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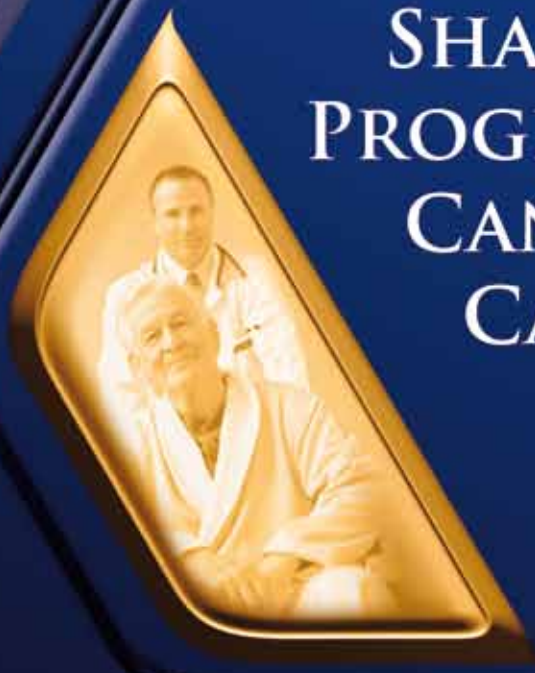
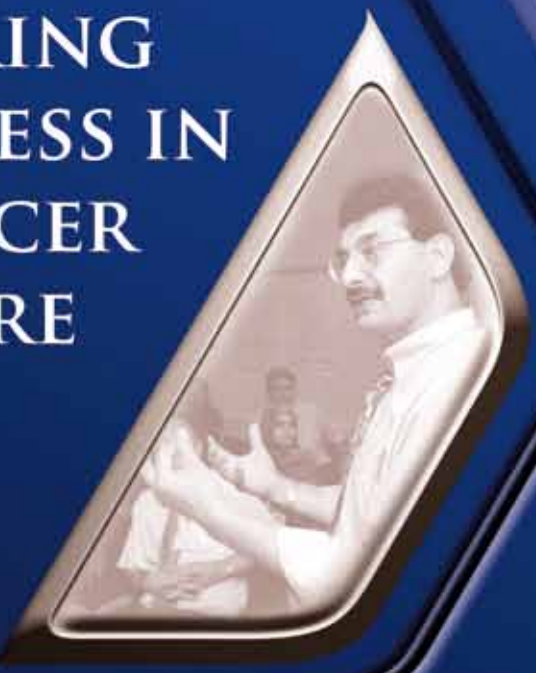
European School of Oncology

Learning to care

Sharing Progress in Cancer Care





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Be a champion for change

Peter Selby, Guest Editor

An estimated 50,000 people who die from cancer every year could still be alive if the quality of diagnosis and care in European countries with the poorest survival rates were as good as the median across Europe. That number rises to 100,000 lives per year if countries with the poorest outcomes could improve to the 75th percentile for Europe. Even among the best-performing cancer systems, some sections of the population have better access than others to high-quality diagnosis and care, depending often on where they live, their socioeconomic status, age and other factors.

These disparities are not OK, all the more so because we know what has to be done to achieve the best outcomes: active programmes on prevention, lifestyle changes and screening; prompt access to diagnostic testing; prompt access to excellent specialised multidisciplinary care (including supportive, survivorship and palliative care); programmes to promote access for disadvantaged groups; and research and innovation.

We know this thanks to decades of high-quality work on clinical trials, service organisation, clinical epidemiology and comparative effectiveness research, which have been analysed, carefully considered, collated and presented by oncology professionals, cancer researchers, patient advocacy organisations, and governments, individually and together.

Much of this is summarised in documents such as The European Cancer Patient's Bill of Rights (*ESMO Open* 2017, 1 (6) e000127) and the publications coming out of the EU Joint Actions on cancer (bit.ly/QualityImprovementGuide, bit.ly/Cancer_Innovation). A vast library of evidence-based guidelines and expert consensus recommendations have been published on specific aspects of diagnosis, treatment and care – most recently, a cancer-type-specific series of Essential Requirements for Quality Cancer Care (bit.ly/EssentialRequirements).

So why are so many patients still being let down?

Resources clearly matter. Yet while outcomes are generally better in wealthier countries, plenty of countries achieve better outcomes than others for similar or lower health spend. Prompt access to diagnosis and multidisciplinary specialised cancer care are within the reach of most healthcare systems. If patients are diagnosed early and managed well, outcomes are better and less is spent on re-treatment and end-of-life care.

