidities and previous treatment. Those attending will include clinical oncologists, pathologists and, less often, geneticists, bioinformaticians, molecular biologists and even occasionally bioethicists.

In 2020 Luchini and colleagues conducted a review of 40 publications analysing this approach. Of 1,107 molecular tumour boards, indications for molecular-based therapies were found for 17.6% of cases (*Trends Cancer* 2020, 6:738–744). “It’s a very significant proportion... the approach improves outcomes,” he says. Given the increasing complexity of information provided by molecular diagnostic and oncology therapeutics, he argues that, “an oncologist alone cannot know the histological variant of pancreatic ductal adenocarcinoma is enriched in microsatellite instability for example, and at the same time, a pathologist alone cannot make the diagnosis.” Lolkema

agrees, “It’s really key to the implementation of these types of testing,” and adds that the molecular tumour board is not just there to interpret a test once it’s there, “it’s also there to make sure that the testing is done in a proper way.”

Pulling staff together for molecular tumour boards does require some co-ordination, however. But as Luchini points out, one of the few positive consequences of the Covid pandemic has been the introduction of more online tools for such meetings, which can facilitate inclusion of experts from other institutions. Lolkema emphasises how important it is for molecular tumour boards to feed into a clinical trials unit, so that patients can be matched to trials if there is no approved medication corresponding to mutations found.

As the biomarkers used for molecular diagnostics increase, new tools have been developed to assist clinical decision making, such as ESCAT, the ESMO Scale for Clinical Actionability of molecular Targets (*Ann Oncol* 2018, 29:1895–1902). First published in

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2018, it provides a standardised method for identifying patients with cancer who are likely to respond to the most appropriate precision medicines based on tumour DNA mutations. The classification also enables mutations to be upgraded or downgraded in response to newly available data.

Commercial products are also appearing; for example, Roche has launched a platform called Navify, which it describes as “a fully integrated portfolio of scalable, secure workflow solutions and apps designed to support care teams with analytics and actionable insights”.

ESCAT provides a method to identify patients likely to respond to precision cancer medicines, based on tumour DNA mutations

With more complex testing and bioinformatics, these types of tools become essential, though Lawler warns it is important not to become too reliant on ‘black box’ style solutions: “There should be more health data research and bioinformatics training within health services, so that... the people who are doing the primary analysis are clear as to what the informatics do, rather than just simply relying on the algorithm to spew out the result at the other end.”

With the growth of an infrastructure to interpret results, Lawler says it is now important that we move away from single-gene tests, towards multiple biomarker panels, which ultimately provide a better use of resources. “Sequentially,

doing single-gene analysis on samples from patients is not the way to go, and one that uses up valuable resources such as tissue samples [that] may be limited. It’s not cost-effective and it’s also probably fairly slow compared with being able to look at multiple targets at the same time through cancer [biomarker] panels.”

The time it takes to complete NGS is still an issue, however. In his analysis, Luchini says the mean time from sequencing to getting a recommendation from a molecular tumour board was 38.4 days, which ranged widely from 12.4 to 86 days. “[We have to] improve the turn-around time to try to have molecular sequencing results in about two or three weeks at the maximum,” he says.

Bolaños agrees, based on the experience of the patients she advocates for, and she says that part of the problem often comes down to a lack of local access to these services. “If local healthcare facilities could perform NGS-based genomic testing in-house, in an economically efficient way, more patients could access the service, test turn-around times could be reduced, and patients’ own physicians could use these insights to guide treatment decisions,” she says.

But NGS does need experienced practitioners, which in many countries has led to testing being limited to a centralised, or hub and spoke, lab system. “There’s a lot of consolidation going on in the pathology landscape, where people are centralising these types of tests, says Lolkema. “I think for a good reason. It’s not trivial to do NGS in a proper way.” Lawler agrees that testing needs to be rigorously

benchmarked, but stresses the need to keep the patient “at the centre of any sort of decision making process,” so centralisation must not come at a cost to patients.

“There’s more scepticism about the larger panels... But someone has to collect all the data to get the evidence”

Some clinicians remain sceptical about the NGS approach to molecular diagnostics, though they are probably a minority. “There are vested interests that sometimes make people sceptical about change in general, and especially change that will alter the distribution of the main asset, which is patients. So that is always a difficult political issue,” says Lolkema. “There’s more scepticism about the larger panels, and rightfully so, because there needs to be a more robust evidence base before we can actually implement that into regular care. But someone has to start up the process to collect all the data and to make sure that we get the evidence to actually implement.”

Will NGS diagnostics widen inequalities?

For many patients though, NGS is still not being offered. “Anecdotal evidence from Lymphoma Coalition member organisations indicates testing is not readily available, especially the most sophisticated test,” says Bolaños.

Cost is a key issue here. It is not always easy to show cost-effective-

ness, but Lolkema suggests that the problem lies more in perceptions of the cost than the true cost, “because the actual costs are not that big.” The maximum cost is €5,000 per patient, he says. “If you look at any type of surgery or any type of generic chemotherapy, it’s much more... As a society, we’re not looking at costs in the right way.”

Luchini argues that the real cost issue relates not to the tests so much as to the precision drugs that the tests may indicate will or won’t benefit a given patient. Yet anomalies with the reimbursement process can result in patients being reimbursed for very expensive drugs, but not for the tests that, for a fraction of the cost of the drug, could select patients for that treatment. This is currently a problem in the Netherlands with selecting men with prostate cancer for a particular precision drug, says Lolkema. “[We are] reimbursed for the treatment, which costs about €50,000 per year, but we do not have the reimbursement for the €1000 tests to actually select patients to get on [the drug]. So that’s crazy... We’re talking to healthcare insurers to change this.”

“The lack of dedicated diagnostics budgets and the siloed nature of resource allocation within certain healthcare systems have significantly delayed diagnostics commissioning,” adds Bolaños. Scotland provides an example of good practice, where decisions on test reimbursement and drug approval are made by the same key stakeholders to ensure alignment. In Belgium guidelines are regularly reviewed to ensure biomarker reimbursements keep up with current testing guidelines.

But in some parts of Europe the range of tests reimbursed remains low, particularly in eastern European countries, though as Lolkema notes, the underlying problem is the prohibitive cost of the drugs that any NGS test may indicate. Lawler worries that the growing importance of precision medicine could widen the existing inequities in cancer survival across Europe. “I do worry about there being a potentially multi-speed Europe, where, if you’re able to afford it, you’re able to deliver whole genome sequencing,” says Lawler, who was one of the architects of the European Cancer Patient’s Bill of Rights, launched in 2014 (*ESMO Open* 2016, 1:e000127), “It is important that we try to ensure equity across Europe.”

“Just because NGS testing is done doesn’t mean an indication for targeted therapy will be found or that the therapy is accessible”

Bolaños also sees dangers for equity with the current situation, not just geographically, but between ethnic groups whose genetic profiles and susceptibility to cancers will differ. “If all the algorithms are built based on the data that is already available, and most of the data available is coming from higher income countries, in the end, we are just making a wider and wider gap.” She would like to see greater efforts to make sure that the genomic data used to build

knowledge is collected globally.

She also advocates for greater efforts to ensure patients have the information they need. Awareness among patients is generally limited, she says, although those living with advanced cancer may be better informed. She stresses the ethical imperative to avoid giving false hope: just because NGS testing is done, it does not mean that an indication for targeted therapy will be found – and even if it is, the targeted therapy indicated may not be accessible.

“There is concern that genomic tumour testing may hold psychological risks. It is possible that patients with a cancer diagnosis may hold high hopes for getting new treatments, and feel disappointed if no actionable result is found,” she says.

A *Guide for Patients* on personalised medicine and a short leaflet giving 10 questions patients can ask their clinician, developed by the European Cancer Patient Coalition in collaboration with Lawler and others, were published in 2021 (bit.ly/PersonalisedMed-PatientGuide, bit.ly/PersonalisedMed-10Questions).

A role for liquid biopsies

How quickly molecular diagnostics moves further into standard care remains to be seen, but one innovation that may help is the liquid biopsy. Circulating tumour DNA (ctDNA) can be detected in blood samples, allowing NGS without directly sampling from the tumour site. It is early days, but the TARGET pilot trial (Tumour chARacterisation to Guide Experimental Targeted therapy), carried out at the Christie Hospital in

Practice Point

Manchester, from 2015 to 2021, indicated that, across a wide range of advanced tumours, mutations in DNA taken from circulating tumour cells concurred well with those in DNA taken from the same patient's tumour tissue, with a significant reduction in turnaround time (*Nature Med* 2019, 25:738–743).

“The bottom line from that was that you can use a liquid biopsy to look for a range of different mutations and then get a result back in a relatively quick time-frame, so that you can make a clinical decision for a patient, particularly in trying to match patients to clinical trials,” says medical oncologist Matthew Krebs, who led the trial. Krebs has now launched a UK-wide trial recruiting thousands of patients via 18 cancer centres.

“Broadly speaking, about 40% of people will have something potentially actionable. That doesn't mean that all those patients will get on to a matched treatment... I'd say between maybe 10 and 15% of patients currently get mapped... but we're aiming to get that to up to 20%,” says Krebs.

His trial is using two commercially available liquid biopsy assays, from Foundation Medicine (owned by Roche) and the diagnostics company Guardant Health. They can both provide comprehensive genomic profiling – point mutations and insertions, deletions and fusions, plus other factors such as copy number changes and, in some cases, microsatellite status and tumour mutation burden.

Currently, one liquid biopsy for EGFR in lung cancer is reimbursed in some European countries. “We hope in the coming years that there

will be more reimbursed indications for use of liquid biopsy – I think that is coming,” says Krebs, though he adds that it is unlikely to ever completely replace tissue biopsy and sequencing, as not all tumour locations shed DNA into the blood, particularly in the early disease stages.

Lolkema suggests that liquid biopsies might become important in tracking progress of already diagnosed disease, such as response to treatment or resistance mutations, “Those things can be very effectively sampled from ctDNA.”

Looking ahead

Looking to the future, can we expect all tumours to be fully sequenced? “Research today is the clinical practice of tomorrow,” says Luchini. “We know that there are new opportunities, so it is an ongoing process.”

“As our understanding of biomarkers increases, we may eventually need no more than a selected, but flexible, panel of genes”

Lolkema believes that, as our understanding of biomarkers increases, we may eventually need no more than a selected, but flexible, panel of the genes known to play a role. “I think it is going to be bell-shaped; we're going to go bigger until we're confident enough to say: Okay, if we do this panel, we will get everything.” To reach that point, he thinks we may first need to sequence up to 5 million

whole genomes, to make sure we have learned everything we need to know to design appropriate diagnostics.

Initiatives such as the AACR Project GENIE, that provide access to cancer genomic data with clinical outcome annotation for tens of thousands of cancer patients treated at multiple institutions worldwide, will be important resources to speed up this process.

Lawler's hopes for the future are that NGS might be able provide even broader information, to help select the best treatment for each patient. “I could see scenarios where we'd be identifying a lot more, [such as] using molecular markers to identify which therapies are leading to side effects.” This might allow oncologists to know in advance, for example, which patients are likely to suffer from peripheral neuropathy if treated by oxaliplatin.

For the moment, this is just speculation. What is now crucial, says Bolaños, is to keep making the case for improved access to molecular diagnostics where it would benefit patients. “We need to generate more and better evidence to demonstrate the clinical and economic value of these tests. And new, transparent pricing and reimbursement models which reward innovation are urgently needed to ensure the best outcomes for patients.”

This article was first published on the Cancer World website on 18 March 2022 (bit.ly/MolecularDiagnostics-Clinic)

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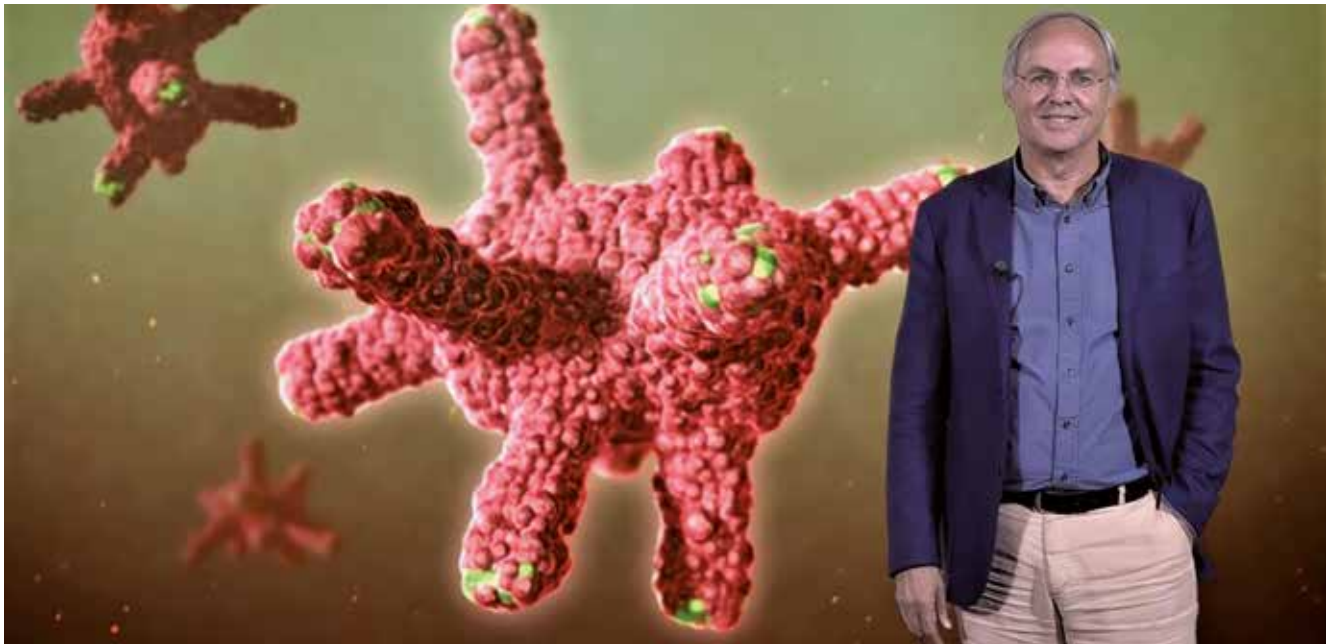


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The development of organoids for cancer research

An ode to the scientific method

Mini-organs, grown from human tissue in the lab, are much more reliable than classical cell line and animal models for learning how diseases like cancer develop and can best be prevented and treated. The breakthrough discoveries that led to their development won **Hans Clevers** the 2021 Pezcoller Foundation–AACR International Award for Extraordinary Achievement in Cancer Research. His acceptance speech, published below, highlights the basic principles of experimental science as key to his achievements.