A bigger barrier may be overcoming resistance to change and innovation, whether that comes from health professionals protecting their own interests or simply 'routinism'. Changing the way things are done can be uncomfortable and take time and effort, so it's easier to stick to the old ways, and blame substandard outcomes on lack of resources. Efforts to improve practice can also be wasted by trying to 'reinvent the wheel' instead of learning from the experiences of others and looking around for evidence-based best practice.

Our patients deserve better. It's up to all of us to make sure they get it. We all have a duty to look critically at how we deliver care, to ensure that readily affordable changes and well-evidenced innovations are quickly taken up. We need to work with patients and advocates to make clear what we expect from governments. We need to encourage young leaders to become champions for change, and provide them with best-practice literature in a brief format designed for practical application, and give them the skills and the networks to help them make the changes that will help end this needless suffering and death.

To comment on or share this Editorial, go to bit.ly/CW82_champion_change

Peter Selby is Professor of Cancer Medicine at the University of Leeds. He played a leading role in developing the landmark 1995 Calman–Hine report into improving cancer services in England and Wales, and is co-author of the *European Cancer Patient's Bill of Rights*

Improving outcomes – a practical guide

After 25 years of trying to improve the way we organise and deliver cancer care we now have a fairly clear idea about what changes are needed to get the best patient outcomes. Finding ways to make those changes happen at every level and in every country remains a challenge. **Anna Wagstaff** asked key figures from across Europe for their advice.

If you want to make a big difference to the quality of patient care and outcomes for large numbers of patients, you need to look beyond your own individual practice, particularly when many different specialists and services are involved in a complex pattern of care for each patient.

This argument convinced a mid-career medical oncologist and researcher, with a special interest in measuring quality of life, to take responsibility for defining a set of principles that marked the beginning of a transformation in the quality of cancer care delivered across England and Wales, with a resonance well beyond the UK.

The year was 1993, the oncologist was Peter Selby, and the man who convinced him was Kenneth Calman, then Chief Medical Officer for England. The principles – drawn up by a panel of highly experienced and dedicated cancer specialists – were set out in what became known as the Calman–Hine report (1995).

The report drew on evidence generated in a number of countries and on early epidemiological studies exploring the link between outcomes and caseload in tricky, high-risk cancer surgeries, as well as studies on psycho-oncology and quality of life, screening and early diagnosis.

Its unique and lasting contribution was to flip the focus away from the perspective of health professionals towards the perspective of the patient. Calman–Hine developed the concept of cancer care and cancer services as an integrated patient-centred package, with contributions from specialists in multiple disciplines and professions working as a team, delivered across primary, secondary and tertiary settings, and centred on the needs of each individual patient with systematic monitoring of treatments and outcomes.

A series of Improving Outcomes Guidance translated the Calman–Hine principles into service delivery guidelines for the more common cancers, specifying what should be involved in diagnostics, treatment and care, who should deliver it, and how.

Then in 2000, England published the world's first comprehensive national cancer plan (drawn up by Mike Richards, the world's first national cancer director), which addressed wider issues of organisation and structure, identifying regional cancer networks as the key to integrating care between primary, district hospital and specialist centres, so that no treatment would be delivered in a setting lacking appropriate experience and expertise.

In terms of defining what should be done, England appeared to be ahead of the curve. But turning that vision into reality took a lot longer than Selby had expected, and remains to this day a work in progress.

"I was relatively inexperienced, and I thought that once the report had been endorsed by the government, change might come quickly," says Selby. "It doesn't surprise me now, because I'm old and wizened and I realise that bringing about change is a process of being grindingly relentless over a long period of time."

A European story

This is not just a British story. At the time Kenneth Calman commissioned his report, policy makers, public health professionals and clinical leaders across Europe were looking at how to address the escalating complexity of cancer diagnosis and treatment, with growing demands for patient centred care and more effective oversight of the quality of care.

It wasn't long before Denmark and France published their own comprehensive national cancer plans, followed by other countries, and backed in some cases with the staff and budget to oversee their implementation. Many of these plans are now in their third or fourth iteration.