Some twenty years ago, I sailed with my two little sons Sander (aged 7) and Max (aged 5) on the Ijsselmeer, formerly a large inner sea in the centre of my country. We passed by a beautiful row of newly built

windmills, painted in soft colours and shining in the sun. We were mesmerised by the rapidly rotating wings of the windmills. Suddenly Max asked: “When the mills stop turning, will our boat also stop?” Max believed that the

rotating windmills were causing the wind to blow.

This seemingly simple line of reasoning touches upon the core of science. Max is curious about the world around him, formulates a good question and defines

an answer. One could call this answer of the five-year old boy ‘a hypothesis’. Max’s hypothesis is a useful one, because it can be tested in a simple way. And, as you will realise, such critical testing will prove Max wrong: when the windmills are stopped – for instance for maintenance – it will turn out that the boats on the IJsselmeer will still be perfectly capable of continuing to sail.

“The critical assessment of fact, cause, and consequence requires... a lifetime of effort, discipline, and energy”

The first part of this ‘question-and-answer’ game is deeply rooted in human nature. Even young kids like my son Max play this intuition game without any effort. But the next step, which turns this game into science – the step of critical assessment, of deciding what is fact, and what is cause and consequence – turns out to be very hard. While intuition comes naturally to all of us, the critical assessment of fact, cause, and consequence requires lots of education and – after that – a lifetime of effort, discipline, and energy.

During the Covid pandemic, we have witnessed an endless stream of highly creative thoughts, beliefs, and opinions that all are very believable, but that would evaporate when subjected to critical scientific assessment. But the originators of these highly creative thoughts, beliefs, and opin-

ions, are typically very reluctant to take the second, scientific, step.

The amazing history of science

Science has only arisen once in the history of mankind. Not in ancient Egypt or China, not among the Mayans and Aztecs of South America. The cradle of science was located in Athens.

The ancient Greeks were no longer satisfied with their myths and religions and started to search for the laws of nature. Thus, the ancient Greeks have given us the mathematics of Euclid, Archimedes and Pythagoras.

The Roman empire had a definite interest in technology, but – I am sorry to say here – the Romans didn’t care much about the science of the Greeks. Only in the renaissance did science re-emerge: a key player was the Italian Galileo Galilei, who made up for the Roman disinterest. And the Englishman Francis Bacon put the cherry on the science-pie: he invented laboratory experimentation.

Albert Einstein has summarised the emergence of science in the history of the world as follows: “The development of Western science has been based on two great achievements, the invention of mathematics by the Greek philosophers, and the discovery of finding out causal relationships by systematic experiment in the Renaissance. In my opinion one need not be astonished that the Chinese sages did not make these steps. The astonishing thing is that these two achievements occurred at all.”

The successes of the scientific method in the past two centuries have simply been overwhelming. Just look around you: almost everything that you see exists only because of science. Yet, the world has never really embraced science. Most people don’t know how science works. There is often distrust of scientific conclusions, and fear of unexpected consequences of science. Just think of the unfortunate fear of Covid vaccines.

The British biologist Lewis Wolpert states the following in his book *The unnatural nature of science* about the uneasy relationship between man and science: “Science can be quite uncomfortable to live with. It offers no hope for an afterlife, it tolerates no magic and it doesn’t tell us how to live.”

“Francis Bacon put the cherry on the science-pie: he invented laboratory experimentation”

It is this two-step mechanism of trying to understand the world around us that has always intrigued me and that I have tried to exploit in the research in my lab: On the one hand there is the first step: human intuition, which allows us to ask and answer all sorts of questions and is a never-ending source of creativity. On the other hand there is the second step: the rational, scientific approach that subjects these questions and answers to harsh and

critical evaluation, often involving experiments in the lab. And, more often than not, resulting in a negative answer.

The hypothesis was creative and attractive, but wrong. Go back to square one and start all over again.

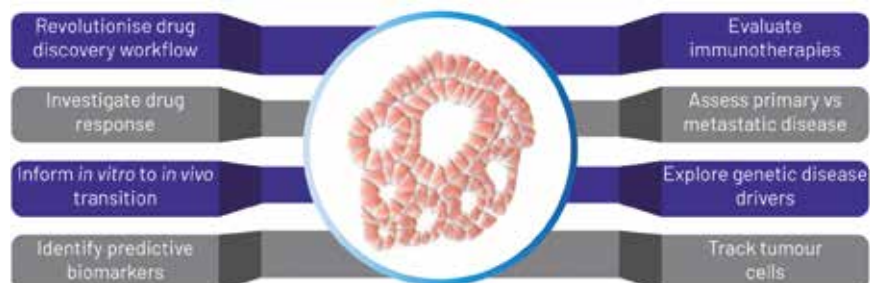
My own science journey

I was asked to tell you a bit about myself and my journey in Science. I was born and raised in a small village in the catholic south of Holland. As soon as I learned how to read, I devoured many books every week – on every imaginable subject, but I liked the books about scientific discoveries most. You could call me a nerd already at Kindergarten: I remember vividly how the teachers there would stand around me and ask what I wanted to become later in life: biologist!

Indeed, as an 18-year-old, I started my study of biology at Utrecht University in 1975. I was immediately deeply disappointed. I felt biology was not yet an experimental science, unlike chemistry and physics. We learned endless lists of Latin words and names, and nothing much else. I decided to also go to medical school and graduated in both.

The attraction of the medical profession was inevitable: clear social status, transparent future and every day filled with lots of social interactions. And most importantly, every day I was given a number of problems and could solve at least some of these. This type of instant gratification does not exist in science, where one has to work for months to obtain

Tumour organoid cancer research applications



Source: Organoid image taken from Y Ohta and T Sato (2014) Intestinal tumor in a dish. *Front Med* vol 1, article 14, Figure 1. Republished under a Creative Commons Licence

a result, and then most of the time the outcome is negative and one has to go back to the drawing table. Moments of gratification are rare and far in between.

I was offered a training position in paediatrics but was also advised to start with one year of research. In that year, I learned that my heart was in science, despite all its challenges.

I quit the hospital and went to Harvard with my wife Eefke, to learn the tricks of a magical new toolbox in biology: DNA technology. Four years later we returned to Utrecht and I started the journey in my own little lab that has taken me to this stage here today.

In my little lab, we asked a simple open question: How do white blood cells, the cells that fight virus infections, get produced in our body? I soon became head of the immunology department and learned how to combine managerial tasks with the science in my lab.

We found an interesting gene. While we were researching this gene, we didn't learn much about the white blood cells, but totally unexpectedly we solved a key

question in a very different scientific discipline – developmental biology, which studies how embryos create a complete body from one fertilised egg cell. And we also solved how colon cancer comes about.

“We didn't learn much about the white blood cells, but totally unexpectedly solved a key question in developmental biology”

I can be totally honest: we were never looking for these discoveries, we just stumbled across these. This is called serendipity: discoveries that were made without looking for them.

Because our discoveries led us away from studying the immune system, I decided to leave Utrecht University Hospital and moved my lab (grown to thirty young researchers) to the nearby Hubrecht Institute of the Royal Netherlands Academy of Arts and



Hans Clevers (second from left) and his wife Eefke Petersen, pictured after the award ceremony standing next to the president of the Pezcoller Foundation Enzo Galligioni, and his wife, Annaluisa Grossi, with Adriana Albini, *Cancer World* editor, on the right

Science. I became director of the Institute and could almost completely devote myself to my lab.

We decided to focus on colon cancer and on the ‘healthy counterpart’ of colon cancer cells – stem cells. It was known that all organs in our body should harbour dedicated stem cells, whose sole task is the maintenance and repair of the organ in which they reside, throughout life. Every organ was believed to be maintained and repaired by a unique stem cell type. There could exist as many

“The first four to five trials yielded negative results, but in 2006 he suddenly stumbled on a new molecular flag named *Lgr5*”

as a hundred stem cell types, but only a handful had already been discovered.

A British postdoc, Nick Barker (now running his own lab in Singapore) expertly applied the Step 1/Step 2 approach that I described earlier. He started this project in 2000. The first four to five tries yielded negative results, but in 2006 he suddenly stumbled across a new molecular flag, named *Lgr5*, that allowed us to identify the stem cells of the gut and subsequently the stem cells of many other organs. Nick created mice in which these stem cells emit a green light. As you know, normal mice don’t emit light, so we could – for the first time – see stem cells in action in a living being.

We soon realised – based on what we were seeing in these mice – that it should be possible to take the light-emitting stem cells out

of these mice and culture them in the lab, in a plastic dish.

I should mention at this point that it was generally believed around the world that normal healthy cells cannot be cultured outside the body and that only cancer cells will grow in a plastic laboratory dish. Because of this dogma, no one in the lab wanted to give this a try. Then, Toshiro Sato, a Japanese gastroenterologist who was new to the lab said: “I will do it”.

He went to the Step 1/Step 2 procedure. Starting from one light-emitting gut stem cell, he wanted to grow many stem cells in the dish, much like one can grow a plant from a seed. But much to our surprise, the stem cell did much more: rather than producing more stem cells, it created a tiny version of a normal gut in the dish.

“Rather than producing more stem cells, it created a tiny version of a normal gut in the dish. Another case of serendipity”

Another case of serendipity – a breakthrough discovery we were never looking for. Toshi called the structures that he was growing ‘mini-guts’.

We then rapidly realised that Toshi’s trick could be played for almost all other organs from mice and man, to grow mini-organs in a dish. The scientific name for these mini-organs-in-a-dish now-

adays is ‘organoid’. The technology is simple. One simply needs to obtain a tiny piece of tissue of an organ of interest and put it in the right cocktail of nutrients. Doctors take such samples routinely from patients and call these samples ‘biopsies’. We just need one millimetre-sized biopsy to start the growth of organoids from individual patients.

Organoids in cancer research and clinical practice

Over the past decade since Toshi’s discovery, we and many other labs have further developed the mini-organ technology and described many applications for basic science, but importantly also for clinical application. To name a few of the applications:

Organ transplants. Mini-organs grown in the lab can be used for transplantation to replace damaged organs. This has been shown in experimental animals for liver and gut diseases and, for instance, for dry mouth disease. Currently, transplantation of mini-organs is tested in clinical trials involving patients in the Netherlands and in Japan.

Drug development. Mini-organs grown from patients with particular diseases can be used to develop new drugs for those diseases. This is now extensively done for cancer.

Personalising medicines. Mini-organs grown from an individual patient can be used as an ‘avatar’ for that patient. Multiple drugs can be tested at the same time on the mini-organs, and the best one can then be given to the patient. This

is called ‘personalised medicine’. This approach is already applied with success for cystic fibrosis, a rare hereditary disease. Currently, many labs around the world are trying the same approach for cancer patients: mini-tumours are grown from individual cancer patients and exposed to a series of cancer drugs. The best one may then be given to the patient.

My lab currently works on a variety of organs and diseases, including cancers, infectious diseases such as Covid and a range of hereditary diseases. The use of the human organoids allows us now to avoid animal experiments, while we believe that we obtain insights in human diseases in a model that comes closest to the human body: the mini-organs.

“Mini-organs grown from patients with particular diseases can be used to develop new drugs for those diseases”

Looking back, it has been a journey with many unexpected turns and surprises. It has been a privilege to pursue the dream that I had as a four-year-old. I hope that I have conveyed today some of my belief in the value and beauty of science, even if it doesn’t always come naturally.

Science prizes are important as they briefly put science and scientists into the limelight. I would like to stress that I stand on this stage, but that the Pezcoller International AACR Award

for Extraordinary Achievement in Cancer Research is awarded for the work of several hundred, young, and always passionate, researchers.

This text was published with the kind permission of Hans Clevers.

The speech was delivered by Clevers at the ceremony in Trento, Italy, September 18, 2021, where he accepted the Pezcoller Foundation–AACR International Award for Extraordinary Achievement in Cancer Research. The first part is adapted from a speech he gave as president of the Royal Netherlands Academy of Arts and Sciences in 2012.

The Pezcoller Foundation–AACR International Award for Extraordinary Achievement in Cancer Research was established in 1997 to recognise a scientist of international renown who has made a major scientific discovery in basic cancer research or who has made significant contributions to translational cancer research.

Clevers, is Principal Investigator (and past Director) at the Hubrecht Institute for Developmental Biology and Stem Cell Research. The Pezcoller–AACR award honoured him for a series of breakthrough discoveries that led to the development of mini-organs, now known as ‘organoids’.

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Not too little, not too much... a lesson for cancer prevention from ancient civilisations

Unhealthy diet and obesity are rapidly becoming a major cause of preventable cancers. **Adriana Albini** looks at why, 2000 years after Hippocrates first preached the health benefits of moderation in what we eat, his message – and what we now understand about the nutritional value of the ancient ‘Mediterranean diet’ that he ate – remain the cornerstones for cancer prevention.

“If we could give every individual the right amount of nourishment and exercise, not too little and not too much, we would have found the safest way to health.” This quotation from Hip-

pocrates pops up regularly in writings advocating a sensible diet and lifestyle. But what is ‘sensible’, and why is this concept so difficult to grasp and translate into action? It seems that the Ancient Greek

doctor hit the nail on the head 2000 years ago, yet now, more than ever, we are plagued by obesity, fad diets and questionable health and nutrition gurus.

In the European Commission’s

Beating Cancer Plan (bit.ly/EU-CancerPlan), four main prevention strategies are laid out that could drastically reduce the incidence of cancer development: a tobacco-free future; a reduction in harmful alcohol consumption; reduced environmental pollution and exposure to carcinogenic substances and radiation; and better knowledge and health literacy to promote healthier lifestyles.

With the 'HealthyLifestyle4All' campaign, launched in September 2021, Europe is looking to raise health and nutritional awareness and promote better eating and exercise regimes (bit.ly/HealthyLifestyles4All). The initiative aims to work in collaboration with the community, scientists, food producers and public institutions to create structures and initiatives that allow everyone, regardless of culture and social/economic factors, to benefit from an active life and good food, achieving better health.

... Do like the Romans

Although Hollywood films tend to portray Ancient Mediterranean civilisations – the Romans, in particular – as debauched, scoffing slobs, enjoying lavish banquets washed down with torrents of wine, Ancient Greeks and Romans were actually very frugal. Their diets were based on grains, legumes, fresh fruit and vegetables, small portions of meat and fish, mostly grilled, a few eggs, some cheese, a little milk, usually fermented, olive oil, and virtually no butter. And their sweetener was honey, no refined sugar lurking in their meals. They drank plenty of water, often mixed with wine, which had the added effect of sanitising it. Their meals were structured and

they ate seated at a table with family, friends, or peers. It is true that they did have banquets, where they showed off and enjoyed elaborate food, while stretched out on more comfortable seats, but these were occasional, not every day, events.

It is in their eating habits that we find the roots of what we now call the Mediterranean diet, later enriched with imports from the New World, such as tomatoes and potatoes, which sat happily in a diet which we would now characterise as based on complex carbohydrates, some protein, unsaturated fat, vitamins, and minerals. Yet it was only in the 20th century that these nutritional elements were discovered, isolated, and studied. Tradition, experience, and availability of ingredients were the beacons that guided the ancient civilisations in their food choices.

The Mediterranean diet had to wait many centuries to acquire international fame, which eventually came thanks to a book, *How to eat well and stay well the Mediterranean way*, written by a polymath scientific researcher, Ancel Keys, and his wife, in the 1970s.

Keys discovered the health benefits of the Italian diet in the course of a long study into the effects of high cholesterol on health. In the 1940s the American scientific community was puzzled by a 'pandemic' of cardiovascular disorders that mainly affected business executives, who were presumed to be among the best-fed people in the US, if not the world, prompting researchers to look into correlations that could explain this conundrum.

The 'sudden' death of President Franklin D Roosevelt in 1945 acted as a catalyst for the launch of com-

parative studies into nutrition and lifestyle. It was caused by a cerebral haemorrhage brought on by cardiovascular disease, but as his poor health had been kept secret, the news shocked the American public.

Only three years later, in 1948, the Framingham Heart Study was born – a long-term, ongoing cardiovascular cohort study (framinghamheartstudy.org). It was a director of the project, William B. Kannel, who in 1961 coined the term, if not the concept, of 'risk factors'.

The 'sudden' death of Franklin D Roosevelt in 1945 acted as a catalyst for the launch of studies into nutrition and lifestyle

Meanwhile, Ancel Keys had started his own mega project – a longitudinal epidemiological study called the Seven Countries Study that began formally in 1958 and ran for about fifty years (sevencountriesstudy.com). The task of comparing health, nutrition, and lifestyle in so many different environments was not an easy one, and Keys proceeded with extreme caution, following a rigorous approach, with a rather humble attitude, all explained in detail in the results that were published in 1980, in the book *Seven countries: a multivariate analysis of death and coronary heart disease*. The study highlighted important correlations between cholesterol levels and cardiovascular disease. Keys also suggested that the high levels of longevity in Sicily could be

If we could give every individual the right amount of nourishment and exercise, not too little and not too much, we would have found the safest way to health.
-Hippocrates



attributed to the Mediterranean diet, with its low content of animal fats.

Knowledge is not enough

Keys knew that this study was not, and could not be, comprehensive or conclusive, but its value was nevertheless immense in understanding the role of diet in the prevention of disease. If you asked the average person today what the healthiest diet is, they would probably list the components of the Mediterranean diet – the right balance of carbs, protein, fat, and plenty of fresh fruit and vegetables. Lack of information and/or willpower are not the number one culprits in our inability to eat well. Many com-

ponents trick us into making poor food choices, and malnutrition is a puzzling – but perhaps explicable – phenomenon in countries where food is abundant.

As Harvey Levenstein pointed out in his book *Fear of Food*, “good taste is not a guide to the healthfulness of food”. If, in our remote days as hunter-gatherers, ‘sweet’ equalled ‘safe’, or ‘safer than bitter’, and helped us choose the best and most nutritious pickings, it is certainly not a good indicator in today’s world, where taste is masked, created, and confused by the way in which food is produced and preserved. Yet, our brains are still tuned into encouraging our search for sweet morsels. Sugar,

together with salt and fat, trigger our brain’s reward system, which releases endorphins and prompts us to repeat the behaviour, in order to keep on having that ‘buzz’. Not surprisingly, the same circuit is involved in addiction to drugs. We get used to higher levels of endorphins, and we then take more of the substance that triggers our brain into releasing them.

And this is what ‘junk food’ is – a high concentration of fat, sugar and salt that can lift our mood in seconds. Add to that the clever packaging, and the ‘halo effect’ of advertising – whereby we subconsciously attribute the beauty and allure of the slim woman to the bar of chocolate she is eating, or the

health and vitality of rosy kids to their enjoyment of burgers and fries – and our ability to take ‘responsible decisions’ is swamped by the ancestral wirings lodged in the depths of our brains.

A great number of studies correlating diet to cancer risk have been published in the past twenty years. Much of our knowledge comes from data generated by the ‘European Prospective Investigation into Cancer and Nutrition’ (EPIC) study, which is one of the largest cohort studies in the world, with more than half a million participants recruited across 10 European countries and followed for almost 15 years (<https://epic.iarc.fr>). At recruitment (1992–1999), detailed information on diet, lifestyle characteristics, anthropometric measurements, and medical history was collected, to identify correlations at later stages.

Biological samples were collected from more than 350,000 individuals, which are stored at the International Agency for Research on Cancer (IARC): nine million aliquots were available for one of the largest biobanks in the world for biochemical and genetic investigations on cancer and chronic diseases. The EPIC data have led to a great number of studies correlating diet to cancer risk.

Follow-up measures of lifestyle exposures have been collected and centralised at IARC. Almost 1,650 publications in PubMed are available (August 26 2022) with “European Prospective Investigation into Cancer and Nutrition” as keyword, starting with the presentation of the study by Riboli in 1992 (*Ann Oncol* 1992, 3:783–791).

Nutrition and lifestyle, in particular, have long been established as

risk factors for colorectal cancer. A more recent publication, co-authored by Riboli himself, presented lifestyle-based risk models that may aid the identification of individuals at high risk, and can be used to guide referral to screening and motivate behaviour change (*BMC Med* 2021, 19:1).

Much of our knowledge comes from data generated by the EPIC study, which is one of the largest cohort studies in the world

The investigators developed and validated a lifestyle-based risk prediction algorithm to predict risk of developing colorectal cancer in an asymptomatic European population.

Another very interesting paper on the topic was published the same year in *JAMA Network Open* (vol4:e2037341). An ‘umbrella’ review, analysing almost 10,000 publications in meta-analysis, found convincing evidence of an association between lower risk of colorectal cancer and higher intakes of dietary fibre, whole grains, dietary calcium, and yogurt on the one hand, and lower intakes of alcohol, red meat, and processed meat on the other.

At the beginning of 2021, the US Department of Health & Human Services published the 2020–2025 *Dietary Guidelines for Americans*, with the subtitle ‘Make Every Bite Count’, to encourage healthy eating patterns at each stage of life and recognise that individuals need to make shifts in their food and drink

choices to achieve a healthy pattern. The Guidelines also explicitly emphasise that a healthy dietary pattern is not a rigid prescription. These kinds of guideline are very useful to orient citizens and to provide them with accessible information and advice.

To move towards a healthier society, in addition to helping people make better nutritional decisions for themselves and their children, it is also necessary to involve food producers, restaurants, and supermarkets, in establishing a different food culture. This should include, for instance, reducing portions and relocating comfort foods to higher shelves, away from their prominent position near the tills, where they lure bored children and stressed-out customers. The current culture of big portions promoted by restaurants, lower prices for high-calorie foods, and higher prices for fresh fruit and vegetables, make us prone, among other issues, to putting on too much weight too easily. Once it is on, we seek short cuts to losing it quickly, and we can end up embarking on dangerous fad diets that take us even further away from a sense of what proper nutrition is.

Ultimately, we should just pay attention to what Hippocrates told us 2000 years ago: not too little, not too much.

With the contribution of Francesca Albini, PhD

This article was first published on the Cancer World website on 23 April 2021 (bit.ly/CW-PreventionLessons)



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Preventing burnout

Are we too focused on personal resilience?

The risk of burnout, which was always high within the oncology profession, has been exacerbated by the added pressures of the pandemic. **Simon Crompton** asks whether focusing on the individual, and helping them become more 'resilient', is the way to address the problem, or whether more attention needs to be given to changing workplace culture.

Burnout. That short word barely conveys the dispirited cycle of weariness, negativity and powerlessness health staff experience when high aspirations to help and cure are consumed in an unattainable to-do list.

"You're trying your best but nothing's moving and you just feel like in a constant circle," said one nurse in the UK trying to explain what it was like to work in an understaffed department. "It got to the point, I was on a night shift, and I just cried. I just sat and I cried and I said 'I can't do this.'"

The special risks of burnout among health service staff, who work under the unspoken expectation that other people's needs come first, have long been evidenced in surveys. They work long hours and often in organisations facing resource restrictions or cutbacks. High demand, low resources: something has to break somewhere. And when it comes to oncology, where there is long-term contact with patients whose lives are being turned upside down, the demands

can be particularly extreme.

A 2019 Canadian study found that nearly three-quarters of the 418 oncologists surveyed experienced symptoms of burnout – emotional exhaustion, depersonalisation and feelings of a lack of personal accomplishment (*JCO Oncol Pract* 2022, 1:e60–e71). A pan-European survey on the working conditions of young oncologists published in 2013 found that more than four in every five respondents from Central Europe suffer from burnout (bit.ly/YoungOncol-Burnout), .

"The very thing that draws people into oncology makes them especially vulnerable to burnout"

The very thing that draws people into oncology makes them especially vulnerable to burnout, believes David Cameron, Consultant Medical Oncologist at NHS

Lothian, in Scotland, Professor of Oncology at the University of Edinburgh, and joint lead for the Edinburgh Experimental Cancer Medicine Centre.

"I think anybody in a profession where you are caring for someone with a problem is going to be at risk of burnout, if you carry any proportion of that individual's physical or emotional pain internally," he says. "I'm convinced that the people who make good carers have the ability to empathise with the people they care for, because you need that to read them emotionally, to help them psychologically.

"And I think the risk of burnout may be greater for oncologists than some other medics, because there are not that many other professions where – not just day-to-day but month-to-month, sometimes year-to-year – you are dealing with individuals facing the challenge of their own mortality, which you have to help them address, as well as trying to prevent them dying."

Johan de Munter, President of the European Oncology Nursing



© Vanni Cuoghi, 15x10cm acquerello-su-carta, 16 March 2020

Society, is so concerned about burnout and its causes that he made addressing it one of the priorities of his presidency. The need for self-care among cancer nurses, given the growing threat of burnout, was also the theme of the 2022 European Cancer Nursing Day (bit.ly/CancerNurse-Selfcare).

Increasing care demands, staff shortages, lack of recognition, changing healthcare environments and lack of support mechanisms

are all contributory, believes de Munter.

“I think for cancer care professionals, burnout and compassion fatigue are encountered on a day-to-day basis because of the stressors in their workplace,” he says. “We see people who feel emotionally lost, who are exhausted and cannot do any more and have a reduced sense of personal value.”

The arrival of Covid in 2020 inevitably made the strains on

oncology staff worse. Already overstretched oncology workforces were faced with severe staff shortages, the need to protect highly vulnerable patients and the possibility of contracting a potentially fatal disease themselves. Absenteeism induced by burnout exacerbated the problem. The exact impact of that has yet to be thoroughly assessed, but two online surveys conducted by the European Society for Medical Oncology (ESMO) Resilience Task Force during Covid provided an indication.

“We see people who feel emotionally lost, who are exhausted and cannot do any more and have a reduced sense of personal value”

The first survey, conducted between 16th April and 3rd May 2020, found that 38% of the 1,520 oncology staff participating had experienced feelings of burnout. The follow-up survey, conducted between 16th July and 6th August 2020, found that the proportion of respondents reporting feelings of burnout had risen to 49%. The proportion of professionals at risk of distress increased from 25% to 33% between the two surveys.

Fay Hlubocky, a specialist in psychosocial oncology at University of Chicago Medicine, concluded in a 2021 *JCO* editorial that “the realities of the COVID-19 cancer care era resulted in a multifold increase in oncologist distress,” and that as a result “organizations have

a responsibility to support oncologists in living authentically to their intrinsic core values,” (*JCO Oncol Pract* 2021, 17:365–374).

So after decades of concern about oncology burnout, has the clear threat to staff psychological wellbeing caused by the pandemic brought the issue to a head? Is there now not just a new opportunity, but, as Hlubocky says, a moral imperative to address burnout in oncology and other fields of medicine head on? Certainly the number of articles written on the subject during the pandemic, and proposing solutions, would suggest a new momentum.

The individual or their working environment?

The emphasis in many is on building the resilience of individuals, making them less susceptible to burnout. Hlubocky, for example, proposes that cancer organisations “should prepare, plan, and implement interventions to build a supportive, ethical work climate to restore resilience using optimal, evidence-based programmatic interventions,” including stress management, peer-to-peer support and mindfulness-based approaches.

A recent scoping review on how to address and mitigate burnout in clinical oncology came to a similar conclusion, saying that organisational and individual interventions such as mindfulness and motivational packages, training in communication skills, stress management, relaxation, mindfulness, self-efficacy, resilience and work-life balance “can ensure job satisfaction, a supportive working environment,

job retention for oncologists, and improved patient care,” (*Front Public Health* 2021, 9:677915). Mindfulness to improve resilience is recommended in many papers.

But is individual resilience really the main cause of the problem? Does it offer the solution? Or is there need for a broader structural and cultural change at a workplace level?

Johan de Munter believes that change is needed at every level. Yes, there is definitely need for small-scale local actions that might help support those working in oncology – where training and classes (including in mindfulness) will play a role. But on a broader level, employing organisations need to look at how staff are managed and whether they are following policies and best practice guidelines on staffing levels, support and supervision, occupational safety and resourcing.

“We need to give people opportunities to evolve, to learn, participate, raise their voice and be involved in their organisations”

de Munter argues that the most important priority is to create a democratic culture where employees can openly talk about the problems they are experiencing and address them together. “Acknowledgement is very important,” he says. “We need more deep democracy, where everybody can speak up. We need

to give people opportunities to evolve, to learn, participate, raise their voice and be involved in their organisations next to care of patients. In that way you create an open culture, not a top-down culture saying what you have to do.”