In 2009, the European Partnership for Action Against Cancer (EPAAC) became the first in a series of European 'Joint Actions' on cancer control that sought to share best practice on the development and implementation of national cancer plans as well as on issues from prevention to screening, cancer registries and benchmarking, psycho-oncology and survivorship. The publications arising from these Joint Actions are all published on the EPAAC and CanCon sites. The most recent Joint Action – iPAAC – was launched in April 2018.

In 2017, ECCO launched a European clinical collaboration to define the essential requirements for delivering safe, high-quality, patient centred care in different cancer types, focusing on what is required at the service–patient interface.

Measuring the impact

There can be little doubt that these efforts have contributed over time to the improvements in survival shown across the board by cancer registries, which have themselves been important drivers of improvement by the mere fact of revealing survival differences between countries and regions.

How much of the improvement is due to better technologies – drugs, imaging and radiotherapy equipment – and how much to changes in the

Policy-led change: improving early diagnosis

Since the mid 2000s, Denmark has been making significant progress in diagnosing cancers quicker.

Why? Comparative data showed that delayed diagnosis was a contributing factor to poorer cancer outcomes recorded for Denmark – and the UK – compared to countries with similar resources and health systems.

How? The Danish government, through its national cancer plan, classified "potential cancer" as a medical emergency. It introduced a three-pronged strategy, comprising:

- New diagnostic pathways to speed up referrals for patients who show specific organ-related symptoms;
- Diagnostic centres where GPs can refer patients with suspicious but non-specific symptoms, such as weight loss or night sweats, to identify the cause;
- New options for GPs to access diagnostic tools such as CTs and ultrasound scans without having to refer their patients to hospital, to speed up a "yes/no" answer where symptoms are assessed as "low risk but not no risk".

Aim? The goal is to reduce the time from first suspicion of cancer to the start of treatment, with the aim of improving outcomes.

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Impact? A study of the impact on cancer prognosis indicates that the prognosis of symptomatic cancer patients diagnosed through a primary care route has improved across the time the new referral pathways were introduced, and that the expedited referral contributed to that improvement (*BMC Cancer* 2017, 17:627). A study comparing waiting times and outcomes for patients diagnosed with glottal cancer, where delays in diagnosis are known to be an important factor in prognosis, found that those diagnosed after the new referral system was implemented were diagnosed earlier and had significantly lower adjusted HR of disease-specific mortality (*Eur J Cancer* 2016, 59:46-56).

way care is organised and delivered is a matter of controversy. It may not even be a meaningful distinction, because one thing we have learnt – although this understanding has itself been poorly disseminated – is that realising the value of new drugs and equipment depends heavily on learning how to use them to best effect, and then spreading that knowledge effectively throughout the system.

Another thing we have learnt is that, despite encouraging signs 10–15 years ago of a narrowing of the survival gap across Europe, disparities in outcomes remain stubbornly entrenched, as highlighted by the European Cancer Patient Coalition among others (eg bit.ly/ECPC_disparities). These translate into tens of thousands of needless deaths and long-term physical, emotional and functional damage every year. Much of this could be avoided if health systems were quicker at implementing comprehensively documented changes that have been shown to make a difference.

Making it happen

There are no league tables documenting disparities in the speed and efficiency with which healthcare systems innovate and improve the quality of service, but these differences clearly exist. This was starkly demonstrated in the 1980s onwards, by the differential speed of uptake of a surgical technique for rectal cancer that had been conclusively shown to have a dramatic impact on the rate of recurrence (from around 30% of cases down to 3.5% or lower) and consequently on both reoperations and survival.

Total mesorectal excision (TME) was developed in the mid-1980s by a British surgeon, Bill Heald, in partnership with pathologist Phil Quirke and radiologist Gina Brown. The Swedes and the Norwegians called in Heald and his team to train their clinicians, and rolled out the new technique, so that by the late 1990s almost every patient who might benefit from the technique in those countries received it.

The UK, by contrast, was in the slow stream. In 2000, Bill Heald had to resort to a media campaign to draw attention to the fact that Scandinavian patients were benefiting from a procedure that was still not delivered as standard across the UK. Indeed, as Selby comments, "even today, Phil Quirke is running a charity-funded programme for improving uptake of appropriate surgical techniques including TME, 30 years after Bill Heald and 25 years after Sweden."

When, in 2008, a programme to roll out TME was launched in Spain, they called it 'Vikingo', in honour not of the country that was so key to the development and teaching of the technique, but the countries that had made it routinely available to patients.

What's the Viking secret?