David Cameron strongly echoes de Munter’s emphasis on giving oncology professionals opportunities to help shape the environment – including the knowledge environment – that they work in.

He argues that meaningful change hinges on creating structures that allow staff to step back, escape the everyday, and contribute to the bigger picture, which includes channelling oncology staff into activities that help them see that they can improve the lot of people with cancer, beyond caring for individuals. This might be through research, communication, teaching or other activities.

“One of the things that has enabled me to go on looking after cancer patients is contributing to research to try and improve their outcomes,” he says. “There is a strategic way in which organisations can say: yes, the reality of cancer can be awful, but there’s lots you can do to make it less awful in the future. To me that’s research. For some people it’s management, service organisation, or conducting service reviews, or work with patients focus groups.”

“But we all need something that offloads some of the pain we see from individual patients, which can seem relentless. Something that allows you to step back from a series of bad news consultations, for example, and sit down and design something which will

try and reduce the frequency of these awful conversations.”

This is the culture that Cameron, who specialises in breast cancer, sees in his colleagues and managers at the Edinburgh Cancer Centre in NHS Lothian. It is, he explains, a matter of sending out the right messages to clinicians from the moment they start work at an organisation. And then giving them the working structures to permit collaborative projects.

“One of the things that has enabled me to go on looking after cancer patients is contributing to research to try and improve their outcomes”

“I think it is essential in areas like oncology that, from day one, you do not give messages that create the expectation that you come in on a Monday morning, roll up your sleeves, go home on a Sunday night – and you’ve done nothing but look after sick people. This is a recipe for fast burnout. You need to give them opportunities in their working week to think, to work, to cooperate, to collaborate, to construct. So that’s a matter of employers structuring. It needs to be embedded in the service philosophy of looking after your staff and thinking: what do they need? And I don’t think that’s simply a matter of mindfulness training.”

Other changes would help. Cameron says organisations need to better understand what motivates oncology staff and gives

them the kind of positive feedback that makes a potentially gruelling job rewarding. Because of clinicians’ often long-term relationship with cancer patients, knowing about positive outcomes when they have left treatment can give a real sense of purpose. Cameron remembers long-term follow-up clinics for breast cancer patients in the past, which allowed clinicians to see how they had contributed to people’s longevity and happiness. Unfortunately, such clinics rarely exist now – they are seen as contributing little to reducing the risk of cancer recurrence.

“Sometimes managers don’t understand that some long-term follow-up isn’t necessarily a waste of resources. As well as enabling measurement of the effect of the treatments given, and supporting a patient’s recovery, it can be an efficient way of giving positive feedback to the staff, and reducing burnout.”

The need for wider cultural and organisational measures to reduce burnout appears universal. But it is often hard for organisations to acknowledge, and in some countries for clinicians and researchers to make their voices heard.

Several studies have pointed to a significant oncology burnout crisis in eastern European countries. A 2020 study based on a survey of 637 oncologists in eastern Europe concluded that 44% of participants were at high risk of emotional exhaustion, and nearly half had a diminished sense of personal accomplishment, with young oncologists most vulnerable (*JCO Oncol Pract* 2020, 16:e366–e376). Its conclusions point to significant structural,

organisational and resourcing problems as the root cause.

Lower financial and human resource investment in all aspects of oncology care compared with western Europe, and lack of availability of radiotherapy units and modern radiotherapy techniques, were key factors. “We hypothesized that burnout due to limited availability of radiotherapy resources hinders the ability of young oncologists to give the best possible care to patients,” says the study.

That said, overstretched health budgets are also impacting on oncology professionals in western Europe, in an indirect way, as Cameron points out. The practice of reducing costs by cutting the numbers, salaries and pay grades of secretaries and administrative staff only throws the work back onto frontline clinical staff, he says, reducing their ability to do what they’re paid for, and increasing burnout.

On the human resourcing side, de Munter points out that making it easier for cancer nurses to move across Europe, by harmonising education and recognition, could be good for the staff and help relieve pressure on health services.

“People need to think more about the mobility of oncology staff. Currently, different levels of education and recognition makes it difficult to move healthcare staff across Europe. If we recognise this as an important issue, and it becomes easier to move staff to areas of high demand, we will all be able to support each other much better. Having the right education and recogni-

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tion can increase your resilience, make you feel empowered and reduce your chances of burnout.”

de Munter acknowledges that the root causes of burnout will vary from country to country, and that there is no one-size-fits-all solution. And certainly it is easier in some settings than others to create an open culture about the stresses, exhaustion and compassion fatigue that individuals are facing. Acknowledging that you are burnt out is hard in itself – but it feels almost taboo in many high pressure, results-orientated work settings.

“There is a lot of shame about the issue,” says de Munter. “As healthcare professionals we know we need to be passionate about the job and about patient care, so it’s very difficult to say ‘I can’t do

it any more’. People don’t want to be labelled as burnt out. But I think it is possible to create an environment where people can talk openly to colleagues about it – this can be done, for example, by introducing supervision moments on the wards. Discussions also need to take place on a regional, national and European level to acknowledge that this is a real problem and doesn’t only reflect on individuals.”

Just as it’s hard for individuals to acknowledge they are struggling, it is not easy for organisations to stare the issue of burnout full in the face, acknowledges de Munter. It requires them to acknowledge the realities of resourcing problems, staff shortages and unmet needs. But the potential gains are enormous.

Whatever the country or setting, openness and honesty are the key.

“The first step is always to recognise the problem and talk about it,” he says. “I’m convinced that the organisations that have the courage to do this, the power to do this, to reflect in this way, emerge much richer. It’s the responsibility of healthcare managers, hospitals, boards, to think about this and reflect on that problem, and if they do, they will empower themselves and be ready for current and future challenges.”

This article was first published on the Cancer World website on 10 June 2022 (bit.ly/CW-PreventingBurnout)



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North and South – learning faster means learning together

The Global North may have the lion's share of cancer researchers, facilities and research funding, but it doesn't have all the answers. **Swagata Yadavar** looks at efforts to speed up progress in slowing the accelerating burden of global cancer, through a more collaborative approach to research that draws on the knowledge and expertise of low- and high-income countries alike.

When you look at the vast waiting area in Mumbai's world leading Tata Memorial Cancer Hospital, pictured above, what do you see? A crowded chaotic scene where sick patients and their relatives sit around for hours, waiting, hoping for someone to call their name?

That's certainly part of the story, but as Canadian oncologist and health services researcher Christopher Booth learned in the course of his visits to India, there's a lot more to scenes like this one than meets the eye.

Every day, huge numbers of patients who have often travelled

long distances, turn up without any appointment at public cancer hospitals across India, says Booth. "They might wait all day, but eventually they see the surgeon, who will then walk them down the hall to see the oncologist. On the same day, the patient gets a CT scan, radiation planning and has a PICC

line inserted. Treatment starts a few days later.”

Contrast that, he says, with a patient diagnosed, for instance, with colorectal cancer in Canada. “They will get a colonoscopy after months of gastrointestinal bleeding, after which they will be told they have cancer. They will have to wait two weeks to see the surgeon, who will refer them separately to chemotherapy and radiation specialists. The patient will wait several weeks for these consultations. This will be followed by separate appointments for a liver CT, PICC line insertion, and radiation planning. Finally, after many weeks, the patient will start chemotherapy and radiation.”

“Now which system is truly patient centred?” he asks.

Learning from the Global South

Booth, now Director of the Cancer Care and Epidemiology division at Queen’s University, Ontario, Canada, got his first insight into cancer care in a Global South setting when he opted to take a three month sabbatical working at the Regional Cancer Centre, Thiruvananthapuram, in the Indian state of Kerala, on the country’s southwest coast.

The Centre is recognised as an international leader in the delivery of cancer care in low- and middle-income settings, and Booth was there to teach... and learn. “The traditional paradigm of global health is that high-income countries teach low-income countries how to do things, and then they send money. The reality is we can learn just as much from low-resource health sys-

tems as they can learn from us, we just need the humility to recognise it,” he says.

More isn’t always better

It’s a point echoed by Bishal Gyawali, a medical oncologist of Nepali origin, and colleague of Booth’s at Queen’s, who has a strong international following for his incisive analyses on what claims for the value of new drugs can truly be made on the basis of the clinical trials. Gyawali points to the example of the adaptations that oncology services in the Global North made during the COVID pandemic – shifting some consultations online or by phone to minimise potential exposure to the virus, cutting out imaging and tests and even some drugs that were deemed not worth the added risk.

“The reality is we can learn just as much from low-resource health systems as they can learn from us, we just need the humility to recognise it”

Cancer services in low-resource countries have always done these things, says Gyawali. Lack of resources is part of the story, but it’s also about minimising the number of appointments and journeys that patients have to make, and freeing up health professionals to spend time with people who need to be seen face to face.

The potential advantages of using more remote consultations and communication, and less imaging, tests and interventions that in many patients convey marginal benefit if any, were listed by many oncologists among the lessons learned from the Covid-19 lockdown (see for instance the *Cancer World* survey on Lessons from the First Wave, bit.ly/Covid-Cancerlessons).

Could those advantages perhaps have been learned even without the pandemic, had oncology services in better resourced countries ever asked about what they could learn from some countries in the Global South?

A caring, community approach

Then there’s the issue of overcoming the inequities – lower awareness, later stage of diagnosis, poorer access to treatment and follow-up – that combine to explain often fatal differences in outcomes along socioeconomic, ethnic and geographic divides. These are issues in every country and region. But oncologists working in countries where resources are particularly stretched tend to get more involved in trying to mitigate these disparities.

So says Nazik Hammad, a medical oncologist originally from Sudan. Now an associate professor at Queen’s, Ontario, she has been part of building up the University’s growing capacity in Global Health, – an area of work she directed for a year in 2019/2020. Her principal interest, however, is in improving training opportunities for young African oncologists. For the past

“Oncologists in low- and middle-income countries play very complex roles, they are leaders and stewards of resources”

six years she has co-chaired the training committee of AORTIC, the African Organisation for Research and Training in Cancer, and she has been impressed by the responsibility trainees feel for leading change at a societal level.

“Oncologists [in low- and middle-income countries] play very complex roles, they are leaders and stewards of resources,” she says. They are much more engaged in their communities, with policymakers, while oncologists in higher-income countries are more interested in the latest clinical trials and latest drugs. “For example, oncology residents in Kenya run a volunteer clinic for CML [chronic myeloid leukaemia] patients every Saturday. Others run outreach clinics in neighbouring rural areas, which residents in high-income countries rarely do.” Hammad suggests that working with colleagues in Africa and other Global South countries may lead researchers from better-resourced countries to reflect more on cancer inequities in their own communities.

That sense of responsibility for people beyond one’s own patients is one that Booth recognises from his time at Kerala’s Regional Cancer Centre – a place that provides free and subsidised care to more than 16,000 new patients each year, most

of them quite sick with advanced cancers. He talks of being struck by the way that, despite this high patient volume and a gruelling six-day a week, his colleagues not only strived to improve the lives of their patients, but often spent their only free day offering cancer awareness and screening opportunities to some of the most destitute communities in the area.

In a commentary published in *JCO Global Oncology* (2016, vol.2, pp353-355), Booth also talks about how working in Kerala helped reaffirm the humanistic ideals that brought him, and so many others, into oncology, in the first place. He highlights studies showing that almost half of medical oncologists in the US experience burnout – a condition strongly associated with depersonalisation, which can lead to loss of empathy and treating people like objects. And he contrasts this with his experience of the physicians he worked with in Kerala, who, despite the sheer number of very sick patients they care for, still seem to manage to retain their sense of compassion and focus on the human things that matter most.

Could oncology services in high-income countries have anything to learn from that?

While there, Booth also took the opportunity to join the team

“Despite the sheer number of very sick patients they care for, they still seem to manage to retain their sense of compassion”

of health professionals and volunteers who work with Pallium India – Kerala’s world-renowned palliative care organisation – as they travelled the narrow streets of Thiruvananthapuram, providing “comfort in face of scarce resources”. Booth described the experience in his *JCO* commentary, and wrote of the lessons his own health system might be able to learn.

What impressed him was the remarkable breadth of medical, emotional, and psychosocial problems the teams were able to address. “Pallium pioneered a palliative care model that engages trained volunteers who work alongside physicians and nurses to support patients at home,” says Booth. He believes the system would have “immense benefits in Canada for our many isolated patients and also for the volunteers who would experience a special form of human connection.”

Learning together

So there’s a lot that oncology in higher income countries can learn from the culture and practices in many lower-income parts of the world. But in terms of the big picture of conquering cancer at a global level, some of the really big gains from learning greater respect for what lower-income countries can contribute are likely to come from enhanced opportunities to learn faster together.

As Gyawali explains, these opportunities relate primarily to research to find sustainable and effective solutions for the 70–80% of the global population that currently lack access to even basic diagnostic and treatment services or the most basic cytotoxic drugs.

This is the so-called ‘cancer groundshot’ agenda (*Lancet Oncology* 2018, 19:288–290), that Gyawali and others began promoting in response to the \$1.8 billion ‘cancer moonshot’ initiative, launched by the Obama administration, in 2016, which has a strong focus on high-tech science.

The groundshot approach, as Gyawali explains, focuses on implementation of treatments that are already known to work, and incentivising research on affordable and cost-effective interventions for cancer control that can be applied globally to reduce cancer morbidity and mortality. This type of research requires strong input from people grounded in the realities of the target countries.

The need to challenge barriers that hold back research in these settings – first-world priorities, attitudes and assumptions, as well as lack of investment in research capacity in more low-resource countries – was highlighted in a *Cancer World* article on Decolonising cancer research (bit.ly/CW-Decolonising).

But there is a related set of issues around learning how the Global North and South can collaborate effectively in research where all expertise is respected and valued. An interesting analysis published in *Nature: Scientific Reports* shows that, when measured by the percentage of trials with low risk of bias, the quality of trials conducted in low- and middle-income countries was on average lower than those conducted in high-income countries. However, trials conducted across both low/middle-income and high-income settings tend to be of higher quality than trials done in

high-income settings alone (*Sci Rep* 2015, 5: 13221). This shows that collaborating on trials can be mutually beneficial for both parties.

For such mutual benefit to be realised, however, requires finding the research questions of mutual interest. As Gyawali and co-authors point out in a commentary in *Nature: Cancer*, low-resource countries seek to prioritise co-development collaboration on interventions that are affordable and simple to adopt in standard clinical practice, while richer countries are likely to prioritise collaboration on interventions that would also address unmet needs in their own country (*Nat Cancer* 2020, 1:142–145).

Trials conducted across both low/middle- and high-income settings tend to be higher quality than trials done in high-income settings alone

Trials exploring the risk/benefits of drug repurposing – testing drugs approved for other indications within an oncology setting – offer obvious potential for mutual benefit. The *Nature: Cancer* article references trials of repurposed drugs that have proven to be beneficial for both high- and low/middle-income countries. ASCOLT, for example, a randomised controlled trial testing the risk/benefit of adjuvant aspirin in patients with Dukes C or high-risk Dukes B colorectal cancer, was initiated in Singapore and is now running in more than 65 locations in both high-income and low/middle-income countries.

Another large randomised controlled trial, ADD-Aspirin (addaspirintrial.org), is currently running in the UK, the Republic of Ireland and India to find out whether regular aspirin use after treatment for an early-stage cancer can prevent recurrence of cancer and prevent death. Ensuring adequate patient recruitment is listed as one of the rationales for recruiting in all three countries – India, with its population of almost 1.4 billion, being an obvious asset on the numbers front. Other listed benefits include increasing the global impact of the results – patients in low/middle income countries derive benefit – and “developing research infrastructure for future trials,” which bodes well for future North–South collaborations.

Gyawali contrasts this mutually beneficial collaboration with predatory practices used in some cancer trials, which use low/middle-income countries to inflate the benefits of their drug by comparing it to a control arm that is no longer standard of care in the target market. “They prove their drug works because control arm patients did not get good treatment, and they get the drug approved in high-income countries, but the patients in low- and middle-income countries can’t access the drug because of its cost,” he says.

A new way of working?

Collaboration in oncology has been around for quite a while, says Hammad, but it has become more common over the past five to seven years, with the researchers in the Global South being the initiators. “The young cadre of colleagues

[from Africa] are very articulate, showing the world that they can produce reliable research and have a strong voice because they have the numbers and the resources,” she says.

The change is reflected in data on the number of clinical trials taking place in low/middle income countries, which almost quadrupled over 10 years, from 363 in 2007 to 1,389 in 2016 – though is still only one-third the number in high-income countries (*BMJ Open* 2015, 5:e008932).

Nirmala Bhoo Pathy, Associate Professor of Epidemiology at the University of Malaya, in Kuala Lumpur, recalls instances in the past where Western researchers have come in, collected data, secured a large research grant and published, without including the investigators from the region. But she agrees that the situation has improved over the past seven or eight years. She welcomes efforts countries like the UK – a major funder of cancer research – are making to avoid abuse, citing tightened requirements on applicants for Official Development Assistance, which provides government funding for projects in low- and middle-income countries, to demonstrate how their research will benefit the developing country.

She also cites an example from her personal experience, which started when her own University invited Liam Murray, Director of the Centre for Public Health in Queen’s University, Belfast, to spend some time in Kuala Lumpur as a visiting lecturer. Hearing of her work in clinical epidemiology and prevention, Murray invited Bhoo Pathy back to Belfast, as a visiting lecturer at Queen’s University.

“I think that’s such a heart-warming story, because there was somebody who was kind enough to acknowledge that there are things to learn from the partners from Asia, and that we can bring value and enrich the experiences of their students,” says Bhoo Pathy, who continues in her capacity as a visiting academic at Queen’s, Belfast.

Murray also encouraged Bhoo Pathy to look at the UK Biobank cohort dataset (ukbiobank.ac.uk/) – a large-scale globally accessible resource containing in-depth genetic and health information from half a million participants – to see whether it could help her pursue her research priorities.

“There was somebody who was kind enough to acknowledge that there are things to learn from partners from Asia, and that we can bring value”

The suggestion bore fruit, and Bhoo Pathy is now the principal investigator of a UK biobank-approved study looking at the association of cancer therapy with cardiovascular-related comorbidities in cancer patients, to improve identification of those patients at greatest risk of cardiovascular complications, and tailor their management accordingly.

While that may be a single example, individual actions can be important in driving broader change. The global oncology programme at Ontario’s Queen’s University is an interesting example

of how individual efforts, such as Hammad’s work in Africa and Booth’s work in India, together with other colleagues, organically evolved into the University’s own global oncology programme, which now has links with oncologists across Latin America, Africa and South Asia.

“The team’s work now has many collaborative projects with our colleagues in low- and middle-income countries that focus on health services research, health policy and education, with the aim of improving global equity in cancer care,” says Scott Berry, the University’s head of Oncology. “The focus for us has always been on establishing strong relationships with our partners. We are focused on finding colleagues with similar goals and identifying and working on projects that address the needs that are the most important for them,” he says.

This kind of collaboration has led, for instance, to the launch of an initiative to study patterns of cancer care at the National Cancer Institute, Sri Lanka (NCISL), which treats one third of all cancer patients in the country. While Sri Lanka’s National Cancer Control Programme maintains a cancer registry, it does not collect data on cancer outcomes. This collaborative initiative involved creating an ‘inception cohort’ – a group of patients with breast and colorectal cancer, who were recruited upon registration at the NCISL. Following this cohort will allow researchers to gain valuable insights into patient demographics, cancer diagnosis, gaps in treatment delivery, outcomes, co-morbidities and health-seeking behaviour.

Such an extensive database had

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not previously been possible due to lack of funding and technical support, says Sanjeeva Gunasekera, a paediatric oncologist at the Sri Lankan National Cancer Institute who works on the project along with Sanjeeva Seneviratne, Professor of Surgery at the University of Colombo, and Don Thiwanka Wijeratne, who is Assistant Professor in Internal Medicine, Queen's University, Ontario, having moved to Canada from Sri Lanka, where he completed his post graduate training.

This initial collaboration led to developing contacts with oncologists across the world, which in turn has led to multiple other collaborations, says Gunasekera. For their part, Queen's University's global oncology team can use the lessons learned from this collaboration as a successful case study to guide collaborative work on similar cohort studies in other low-resource settings, he said.

The road ahead

A change in attitudes and culture remains key to realising the opportunities of more collaborative approaches to mutual learning in oncology. But other barriers will need to be overcome.

Differences in regulatory requirements is one such barrier, which will be familiar to many European researchers who had to navigate their way through the initial EU Clinical Trials Directive. Sunu Cyriac, a medical oncologist at the Amala Institute of Medical Sciences, in Thrissur, Kerala, cites the example of a project planned in partnership with Imperial College, London, which had to be



Learning from one another. CS Pramesh, Director of the world-renowned Tata Memorial Cancer Hospital in Mumbai, and Priya Ranganathan, Professor of Anaesthesiology at the Tata Memorial, are two of the many leading oncologists from the Global South who have spent time at Queen's University, Ontario, as visiting professors. They are pictured here with Chris Booth, Director of the Cancer Care and Epidemiology at Queen's, who has made many visits to the Tata Memorial and other leading cancer centres in India, to teach and to learn

shelved due to India's stringent laws regarding sharing of biospecimens and data. The project would have involved study of the microbiome in cancer patients, but he could not get approval. India's stringent financial regulations can also pose an obstacle to receiving research grants from abroad, which makes it difficult for smaller institutions to pursue international collaborative research, he adds.

Along with regulatory requirements, the high cost of conducting trials, logistical challenges associated with ethics review, drug supply, and biospecimen collection and management are all listed as challenges in conducting international clinical trials in cancer, in a 2019 study published in the *British Journal of Cancer*.

The availability of trained clinical researcher time also remains

a huge constraint. As Gyawali points out, doctors in low-resource countries are extremely busy with patient load; they see 10–20 times more patients than in high-income countries, leaving little time for research work. Supporting the training of new cadres of oncology researchers from the Global South, and funding protected time for clinicians to carry out research work, will both be key to realising the potentially immense progress on the 'cancer groundshot' agenda that could be made through more collaborative mutual learning.

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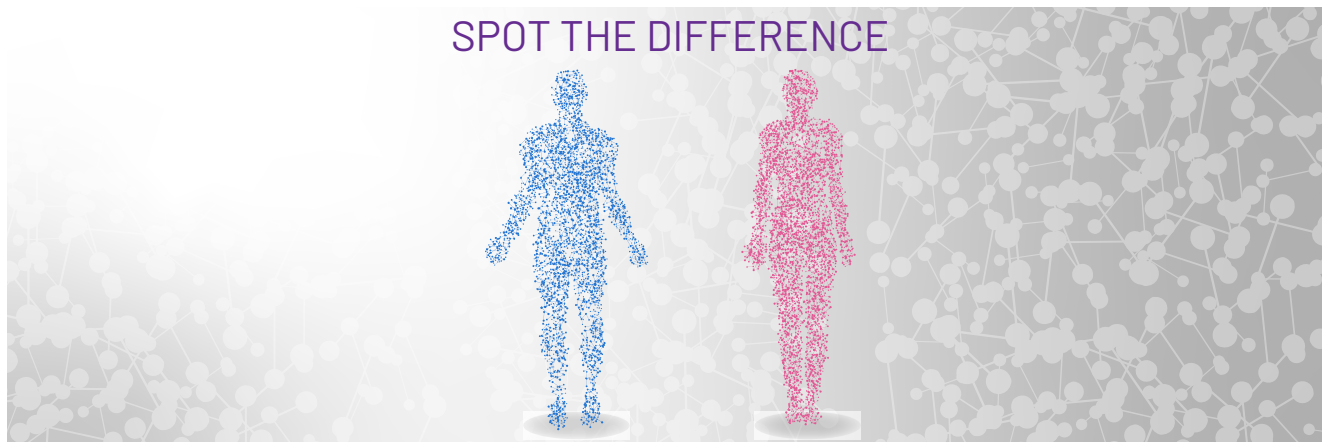
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Woman or man?

Is precision cancer medicine overlooking key biological differences?

Women differ from men in our immune surveillance, body fat, liver and renal function, plasma volume, organ blood flow and more. As precision medicine seeks to define in minute detail the molecular biology of every tumour, **Rachel Brazil** asks whether we might be overlooking important biological differences in the host.

"Something that hit me pretty early during my residency as an oncologist was that sex in most cases is a clear-cut binary, pretty obvious biological variable affecting attitudes as well as tolerance to cancer treatment that we still rarely – almost never really – take into account in our everyday clinical work," says Cecilia Radkiewicz, a medical oncologist at the Karolinska University Hospital, in Stockholm. "And yet there are so many reports suggesting that there are clinico-

pathological differences."

It is now very clear that there are not only differences in the rates at which men and women are diagnosed with cancer, but also in their survival, prognosis and response to treatment. The question is: what do we do about it?

Until recently, evidence of the differences in responses between men and women have been largely missing from clinical trials, particularly in drug trials, where women were generally excluded. The thalidomide disaster in the early

1960s led the US Food and Drug Administration (FDA) to issue guidelines in 1977 that essentially excluded women from all trials.

But oncologists such as Radkiewicz are starting to study these sex differences – in her case, using big volumes of data from multiple Swedish population-based health and demographic registers.

What she and others are finding is that there are complex and multi-factoral issues involved in understanding the differences observed.

Differences in incidence and survival

With most cancer locations, men are generally diagnosed at higher rates than women. For example, 2020 OECD data for lung cancer rates in the European Union shows the incidence is 100 per 100,000 in men, but only 45 per 100,000 in women. Some of this difference can be put down to different behaviours and comorbidities, with higher levels of smoking and drinking among men (the gender gap is smaller in Nordic countries, where behaviour differences between men and women are generally smaller).

With many cancers, men also tend to have a worse prognosis when they are diagnosed. “It’s pretty well established that men in general have a more advanced stage of diagnosis for many cancers, and cancer stage is one of the most important prognostic factors,” says Radkiewicz, who suggests men are often not as quick to seek medical advice and are more likely to ignore cancer alarm symptoms.

One cancer where women do have a poorer prognosis and more advanced stage distribution is urinary bladder cancer (*Clin Genitourin Cancer* 2020, 18:26–34). “This is probably caused by a combination of patient and doctor delay, because the classic bladder cancer alarm symptom, visible blood in the urine, in a woman is not really considered an alarm symptom for a malignant disease, but in a man it is investigated much more promptly,” suggests Radkiewicz.

But the stage at diagnosis is unlikely to be the whole story. A 2020 study of malignant melanoma in 1,023 patients diagnosed

between 1987 and 2014, for example, showed that women have better survival than men after adjusting for known prognostic factors (*Oncol Ther* 2020, 8:103–114). “There is a sex difference regarding survival in melanoma even when controlling for [diagnosis stage],” says Radkiewicz, but the reason why many cancers seem to be more aggressive in men is a tricky question to disentangle, she adds: “It’s probably not the same answer for all different cancer types.”

“Why many cancers seem more aggressive in men is a tricky question to disentangle... It may not be the same answer for all cancer types”

In bladder cancer, for example, where women have been reported to have a consistently poorer survival rate than men, the problem seems to be restricted to the specific subgroup of tumours that are treated with surgery in combination with chemotherapy. Radkiewicz postulates this could be linked to differences in the surgical management. “The urinary bladder looks pretty different in a woman compared to a man, because the muscle wall is substantially thinner, and this could result in faster tumour invasion of the bladder wall as well as a higher risk of complications in bladder cancer surgery in women compared to men,” she suggests.

A recent study of outcomes in gastric and oesophageal cancer surgery found differences in the treat-

ment strategies used for men and women (*Gastric Cancer* 2022,25–32). In addition to significant sex differences in tumour location, female patients with oesophageal adenocarcinoma less frequently received neo-adjuvant therapy to shrink their tumours.

One explanation for differences in survival rates is the cancer-promoting effect of sex hormones. “We know that testosterone is a growth factor... and maybe it stimulates tumour aggressiveness,” says Radkiewicz. Drops in oestrogen levels after menopause may explain different incidences and survival in different age groups of women, but evidence shows this can be only part of the story, as there are differences between survival rates for boys and girls in glioblastoma, for example, which are unlikely to be attributable to sex hormones.

Physiology and hormones are not the only biological differences between men and women though. Radkiewicz refers to the findings of a retrospective study she did of lung adenocarcinoma (*PLoS ONE* 2019, 14:e0219206), which she believes indicates that it is “a different disease in women [compared to men], maybe with a different risk factor profile.” Based on 23,465 records in the Swedish lung cancer register from 2002 to 2016, the study showed that the women were on average younger, and more likely to be non-smokers, in better health and more often EGFR positive, whilst men had a consistently poorer prognosis, even after adjusting for the stage of disease progression. While there was insufficient data to demonstrate that the distribution of biomarkers that drive the difference in survival are actually different

Medicine

between men and women patients, Radkiewicz says, “Our study supports that there are tumour biology differences.”