Peter Naredi, past-president of ECCO, and a specialist in liver and pancreatic cancer surgery, has spent much of his career leading efforts to improve outcomes across Europe. He believes that a strong sense of collective responsibility and leadership within the profession in his native Sweden have been key factors for success.

"The system is all of us, working in a certain environment, with certain financial capacity, with certain kinds of regulations. So if we want to change the system, it's us."

In Sweden it was the clinicians and not the government that started the clinical cancer registries, says Naredi. "We saw different outcomes and quite big differences in complications and we wanted to be able to compare treatments and outcomes between regions."

Their motivation was not to show up the best and the worst performers, so much as to use the data to work out what factors were associated with better or worse outcomes. They began by listing 54 indicators, but soon realised it would take a clinician half an hour to complete each form, so agreed on a shorter version that could be completed in under 10 minutes.

"The basis for changing a system is that there must be an incentive – something worthwhile for those who actually do that work. I think that is the red thread through all the system change in things that I have been involved in. You are not alone. You do it with colleagues."

The same principles, he says, have been key to the success of European professional initiatives such as EURECCA, the European Registry of Cancer Care, which was started in 2007 as an ECCO/ESSO initiative to improve the quality of cancer care by data registration, feedback, improvement plans and sharing knowledge.

Naredi was initially sceptical about whether valid conclusions could be drawn from pan-European comparisons, because there is no complete alignment between countries about which treatment and outcome data are recorded. He learnt that, through a process of structured discussion, such as the Delphi process, it is possible to reach a robust consensus even if the data are not perfect.

The profession is key

One of the notable improvements in patient care arising from these consensus-building discussions has been a dramatic drop in unnecessary adjuvant chemotherapy for stage II colorectal cancer. A comparison of countries with widely differing rates of adjuvant chemo use in this group of patients showed no differences in outcomes. "Again the profession is key here," says Naredi, "even if we have different views on what indicators we use."

More recently, Naredi has been a prime mover behind an ECCO initiative to build a European pan-professional consensus around the Essential Requirements for Quality Cancer Care, in terms of how the diagnosis, treatment and care of patients with specific cancers should be organised and delivered.

"When we sit together and write these documents, we open eyes about what others consider absolutely necessary, and what we may consider not so important. And then we come to a consensus. It's about decreasing your own role as an independent speciality and looking at what you can do together."

Naredi accepts, however, that there are limits to what can be achieved through professional consensus, and that governments have a role and a responsibility for improving safety and quality. As he points out, while clinical cancer registries were started in Sweden by the professions, government later stepped in to make gathering and publishing of data on treatment and outcomes compulsory, and that data became crucial to generate the political will needed to drive sometimes painful changes to the structure of cancer services.

"By making the numbers public, it became rather evident that the best outcomes are at high-volume hospitals. So this drove concentration of care to larger units, and the smaller units had to start collaborating with the larger hospitals, for instance with the video multidisciplinary team meetings that we have in all regions nowadays."

We're not all Vikings

What works in some countries may be less effective in others. In Germany, for instance, professional associations may have acted as a brake on improving outcomes because they stand accused of putting their own self-interests first, rather than collaborating.

So says Johannes Bruns, head of the powerful German Cancer Society, DKG, which since the early 2000s has been leading efforts to promote a truly multidisciplinary approach to care, driven by guidelines and backed up with a system for benchmarking and critical review of performance and outcomes.

"The whole problem in our healthcare system is that the main drivers within our system of self administration are the sickness funds and doctors associations. They decide. Only through legislation are you able to

establish good ideas like psycho-oncology, registries, certification, specialist centres. Without that, they all want to work in their own self-interest, so nothing changes."

Each professional society feels responsible for its own step in the pathway of diagnosis, treatment and care, says Bruns, "The sum of all the steps makes the results for the patient, and nobody is looking at how to organise that… Nobody feels responsible in our system."

Changing that attitude, he feels is key to improving patient care – the question is how? "You can organise it like in Sweden, a few big centres, organised like a hospital, and everyone with cancer goes there. But in a system like Germany, with 80 million people, 500,000 cancer patients a year, how do you organise this process?"

The strategy adopted by Bruns and the DKG has been to focus relentlessly on multidisciplinary teams (MDTs) as the only basis for clinical decision making. "This is where the doctors have to talk about what they want to do. That is the best quality assurance intervention we have. In oncology no single doctor should decide on anything alone."