Glioblastoma provides further evidence for very different genetic tumour profiles in men and women, which may explain the differences in incidence and survival. Men are likely to develop more aggressive forms of glioblastoma and at a higher rate. In 2019, Joshua Rubin from Washington University School of Medicine in St. Louis, discovered that particular tumour genomic profiles were associated with increased survival, but which profiles were the most favourable differed between the sexes (*Science Trans Med* 2019, 11(473)). In women, the best survival (3 years) was found with tumours expressing the least integrin genes (which produce receptors for cell attachment), whereas in men the best survival (18 months) was found with tumours that had low expression of cell-proliferation-signalling genes.

Differences in treatment response

The differences in cancer biology are becoming clear, but there are also differences in how men and women respond to treatment, particularly in relation to the levels of toxicity experienced. This has been investigated by Anna Dorothea Wagner, a gastrointestinal cancer specialist and expert in gender medicine at the University Hospital of Lausanne, Switzerland. Gender medicine studies how diseases differ between men and women. From her clinical observations she saw a higher percentage of women than men hospitalised due to the toxic-

ity of their cancer treatment. “Up to now, we really considered men and women as [the same], and I had the impression that this is not right,” says Wagner.

“In oncology, there is a lack of knowledge... there are a few reports about higher toxicity in women, but very few authors have investigated this topic systematically,” she says. Wagner is starting to change this. An analysis of data amalgamated from four chemotherapy trials for oesophagogastric cancer confirmed her suspicions. She found that serious nausea and vomiting (grade 3 or above) was experienced by 16.7% of female patients, but only 9.5% of male patients. All grade toxicities were also significantly higher among women than men for diarrhoea, stomatitis and alopecia, with a trend towards significance in neutropenia and febrile neutropenia (bit.ly/Gender-and-Toxicity).

“About 20% of anticancer drugs have differences in pharmacokinetics, with more rapid elimination in men, leading to higher plasma levels in women”

A separate study of early-stage colon cancer using a database of 28,636 patients also confirmed that women are at greater risk for the majority of toxicities (*JCO* 2018, 36:S3603).

Women appear to be more susceptible to the toxicity of different types of chemotherapy drugs, including increased risk of acute haematologic toxicity, and toxicities

such as mucositis, nausea, vomiting, alopecia and cardiotoxicity. This seems to be the case among patients treated for colorectal, small-cell and non-small-cell lung cancers, Hodgkin lymphoma, glioblastoma, Ewing sarcoma and osteosarcoma (*JCO* 2018, 36:2680–86). There is also evidence of differences in children, with girls treated for acute lymphoblastic leukaemia experiencing higher rates of toxicity than boys, showing this is unlikely to be just an issue of size.

Wagner says sexual dimorphism in drug response is not unique to oncology drugs, and is seen across medicine, due to clear differences in how women and men metabolise drugs, and their sensitivity to them. “We know today that about 20% of anticancer drugs have differences in pharmacokinetics, with more rapid elimination in men, leading to higher plasma levels in women, and these differences are probably responsible for higher toxicities at least in part,” explains Wagner. Both liver and renal function differ between men and women, and women have approximately 15% more body fat than men and greater plasma volume and organ blood flow.

But so far there have been few attempts to characterise these differences, including their impact on the metabolism of anticancer drugs systematically. “We can’t generally say that all toxicities are occurring at a higher grade and higher rate. I would rather describe it as a potential modulation of the toxicity profile of anticancer drugs,” says Wagner. To really understand this requires an analysis of large databases, she adds.

Currently, the formula used for

calculating chemotherapy doses is identical for men and women. “We estimate something called the body surface area, that we use to calculate the dosage,” explains Radkiewicz. “We want to give men and women the same serum level of drug, so the aim is to dose [based on] the fat-free body mass, but we know that women anatomically have more body fat compared to men.” The lower female lean body mass, plus differences in liver and renal turnover in men, could mean that women are receiving higher drug plasma levels and therefore experiencing greater toxicities.

It also may explain why women seem to have a higher response to chemotherapy for some types of cancers. There is also the possibility that lower rates of toxicity in men could be a sign of underdosing, and this in itself could explain their poorer prognoses. “We’ve found in colorectal cancer that this is not the case,” says Wagner. “Despite higher toxicity and higher drug levels of fluorouracil, in colorectal cancer women do not have a higher treatment efficacy. So at the moment there are still more questions than answers.” She thinks there is certainly a need to investigate gender-specific treatment strategies more closely.

In addition to the biological differences, Wagner is also considering whether there are physician biases in the way men and women are treated that might also explain some of the differences in outcomes. “We looked at treatment allocation of men and women with curatively treatable oesophageal and gastric cancers in a population-based study and we found that, among patients with lower oesophageal adenocarcinoma, which is a disease much more fre-

“The optimal timing in women differed by about six hours to that in men, which likely impacts on tolerability, dose intensity and efficacy”

quently arising in men, the women who had this disease have a 20% lower probability of being allocated to curative treatments, such as surgery and chemoradiation. They have a less favourable prognosis because they less often get curative treatments,” says Wagner.

Another curious sex difference can be found in the field of chronomedicine – where drugs are administered at times that line up with patients’ circadian cycles, to improve efficacy and reduce toxicity. Oncologist Francis Lévi from the University of Warwick has been studying the topic for decades, and says recent trials have shown that the optimal drug delivery time differs between men and women. In 2012, Lévi demonstrated that administering infusions of the FOLFOX drug combination of folinic acid (leucovorin), fluorouracil (5FU) and oxaliplatin to treat metastatic colorectal cancer at a specific time of day was beneficial to men, but detrimental to women (*Ann Oncol* 2012, 23:3110–16). A similar study in 2020 with the addition of the topoisomerase I inhibitor, irinotecan, to a FOLFOX regime also showed sex-based differences, with men doing better when infused in the morning and women in the afternoon (*Cancer Medicine* 2020, 9:4148–59). “The optimal timing in women differed by about six hours

to the optimal timing in men, and this has a likely impact not only on tolerability, but also on dose intensity and efficacy,” says Lévi.

Differences in immune systems

Many cancer patients are now treated with immunotherapies, and questions about whether men and women respond differently to these therapies are also being investigated. Different responses might not be a surprise. “We know that there are immunological differences between men and women. If we extrapolate to infectious and autoimmune diseases, we know that men have a higher risk for most infectious diseases, and also poorer outcomes, while autoimmune diseases are more frequently diagnosed in women,” says Radkiewicz.

Women have a more active immune surveillance system, which could explain why their cancer incidences are lower and survival higher than men’s. A 2020 study of sexual dimorphism in colon cancer notes that there are more T cells found in samples taken from women than men, indicating a stronger immune response (*Front Oncol* 2020, 10:607909).

So far, evidence indicates that immune checkpoint inhibitors such as nivolumab and pembrolizumab, on their own, tend to be more effective

Women have more active immune surveillance than men, which could explain differences in cancer incidence and survival

in male cancer patients compared to female, perhaps because in women the tumour environment is initially not immunosuppressed to the same extent as in men. A meta-analysis of data by Fabio Conforti, from the European Institute of Oncology in Milan, showed that, when combined with chemotherapy, women's survival rates improved (*Lancet Oncol* 2018, 19:737–746). He suggests this is because the chemotherapy increases the mutational load of tumour cells and therefore makes the cells better targets for elimination by their more active immune systems.

These early results do show that there may need to be different strategies for treating men and woman with immunotherapies – with therapies for men focusing on reversing immunosuppressant tumour environments, and those for women focusing on increasing the antigenicity of tumour cells. But there is clearly a long way to go before the factors involved are fully understood and the best treatment strategies developed.

Towards gender-adapted treatments

Given what we know, is it time to start treating cancer in men and women differently? “Not yet,” answers Wagner. She thinks much more work is needed first, to understand how the patient's biological sex modifies treatment effects and the tumour biology. “When we have understood this, we have to think about how we can modify the treatment according to the patient's sex to improve the balance between efficacy and toxicity in both men and women on the basis of what we have learned.” She also wants more

investigation into patient and physician attitudes, and how unconscious biases related to gender may be impacting treatment decisions.

“For more than half the pharmacokinetic studies, the question of any potential sex differences has not been addressed at all”

One area where changes might be warranted is in chemotherapy dosing. “You can estimate the individual body composition today very cheaply and relatively precisely by CT scans,” notes Wagner. “This is something you can take into account in decision making for dosing of chemotherapy drugs, but at the moment, this is not done. We need randomised clinical trials investigating sex-specific dosing strategies in oncology.”

With gender being perhaps the most basic biological variable, and one that can easily be assessed with very high precision and low cost, Wagner argues there is no reason to ignore it. The 2014 European Clinical Trials Regulation was designed to improve imbalances, requiring that the subjects participating in a clinical trial should represent the population groups that are likely to use the medicine. Today many clinical trials still do not report results by sex. “We found that, for more than half of the pharmacokinetic studies, the question of whether there are any potential sex differences has not been addressed at all... this is really something I

hope will be changed in the future,” says Wagner. Radkiewicz argues that, where the data is available, we should also now go back and reanalyse existing data to stratify by sex.

Understanding the genetic footprint of cancer is the aim of the burgeoning field of precision medicine. “We have made a lot of progress by exploring the molecular biology of the tumour,” says Wagner, “but the question of how the biology of the host influences the tumour, that has, unfortunately, not been studied with the same enthusiasm. So there is some work to do to catch up.”

In 2018 Wagner started this process and held an ESMO workshop, ‘Gender medicine and oncology,’ to discuss the implications for clinical practice and research in oncology (*Ann Oncol* 2019, 30:1914–24). Clearly there are multi-faceted and complicated factors involved, but after many years of neglect she hopes that the benefits and harms of anticancer treatments will now be evaluated separately for men and women. In an age of precision medicine, we can no longer assume that the effect of a given treatment is the same in men and women. “In oncology, the balance between benefits and risks is often quite subtle, and it's really important to be sure that we have statistically significant benefits in both sexes and the risks are acceptable,” she concludes.

This article was first published on the Cancer World website on 28 October 2021 (bit.ly/CW-PrecisionCancer-Meds-Gender)

When your patient tells you they're still not better, please accept what they say

Psychologist and cancer survivor **Dr Cordelia Galgut** has written extensively about what happens when people's experience of 'getting over' cancer does not match optimistic assumptions held within and beyond oncology. Here she talks directly to health professionals about how they can – and sometimes do – make these patients' lives worse... and how they can make them a bit better.

"A staggeringly high number of patients still suffer from significant health issues years after being declared disease free." The words of Dorothy Keefe, head of Australia's national cancer agency and chair of the 2021 ESMO Congress supportive and palliative care track, may have come as a surprise, maybe even a shock, to many oncologists (bit.ly/SupportiveCare-ESMO2021). To the many survivors who, like myself, live lives blighted by lasting psychological and physical effects that do not recede with time, they came as a relief and a validation of the suffering many of us endure daily, living either with a still present cancer, or beyond it.

Keefe was commenting on the findings of the German FiX study which found that, two years after diagnosis, more than one-third of patients suffered moderate, significant or extreme loss of physical capacity, fatigue, sleep problems, sexual problems, joint pain or anxiety (*Ann Oncol* 2021, 32:S1175–98).

She went on to argue the case for improving levels of care and promoting research into long-term problems. While the 'action points' she advocates are important, it was her opening sentence that mattered to me: Thank you Dorothy Keefe for acknowledging the reality of the lasting physical and emotional issues I have been struggling with since being diagnosed with cancer 17 years ago. I've been waiting for this kind of validation for a long time now, and I know I'm not the only one.

Long-cancer is real

While Long-Covid seems to have rapidly established itself as a diagnosis in its own right, the phenomenon of long-term effects from cancer and cancer treatment, which were highlighted in the German study, have not. The impact on those of us living with these problems has been devastating. When we seek help, our complaints are too often dismissed; we are treated as if the problem is in our

heads, as if **we** are the problem – we are failing to 'do cancer' properly, we need to move on.

While this attitude is sadly common across all walks of life, the medical and related professions can often be the worst, and the failure to listen, acknowledge and empathise with patients who come seeking help for these problems does those patients deep and lasting harm. So while I welcome Keefe's call for improving levels of care and stepping up research into long-term problems, my call to oncologists and all who care for cancer survivors is more fundamental: first do no harm.

What do I know?

I had bilateral breast cancer 17 years ago, and still struggle significantly with its long-term effects, some of which have got worse over time. I am also a psychologist of many years standing, having written extensively about the psychological impact of this disease and spoken to hundreds

of those affected over the last two decades. To date, I have written three books on the subject, numerous articles, blogs and more. I have talked to hundreds of cancer survivors, in confidence – people who would only talk to someone who had had a diagnosis of cancer. Much as I balk at the concept, I am an expert in this field now.

One thing I have learned is that, for vast swathes of us, a cancer diagnosis is something we never truly get over. How could we? I know most of us are taught that extreme life events shouldn't affect us after a year or so at most, but I'm afraid that is not at all psychologically realistic. After all, who gets over the death of a loved one? You just have to learn to live alongside it as best you can. Cancer is no exception, and treatments often still have enduring, extremely unpleasant effects. The serious problems reported in the German study – physical incapacity, fatigue, sleep and sexual problems, joint pain, anxiety – blight many lives. And there is more emerging, word of mouth evidence, that these serious long-term effects are just the tip of the iceberg.

Another thing I've learned is how resistant oncology professionals are to recognising how tough the lives of patients who have survived cancer can be. Too often patients looking for support find that the people entrusted with our care appear unwilling to open their eyes and ears, to listen and acknowledge the reality of the problems we seek help for. In truth, few of us dare raise the thorny subject of life after diagnosis, lest we are told we should be grateful we survived, think ourselves lucky, and be positive, to name only three dominant imperatives.

The worst bit is the unthinking censure, platitudes really, and based

on nothing but entrenched assumptions, e.g., “You shouldn't really be so anxious now,” or “You should be over cancer by now,” or “You shouldn't still be scared of recurrence”.

We're not at fault

This judgemental approach is not forgivable because it does such harm. Telling people or implying that there is effectively something wrong with them if they are still, for example, very scared of getting more cancer, is psychologically very undermining and damaging. Your patient will internalise your ill-considered comments and their narrative will likely then become a horrible mix of, “I know I'm suffering, but he or she tells me I shouldn't be... I'm not doing cancer properly... I'm going mad...”

Feeling lasting terror of recurrence and spread is actually an exceedingly **normal**, pretty much universal emotional response, no matter what someone's prognosis is, because most cancers can come back at any point. It is not a pathology that needs correcting. It's obvious when you think about it, isn't it? A no brainer!

And this dread can get worse over time, as it has with me and many others I have spoken to over the years. Yet I haven't yet met anyone in healthcare who appears to get that, unless they have had a diagnosis themselves.

Do no harm

People can and do feel suicidally low because, on top of the very real problems they are struggling with, they are effectively being told they 'should not' be feeling the way they are – as if they must be doing something wrong. These assumptions about what people should or should



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not be feeling are not based on any evidence or rationale, and perpetuating them can do serious harm. I'm very confident that what I say here is accurate, not least because of all the people I have spoken to over the years, and because of my own cancer credentials.

I know there are reasons why medical people and others in related fields, including my own, often respond in such a dismissive way to the often unrelenting and difficult problems raised by people suffering long-term effects, some of which I explore in my recent book, *Living With The Long Term Effects of Cancer* (2020, Jessica Kingsley Publishers).

I also know that striking the right balance between offering hope and acknowledging enduring suffering is difficult, particularly when that suffering is hard to fix.

And I know that oncologists don't mean to damage their patients or cause upset – on the contrary, you want to help. But many of you in

Please don't...

by Cordelia Galgut

Please don't tell me how I should feel
 Or what I should think about having breast cancer;
 How I should be 'over it' by now;
 How I should be more positive;
 How I should be grateful that I'm alive.
 And please don't say, 'You're overreacting to your situation,'
 'It's only you who feels like this,' or
 'It's time you got on with your life.'
 How can you know? *You* have never been in my situation.

And please don't ask me what I have contributed to my cancer
 Or tell me how brave I've been.
 There was no choice at all.
 It was just the luck of the draw.
 And please don't ask me how my breast cancer journey has been.
 There was no journey
 There is *no* journey, because there is *no end in sight*.
 And for pity's sake, don't say,
 Well, we're all going to die in the end,
 I could get run over by a bus tomorrow.'
 It's different.
You have never stared death head on.
You have never had breast cancer.
 We are on different sides of the track now.

Tell me instead
 That you cannot know what it is like living through this hell.
 Tell me instead that you have an open heart
 And an open mind,
 That you'll listen,
 That you'll try and understand,
 Even when what I'm saying sounds preposterous to you.
It is my reality.

And please, please try and look beyond your own fears,
 Or if you can't, tell me so.
 Having breast cancer is terrifying
 And the terror does *not* diminish,
 Because the fear that it will come back is ever present.
 So please, please don't tell me that I'm one of the lucky ones,
 That I'll be back to normal soon,
 Because *my life* and *I* have been changed forever.

cancer care do not appear to question your utterances, or their probable negative impact on your patients.

A simple request

People like me who suffer from cancer's long-term effects are asking for something quite simple. Have the most open heart and mind you can muster. Listen and really hear. Look and really see. Simply telling people you believe them; suspending your judgement as much as you can, will go a very long way.

Also, please check out some of my writings at cordeliagalgut.co.uk, which include three books as well as articles and blog posts for Macmillan Cancer Support as well as the ASCO patient information website Cancer.Net and for *The Psychologist*, the journal of the British Psychological Society.

They were written for the oncology community as much as for those on the other side of the cancer fence, and they represent the views of many others who have had a diagnosis of cancer, as well.

Many of the sentiments expressed in them are summed up in the poem 'Please don't' (see panel). The emails and letters I've received since this was first published, from people expressing their relief at hearing that they weren't the only ones still struggling – that they weren't the ones at fault – make sobering reading. Their doctors didn't listen.

But you can.

This article was first published on the Cancer World website on 14 October 2021 (bit.ly/CW-BelieveUs)



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A call to action

How Poland is stepping up for Ukraine's cancer patients

Poland's cancer services are trying to treat Ukrainian patients "as if there was no war". But there is a war. **Agnieszka Witkowicz-Matolicz** reports on the challenges faced on both sides of the consulting table to give, and to get, the best care.

February 24, 2022. Julia, a lawyer living near Kiev, is counting down the days until her last chemo.

After which she will still face surgery and radiation therapy on her way to recovering from breast cancer. Before dawn, she wakes to the sound of monstrous rumbling. It's Russian missiles exploding near her home.

"When the war happened, hospitals in Ukraine closed. I didn't know if I would receive medicine at all. After some time, which seemed a very long time to me as a patient, the hospitals opened

again, but there was a huge shortage of medicines."

Julia faced the prospect of traveling to another city, many kilometres away, to get her medicine, but this was almost impossible, as she lived right next to what was then the front line. "There was a moment when I wondered if I would even make it to the hospital," she recalls. She found a drug available for purchase and decided to buy it, but it was very expensive. That's when Julia, a mother of two, opted to continue treatment in Poland. A friend living in Wrocław came to her aid.

She arranged the first medical appointment for March 20.

The hardest time was at the start

On the Polish side of the border advocacy organisations mounted a rapid response. "It was simply a 'call to action'" – recalls Ewelina Puszkina, vice-president of the OmeaLife Foundation, a group founded in 2018 and focused on supporting and advocating for young women with breast cancer. "We posted on Facebook that we were willing to help patients

from Ukraine. It quickly spread on social media and on Telegram. We were flooded with emails and phone calls.”

At this early point in the war, large numbers of Ukrainian cancer patients, at various stages of disease and treatment, needed help, but proper systems had not yet been established. It was therefore up to advocacy groups to do what they could, as Aleksandra Ciompała, of the Alivia Foundation – an advocacy group set up in 2010, “to help cancer patients fight for their lives” – recalls. “Two patients needed urgent transport – a child and an elderly person. People spontaneously got together, and managed to organise everything in 24 hours.”

A voice of reassurance

Natalia Ukhach, a Ukrainian living in Gdansk, Poland, was working in the commercial sector when the war started, and had no involvement with healthcare. Since April, supporting patients has become her daily routine. Ukhach is the woman who answers the phone at the hotline set up by the OmeaLife Foundation.

“The patients are stressed by the war and the disease itself,” says Ukhach. “They are terrified of how they will cope. My first task is to calm the patient down. I help arrange paperwork later.” She has already helped almost 200 patients.

Conversations often follow a similar pattern. “First there is a request for help and concern about whether someone in Poland will help or not. Later there are questions about whether it will be for

free or for a fee, and how to get treatment. My job is to provide information and show the path.”

To be treated in Poland on an equal footing with Polish patients, Ukrainians must apply to a municipality office for a PESEL number (Polish acronym for Universal Electronic System for Registration of the Population). A law adopted by the parliament in March 2022 gives Ukrainians the right to the same healthcare as Poles, including the same cancer care, with two small exceptions – spa treatment and access to treatment abroad paid for by the Polish National Health Fund.

“They are terrified of how they will cope. My first task is to calm the patient down. I help arrange paperwork later”

In the four months between the start of the Russian aggression and the end of June 2022, 3,500 Ukrainian citizens received oncological treatment in Poland, the Polish National Health Fund reports. Of these, 2,900 are adults and 669 are children.

Challenges in the consultation room

At the peak of arrivals of new patients, doctors at major cancer hospitals were admitting several Ukrainian patients a day. Accessing the precise information about the disease and establishing good

communication with the patient – both so vital in cancer care – has proved widely challenging.

“Due to the language barrier, it is very difficult to conduct a medical interview,” says Piotr Sobiczewski, a gynaecologic oncologist at the Maria Skłodowska-Curie National Research Institute of Oncology in Warsaw. “We act as we can. Sometimes we can count on the help of cleaning ladies of Ukrainian origin. But this is not a satisfactory solution, because the medical vocabulary is very different from the everyday one.”

To ease the communications problems, patients may bring along a friend or other compatriot who can speak Polish. Natalia Ukhach often helps out as translator as part of her work volunteering with OmeaLife Foundation.

“Here locally, in Gdansk, I simply go with the patient to the doctor and enter the office. If the patient is being treated in another city – in Warsaw, Krakow, or Poznan – the patient calls me during their doctor’s consultation, turns on the hands-free system on the phone, and I translate over the phone. That’s how the consultation goes.”

Another challenge is the lack of medical records for people who had to leave their homes in a hurry, which can introduce a lot of uncertainty, as Katarzyna Pogoda, a clinical oncologist at the Maria Skłodowska-Curie National Research Institute of Oncology in Warsaw, explains.

“Some of the patients have literally no medical records. Even basic information, such as identifying tumour receptors, is missing. If a patient is already



To help overcome the language barrier, patient information at hospitals including the Maria Skłodowska-Curie Memorial Cancer Centre, is now available in Ukrainian which, unlike Polish, uses Cyrillic script. ©Slawek Kamiński

undergoing treatment, after surgery, I have no way to re-examine this. Therefore, I have to rely on the patients' words and, based on that, infer what type of cancer they had and how to continue treatment. This is often a very big challenge."

Some patients come to the office with nothing but their own personal notes. They have written up by hand their understanding of what they have been sick with and what treatment they have undergone so far.

"Some patients are not fully aware of what treatment they had, they twist the names of the drugs,

and these are serious matters, because we use harsh treatments – radiation therapy, chemotherapy, surgery. Their effects are often irreversible," says Sobiczewski.

Even if the documentation is relatively complete, says Pogoda, the quality of the translation may not be fit for purpose. "Sometimes medical records are translated through online tools. I cannot make therapeutic decisions on this basis."

Doctors also point out differences in treatment schedules used. "At first I thought I had misunderstood the words of the patients. Later it turned out that they were

"I have to rely on the patients' words and, based on that, infer what type of cancer they had and how to continue treatment"

treated in a non-standard way. The regimens differed from the standards we use. We have to tailor treatment for each patient," says Joanna Kufel-Grabowska, an oncologist at University Hospital of H. Święcicki in Poznan.



It can also happen that the treatments proposed by Polish doctors are not the same as those that had been offered in the Ukraine. Julia had opted to have breast-conserving surgery in Ukraine, but in Poland she was only offered a full mastectomy. She therefore decided to return to her country, just for the surgery.

“It was one of the most difficult choices of my life. It was very unsafe to return to Ukraine. On the other hand, I couldn’t imagine my life without a breast.” Julia took a bus, with her children, to Lviv, where she was met by her husband.

After the procedure, she had to return to Poland, just with the children, as males are not allowed to leave Ukraine. She gets emotional when she talks about the experience. “It was very difficult, the road was long, and I couldn’t carry anything heavy.” She is now undergoing radiation therapy in Wrocław.

Julia finds the Polish health service very good. But she is surprised by the queues, which Polish patients also complain about.

“It was one of the most difficult choices of my life. It was very unsafe to return to Ukraine. But I couldn’t imagine my life without a breast”

“At first I was annoyed about why one has to wait all day.

You have to show up at the hospital at 10 am and you can enter the doctor’s office in the afternoon. This is hard to understand for me, but now I accept it,” she says.

Hard choices and an uncertain future

Five months after Russian aggression against Ukraine, there are already noticeably fewer Ukrainian patients in Poland.

Katarzyna Pogoda is now treating ten of them, including a man who developed breast cancer. His family has gone back, and he has decided to stay, to continue

his treatment in Poland. Some patients stop in the middle of treatment and return home, says Pogoda.

“The plans of some patients change and do not coordinate with the treatment plan. Despite everything, we try to treat patients as if there was no war.”

For many Ukrainian patients in Poland, the biggest problems they now face is sustaining the needs of everyday life. Access to accommodation is a particular problem. “It can happen that after treatment we have nowhere to discharge the patient,” says Sobiczewski. “These are people who are still quite sick and need comfortable conditions.”

Ciompala reports that Alivia Foundation is receiving increasing numbers of requests for help with finding a place to stay for longer. “There are also more and more requests for help in finding funds not only for medical treatment, but also for everyday life,” she says.

Julia plans to stay in Wrocław until the end of her treatment, or even longer. Her children go to school there.

“Unfortunately, I don’t know when it will be possible for me to return home. I can’t imagine how the children can return to schools in Ukraine in September. It’s too dangerous.”

She wishes herself health and peace in her country.

This article was first published on the Cancer World website on 22 July 2022 (bit.ly/CW-Poland4Ukraine).



Image: Delivering palliative care in Kerala, India ©Camilla Perkins, camillaperkins.com

Developing palliative care

New WHO guidance helps countries tailor their own path

Countries seeking to develop sustainable, accessible, high-quality palliative care services can now find guidance and resources, drawn from experience and expertise across the world, to help them tailor solutions to their own needs and their existing healthcare systems, reports **Esther Nakkazi** from Uganda.

Delivering palliative care to avoid unnecessary health-related suffering is defined by the World Health Organization (WHO) as “a moral imperative and a human right”. Yet only a tiny proportion of the estimated 57 million

people who need palliative care each year are able to get the care they need.

To assist countries in their efforts to introduce effective palliative care services, the WHO has now published new guidance (bit.ly/WHO-PalliativeCareGuidance).

WHO-PalliativeCareGuidance).

A set of WHO technical tools and a forthcoming ‘compendium’ of resources will address widely varying international needs and circumstances, assisting resource-poor countries to integrate palliative care

Palliative care: what it does, who it's for

The World Health Organization defines palliative care as:

"...an approach that improves the quality of life of patients (adults and children) and their families who are facing problems associated with life-threatening illness or serious health-related suffering. It includes, but is not limited to, end-of-life care. It is not the 'last resort', but should be integrated early in the care of people affected by a life-threatening condition."

For people with advanced cancer, delivering palliative care can help them live more comfortably, and in some cases can help extend their lives.

into universal health coverage.

Recognising that different models are needed for different countries, the WHO is effectively offering a menu of indicators to monitor success in palliative care provision (bit.ly/WHO-Palliative-CareIndicators), leaving countries free to adopt what is most suitable for their particular setting. The hope is that governments will be more likely to invest in palliative care because it is more practicable.

"Governments do not have to re-invent the wheel. They can adapt and adopt them for better service delivery"

"We need to ensure universal access to palliative care, but this is far from the reality," said Marie-Charlotte Bouësseau, Ethics and Health team leader at WHO headquarters in Geneva. "We know that the great majority of populations around the globe do not have access to palliative care." Worldwide only about 12% of palliative care need is currently being met.