MDT decision-making, he argues, ensures that decisions on the treatment and care of every patient are informed by input from at least the core specialisms. It also helps to identify individual team members who routinely flout guidelines, and MDTs should act as 'learning organisations', that build review of decisions and outcomes into their routine practice. "If something goes wrong, or something bad happens, you have to talk critically about what happened. Every time, the whole team must look at that."

Although Bruns believes that only legislation reaches every part of the health system, the DKG has relied on a voluntary approach to changing practice, in order to bring the medical profession on board. They started defining guidelines for the organisation and delivery of breast cancer in 2003, followed by colorectal and then prostate cancer.

In 2008 they turned their attention to promoting organ-based cancer units, such as specialist breast centres, through an accreditation process that used a set of criteria including MDT decision making, adhering to guidelines, minimum caseloads (as a measure of competence), involvement of a defined set of specialist roles, and gathering, reporting and reviewing key treatment and outcomes indicators.

"We are now covering more than 1,400 organ-specific cancer centres, including regional networks, and nearly 120 cancer centres where a variety of tumour entities are treated," says Bruns. Evidence that patients are reaping the benefit comes from comparing treatment and outcome data from centres inside and outside of the accreditation system. Under recent legislation all cancer centres have to report selected treatment and outcome data to cancer registries, set up on a regional basis.

Competition vs collaboration

Improving patient care is something all good doctors want to do, says Bruns, but he says that the way the German healthcare system works means it is easier to get money if you don't work together. He accepts that things are better than 20 years ago, "when surgeons and radiotherapists in the same hospital would compete against one another for money." That changed with the introduction of a system where the payment was given by 'disease reference group' rather than for individual interventions, and Bruns would like to see further changes, with payment at the cancer network level.

However, competing for patients is the single biggest incentive that drives centres to seek accreditation, and to keep standards high for fear of losing it. There are too many hospitals and too many surgeons in Germany, says Bruns, and most patients want to be treated in centres that are accredited.

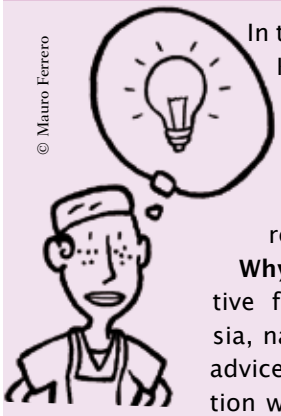
Collaborative learning and sharing best practice can suffer under a competitive system. If the annual audit of an accredited centre highlights persistent problems, the DKG can offer to ask someone from another centre to visit. "We find they are not very happy to bring someone in from another hospital," says Bruns. "They worry that if word gets out that there are problems in their hospital, then cancer patients won't go there anymore. So there is a conflict of interests, and they don't feel they are in a situation to talk about their own professional problems."

To get around this, the DKG tried inviting doctors who had recently retired, but were no longer attached to a hospital, and more recently they have tried, with some success, to partner doctors from hospitals located in different regions of Germany.

"It's easier to talk about their problems with people not near the neighbourhood. We arrange these kinds of meetings because more people come along and will say, for instance, 'I have a problem with infections after a particular procedure. What do you do differently? Tell me what I can change.'"

Might this fear of being open also compromise the openness of discussions within MDTs? That's a possibility, says Bruns. So far, audits have focused on the proportion of patients who were discussed at the MDT, and who was present at the meetings. The question of the quality of the com-

Physician-led change: Improving recovery after surgery



In the 1990s, Danish surgeon Henrik Kehlet led efforts to find how to minimise the stress and trauma of major surgery for colorectal surgery and put patients on a faster more effective road to recovery.

Why? Practice regarding preoperative fasting, postoperative anaesthesia, nasogastric tubes for feeding, and advice on bed rest versus mobilisation were based on traditional wisdom rather than evidence.

How? Kehlet and collaborators developed a multidisciplinary protocol for peri- and postoperative care of patients undergoing colorectal surgery, which became known as the Enhanced Recovery After Surgery (ERAS) protocol. The protocol includes talking to patients and families about what to expect following an operation and how they can help speed up their recovery. The key ERAS principles and collaborative, multidisciplinary approaches have been used to develop similar protocols for other surgical procedures.

Aim? The focus is on stress reduction and a return to function, to recover more quickly from major surgery and avoid the medium-term adverse effects of conventional postoperative care, such as fatigue and a decline in nutritional status.

Impact? The advantages of ERAS protocols for speeding recovery, reducing anxiety and enabling patients to leave hospital earlier have been reported widely, and vary from one surgical procedure to another. One study on the impact of introducing the ERAS protocol for patients undergoing colorectal surgery in Alberta, Canada, reports that patients treated pre-ERAS stayed in hospital for a median of 1.5 days longer than those treated using the ERAS protocol; their risks of developing at least one complication were more than 10% higher, and they were 70% more likely to be readmitted within 30 days (*World J Surg* 2016, 40:1092-103). The net cost savings attributable to guideline implementation ranged between US$ 2,806 and US$ 5,898 per patient.

The international ERAS society (http://erassociety.org/) reviews and updates the protocols. (See also TED talk by Olle Ljungqvist at bit.ly/2JfONqZ)

munication – for example regarding leadership, working atmosphere, and conflict management – is an issue the DKG intends to focus on more closely over the next two years.

Collaboration: who's in and who's out?

The quality of team work is a particular issue when it comes to maximising the contribution that all specialists make to improving outcomes says Lena Sharp, President of the European Oncology Nursing Society. EONS is currently completing a year-long RECaN project, examining the evidence about the impact of nursing on patient outcomes and experiences.

There is a huge variation in the status and training of cancer nurses across Europe, says Sharp. She argues that one of the most effective ways to improve outcomes would be to invest in specialist nurses, train them and integrate them as equal members of multidisciplinary teams.

Specialist nursing makes a contribution to survival as well as quality of life and patient experiences, by monitoring complex treatments and looking for signs that could kill a patient, says Sharp. "Caring for patients is a distinct competence. We sit at the bedside with the patient to do these treatments, we work 24/7 close to the patient, and we have the competence like no one else when it comes to symptom management and self-management."

She emphasises the contributions that patients, families and carers, make to outcomes, and points out that it is primarily nurses who facilitate this, by communicating with patients and answering their questions. "If you feel as a patient that you have an important role yourself, you are more adherent to the treatment, you are more involved in the rehabilitation process, you are more involved with lifestyle issues after treatment than if you leave it up to the healthcare professionals to fix you."

Sharp was shocked to hear that nurses at one hospital included in the RECaN study were explicitly told never to question what a doctor orders, says or does. "Even if it is obvious to the nurse that a mistake had been made, they are told not to speak up."

Even in her native Sweden, widely seen as a relatively equal society, similar signals are often given, though not

Nurse-led change: improving symptom management

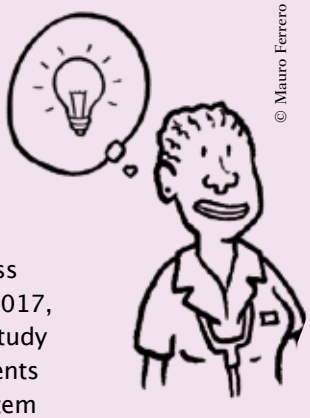
In the early 2000s, a group of specialist nurses began developing an Advanced Symptom Management System (ASyMS) to allow safe and effective monitoring of the side-effects of chemotherapy in patients' own homes.

Why? Patients were increasingly being given more treatment for chemotherapy on an outpatient basis. This meant they had to manage most of the side-effects of their treatments at home, and know when to contact health professionals if any of the symptoms were of concern.

How? Patients are given a mobile phone with the ASyMS software and are shown how to use it to report, daily, on their experience of symptoms relevant to them, graded for severity and for how distressing they are.

This data is analysed by an evidence-based algorithm that triggers one of three responses. For less severe symptoms, patients will receive appropriate self-care advice on their mobile phone. Where symptoms may require intervention by a healthcare professional, clinicians will receive an alert: amber for symptoms that are mild to moderate, but may have persisted; red for oncologic emergencies that need rapid input from clinicians at hospital.

The aim? The overall aim is to reduce symptom burden, improve quality of life and enable patients to stay at home. Managing symptoms in real time can help minimise them or prevent them from progressing and possibly requiring hospitalisation.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Impact? ASyMS is nearing the end of a five-year trial called eSMART, which involves more than 1,000 patients across five countries (*BMJ Open* 2017, 7:e015016). A smaller study has already shown that patients believed the ASyMS system improved management of their symptoms and they felt reassured that they were being monitored at home. Health professionals also reported they found the system beneficial (*Clin Effect Nurs* 2005, 9:202-10). A 2009 study concluded that "the ASyMS system can support the management of symptoms in patients with breast, lung and colorectal cancer receiving chemotherapy… the system could provide a more accurate reflection of chemotherapy-related toxicity and … a better means of monitoring toxicity in clinical practice with the potential to decrease chemotherapy-related morbidity," (*Support Care Cancer* 2009, 17: 437-44).

so openly. "There are places in Sweden where senior medical professionals are still seen to be as close to God as you can get."