Emmanuel Luyirika, Execu-

tive Director of the African Palliative Care Association, said the new tools could be used to call on African governments to act. "The documents clearly define the actions that governments can use to improve and measure access and delivery of palliative care... Governments do not have to re-invent the wheel. They can adapt

and adopt them for better service delivery."

"Once you are able to measure, you can hold people accountable and improve on service delivery," said Luyirika. "But the actions also require governments to invest in their health systems."

World Health Assembly resolutions recognise palliative care as an ethical responsibility of health systems and call for WHO Member States to assure its delivery through comprehensive primary health care services. This mandate is related to the commitment to universal health coverage.

The documents released by WHO include a set of actionable indicators that can be used by countries to monitor and assess the development of palliative care and resources on practical approaches

The new WHO Guidance

In its guidance document, **Quality health services and palliative care: practical approaches and resources to support policy, strategy and practice**, the World Health Organization (WHO) summarises key actions that can be taken at a national, district and point of care level, that can be applied to variety of different palliative care models (bit.ly/WHO-PalliativeCareGuidance). These include principles, of policy making, planning, implementation and building in quality control and monitoring systems.

In its document on **Assessing the development of palliative care worldwide: a set of actionable indicators**, the WHO offers guidance on selecting and implementing palliative care indicators, that can be tailored to the palliative care model and wider health system of each country (bit.ly/WHO-PalliativeCareIndicators).

This includes addressing questions such as:

- Are they effective as indicators of how well key aspects of the palliative care system are working?
- Is collecting/generating the data feasible?
- Are the data a good fit within the country's wider health information system?
- How will the data be used?
- Do all parties involved understand their roles in implementing the monitoring?

Different models for different countries

While not laying down blueprints for the development of palliative care services, the World Health Organization guidance does mention specific examples of good practice (bit.ly/WHO-PalliativeCareGuidance).

Panama gets a mention (page 19) as an example of success in developing “a system of sustainable palliative care delivery that is integrated into primary care, deliberately making use of existing health system structures and integration with the country’s broader offer of UHC [universal health coverage] free of charge”.

Uganda is highlighted (page 27) as an example of increasing accessibility to opioid pain relief alongside strengthening education and under a supportive national policy for palliative care. “With inclusion of palliative care in all medical curricula since 1994, Uganda has a medical workforce that is well informed about palliative care, with opportunities for specialisation.” Also mentioned is the priority palliative care and quality of care get within Uganda’s national health plan in the context of its ambitions for universal health coverage.

South Africa’s use of Palliative Care Standards to accredit hospice and community-based palliative care services, and its mentorship scheme are both highlighted (page 34). “The district mentorship programme facilitates the fast tracking of compliance with palliative care standards and provides a mechanism to cascade good practice in quality care between hospices and partner organizations.”

India is offered as a good example of using remote learning with mentorship from international experts (page 44), which is seen as a model that could be adapted for other countries to “catalyse the development of initial quality improvement capabilities in palliative care”. The Indian programme promoted quality improvement education and collaborative learning among a number of palliative care centres in the country. “Each palliative care centre was matched with an international partner that provided coaching, education and mentorship in quality improvement methods, meeting regularly virtually for teaching, exchange and problem solving.”

to supporting policy, strategy and practice. Countries can select from a set of indicators for monitoring national strategies, policies and plans. These can be incorporated into planning and delivery at the national, district and point-of-care levels.

The WHO documents stress that providing good palliative care is an ethical responsibility for the whole community – not only for health professionals but also the social workers, family caregivers and community caregivers.

“There is very little value in creating access to services that are ineffective, unsafe, are inefficient and not timely enough to provide the care that people need,” said Anna Ray a palliative care expert from the WHO Integrated Health

Services Department.

“The model would not be ‘copy and paste’, because building palliative care is like building a house: we should not build the house the same way in Uganda, Japan or Costa Rica. So I think this adaptation is crucial at local level, to maximize the impact and the quality of what we do,” said Ray.

She said that the indicators were the product of a consensus building exercise involving experts from around the world. But their benefits needed to be verified in the real world.

Uganda is one of the countries that has been selected to use these new indicators to see how they work in practice. Mark Mwesigwa, the country director of the Palliative Care Association of Uganda

(PCAU), said: “When you look at the new model, it empowers people in the community who know that the service is available and they can seek the services. The issue for us now is how best we can actually develop our own indicators based on the framework that has been laid down.”

“I think the important issue here is quality. It doesn’t happen by accident. It takes concerted effort across the health system from all of our different perspectives,” he said.

This article was first published on the Cancer World website on 21 April 2022 (bit.ly/CW-WHO-PalliativeCare)

Steroid use and survival

Association in solid tumours treated with immunotherapy



Steroids are often used to manage toxicities arising from use of immune checkpoint inhibitors (ICIs), as well as to control symptoms such as oedema in brain tumours or pain. But they are immunosuppressive, which raises questions about the unintended impact they may have on the efficacy of ICIs. **Fausto Petrelli**, of the Oncology Unit in Bergamo Ovest Hospital in Italy, led a systematic review and meta-analysis of published studies to help find some answers (*Cancers* 2020, 12:546). **Alberto Costa** asked him about what they found.

Q. Steroids are commonly used in patients with solid tumours for supportive therapy. Your study seems to question the usefulness of this approach. Why?

A. Steroids have beneficial effects in some cancer patients, in particular for control of symptoms of advanced disease (brain oedema, pain, dyspnea, etc), but they have a negative effect on immunity. We found that, in settings where they are not used for curative purposes (e.g. prostate cancer), they may exert a detrimental effect on survival.

This issue is now increasingly debated in the care of patients who are undergoing immunotherapy. The effects on risk of infection, diabetes and sepsis, and on immunosuppression may explain the reduced survival observed in these patients. All these effects may negatively impact on prognosis, in particular in patients

with advanced cancers, whose immune systems are impaired.

No data were derived from adjuvant or early settings, where steroids are usually used only for short periods, for control of nausea and vomiting, or for pain or during radiotherapy. However we did include data from some studies of adjuvant treatment of breast cancer, where steroids were occasionally used in schedules many years ago.

Q. Your paper draws data from 76 articles out of 2,057 screened references. How did you select them?

A. We selected prospective or retrospective studies, published in full and in the English, that reported the outcome of cancer patients according to steroid use (any steroids vs no steroids) independent of the aim of therapy (curative or palliative). The main endpoints were overall survival

and progression-free survival, which were compared between steroid users (intervention group) and standard therapy without steroids (comparator group). We excluded case reports and haematological malignancies, where corticosteroids are the standard of care for those diseases. We then performed subgroup analysis according to the type of study (retrospective/prospective and randomised studies), the reason for steroid use (e.g. supportive vs curative care), type of disease, stage (early vs advanced), risk of bias (high vs low), and type of analysis (univariate vs multivariate).

Q. Based on these data, do you recommend that steroid use should be reduced or even avoided in patients with advanced solid tumours?

A. Bearing in mind the retrospective nature of most of the studies, the more important result is the harmful

effect of steroids in non-small-cell lung cancers (NSCLC), in patients with metastatic disease, and in palliative settings.

This means that, with regards to symptom control, steroid use should be limited in duration and dose, and it should be avoided during immunotherapy, particularly in patients with NSCLC. This recommendation, however, is still already included in major guidelines on administration of immunotherapy; it was not derived from this meta-analysis alone.

For metastatic patients undergoing palliative care, where quality of life is the primary endpoint, steroids are of benefit and should continue to be used.

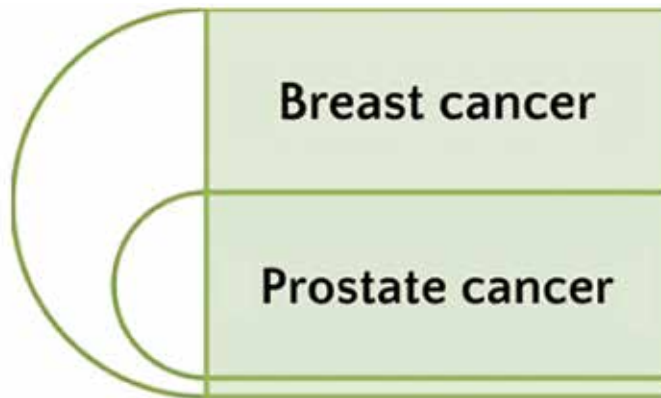
We suggest that, in patients who have stopped active treatment and are on palliative care alone, steroids may be offered, as appropriate.

Conversely, in subjects undergoing active treatment (e.g. chemo and/or immunotherapy), steroids should be used judiciously, and only for brief periods, to mitigate side effects of chemotherapy (delayed or acute nausea and vomiting), or symptoms such as pain, or brain oedema due to brain metastases, or during radiotherapy for bone metastases, for example.

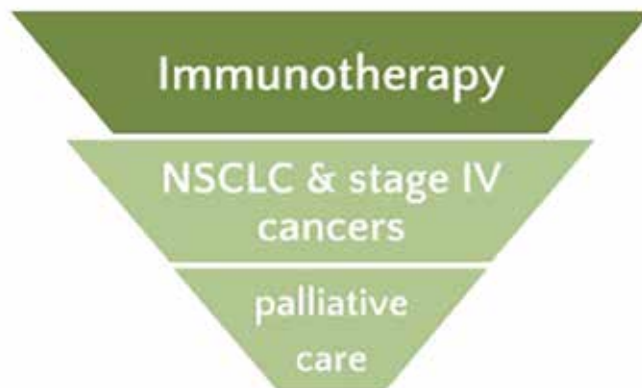
Q. *What is your takehome message?*

A. The takehome messages are synthesised in Table 2 of our paper (*Cancers* 2020, 12:546), which reports subgroup analysis. The message is not alarmist at all. We must continue to use steroids for nausea and vomiting, such as during radiotherapy for brain metastases or for pain from symptomatic bone metastases. We

Safe and effective use of steroids in cancer



Steroids may be dangerous for:



should identify a small subgroup of patients – for me, this would be patients with NSCLC or other solid tumours, in particular those undergoing therapy with immune checkpoint inhibitors where corticosteroids are dangerous.

Unfortunately, we cannot answer questions about the duration and dose of steroids that could be administered safely. Indeed, a randomised study will not ever be designed with this scope. New antiemetic drugs (anti-NK1) now allow for steroid dosage to be

de-escalated in prevention of nausea and vomiting.

In the meantime, based on these results, a cautious policy of minimising steroid use should be pursued by any clinician caring for cancer patients.

This article was first published on the Cancer World website on 11 March 2021 (bit.ly/CW-Steroids-Survival)

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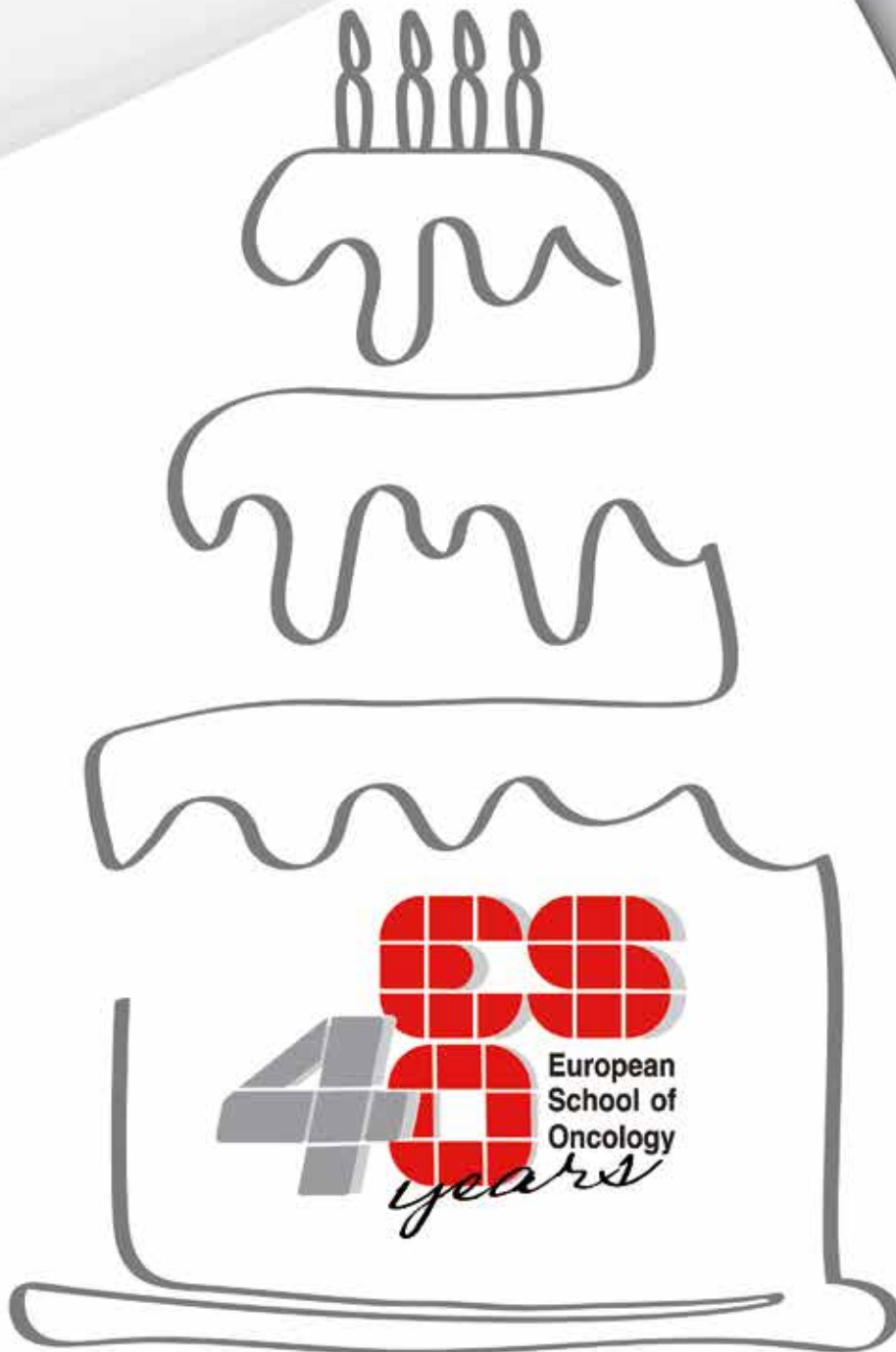
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