Nurses, she stresses, are often as 'guilty' as the medical professions in accepting such a passive role. "Even if there is a simple change that obviously would make a positive difference, they always worry: I'm not sure I'm allowed to do that. Is this included in my role? Can I make this decision?"

Research conducted by one of Sharp's PhD students showed that handovers between nursing shifts on the ward were more effective if they were conducted in front of the patient – not least because it means that the patient can be assured that the incoming shift is aware of their needs and concerns. And yet, says Sharp, even the nurses who had been involved in developing and testing the model still doubted whether they had the right to implement the changes.

At the annual EONS–ESO oncology nursing masterclasses, Sharp's session focuses on teaching participants how and why to speak up when they feel there is a problem, or that things could be done better, but as she points, out, there is a limit to what can be achieved by training nurses if the rest of the team aren't listening.

"In the focus group interviews we did in Germany, we saw they have given up a bit. They say, 'nobody is going to listen anyway so there is no point in speaking.' They are not allowed to have nurse-led services, for instance, as we have in most other European countries. It is a system that has a negative impact on nursing and other groups, and that makes it harder to change practice."

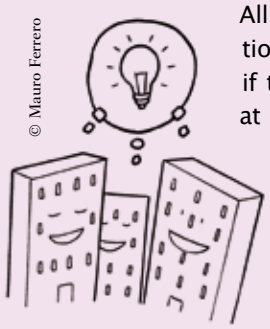
Sharp believes politicians at national and European level should take a lead in changing this culture. "There is a lot that could be done from a political point of view to change the system." The RECaN case studies made her aware of the power that national cancer plans have in forcing systems to change, and she argues for a clause that simply states that all people managing cancer care should be appropriately educated. At a recent meeting at the European Parliament, EONS highlighted the lack of incentives for nurses to go

through specialist training.

"Management can help by including nurses on the boards of larger hospitals, and encouraging professional development by non-medical groups." As Sharpe points out, nurses who take up a research role rarely have the option to continue with their clinical work, which divorces efforts to improve practice from the everyday life of the clinic.

There is also a time problem. Trying new and possibly more efficient ways to do things, developing the evidence and implementing changes in practice, all take time, and nurses don't have any. While Sharp warns against using this as an excuse, staff shortages and working conditions are serious problems, she says.

A culture of change: Is yours a learning organisation?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All organisations do better if they are good at learning and innovating. This applies as much to health services as to commercial corporations.

In May 2008, the Harvard Business Review published a stripped-down description of the building blocks of a learning organisation, which were summarised as:

- **A supportive environment**: Psychological safety, Appreciation of differences, Openness to new ideas, Time for reflection;
- **Concrete learning processes and practices**: Experimentation, Information collection, Analysis, Education and training, Information transfer;
- **Leadership that reinforces learning.**

The article gives a link to an online survey that can be filled out by individuals or entire departments, to rate the organisation they work in. These scores can be used to benchmark against other units, departments or hospitals, or against the Harvard Business School's own benchmark score.

https://hbr.org/2008/03/is-yours-a-learning-organization

Learning from one another

Experiences in the UK, Sweden, Germany, and the RECaN study countries demonstrate that European health services differ significantly in organisation, funding and culture. That doesn't mean that European countries cannot learn from one another about improving cancer outcomes. In fact, says Josep M Borras, Director of the cancer plan for the Catalan region in Spain, this diversity probably offers a particularly rich environment for learning.

Borras has been learning from Europe for more than 20 years. An epidemiologist by background, he joined the management of the Catalan Institute of Oncology in the late 1990s, and immediately started looking around to see what other countries were doing that could be of value.

"The Calman–Hine report was very important for us to see the importance of specialisation in cancer treatment and trying to organise the pathway of patients across the whole care system to improve the results. The concept of networks, for instance, fits very well in the regional organisation in healthcare that we had in Catalonia at that time."

Earlier work on a needs assessment of the region's radiotherapy capacity introduced him to the work of Dutch epidemiologist Jan Willem Coebergh, which highlighted the importance of specialisation in surgery, the need for data and population-based cancer registries, and the value of clinical audit.

When the pan-European clinical audit/registry EURECCA (spearheaded by a Dutch surgeon) was launched in 2007 – starting with rectal cancer – Borras was keen to promote participation. He went on to play a leading role, with Tit Albreht from Slovenia and others, in the European Joint Actions on cancer, which he says were particularly valuable "from the perspective of networking, and from a practical and focused perspective."

One of the aims of the third Joint Action on cancer, launched in April 2018, he says, is to assess the extent to which the research and policy recommendations generated by earlier Joint Actions, including national cancer plans, have been adopted and implemented – all of which comes back to the thorny question of translating cancer plans into cancer practice.

Champions for change

In the 25 years since Calman–Hine was published, Peter Selby says the European cancer community has done a great job in building a consensus around policy recommendations for cancer plans and best practice in various aspects of cancer care delivery.

He believes it is now time to focus on building competence and skills within the professional community to champion improvements in their own

hospitals and wider cancer services. He is addressing, in particular, newly appointed consultants at the same stage of their career as he was when Kenneth Calman came knocking on his door.

His message is: "There are various things you can do. You might do clinical trials. Excellent. You might become a medical director. Excellent. You might run a lab. Also excellent. But you might set out your stall to make sure that the patterns of practice in your patch are the best that they can be. And that is probably the mechanism that will save more lives through your efforts than anything else."

Closing the gap between the worst and the best in Europe, or within a country or a region, is not primarily a question of resources – though resources certainly come into it, Selby insists. "Many of the things we are talking about are really not expensive, because we are talking about quite simple improvements in practice that are far from guaranteed to cost more, and might, if planned carefully, cost less."

There are countries in Europe, he says, who insist there is no money to invest in radiotherapy, yet waste vast sums by delivering all chemotherapy treatments on an inpatient basis, with patients being admitted a day before for tests, remaining there for the days of treatment and staying a further day to be checked out before going home.

"That's a crazily expensive way of delivering those treatments. If you make that change you have money to buy your radiotherapy equipment. And it's nothing to do with expensive smart innovations. It's about learning from other countries about how to do things more efficiently."

Improving early diagnosis is another example where better practice is cheaper, says Selby. "Expensive non-curative treatments are not great value by contrast. Access to scanning and endoscopy will determine whether you make an early diagnosis or not, and access is still slow or non-existent in many countries in Europe."

Delays in diagnosis have been shown to account in large part for the relatively poor survival of patients in the UK and Denmark compared to similar patients in similarly resourced health services, and Selby commends the work done in Denmark to address the problem through reconfiguring the service to allow direct access to investigations (see Policy-led change box, p 6).

A collaborative approach to learning

Naredi, as a cancer surgeon, singles out another Danish innovation – ERAS (Enhanced Recovery After Surgery) protocols – to show how relatively simple and cheap changes can improve outcomes and make big savings. "If you document what you are doing, and inform patients what to expect of this hospital stay, and how they can help to mobilise after surgery, for example, it significantly decreases the number of complications and shortens hospital time," says Naredi (see Physician-led change box, p 9).

Originally developed for use with patients undergoing colorectal surgery, ERAS protocols have now been developed for many other operations, which are being continuously tested and updated. The ERAS Society, says Naredi is a great example of a collaborative approach to learning and spreading best practice.

The use of collaborative learning, documenting and comparing outcomes, and critical reviews that involve everyone who plays a role in care could determine which countries with poorer cancer outcomes succeed in closing the gap with the best.

Borras says that one of the key lessons from working to improve outcomes in Catalonia and at a European level is that you cannot cut and paste from cancer plans in other countries, especially because resources and priorities are not the same.

"People need to think carefully about their own reality. What can they realistically do in practical terms to improve the situation?"

Are the radiologists and pathologists present in team meetings? Do you have the technical capacity to fix problems with the radiotherapy equipment you've just invested in? "The best thing they can do is learn from what they are doing. Learn from their outcomes and the outcomes of other teams, look at the interaction between specialities and how that can be improved." It is often very simple practical things that make the biggest gains in outcomes, he says.

Selby points out that we know what those things are because they've been documented, often repeatedly, replicating knowledge that is already out there. "What is needed now is to apply all this knowledge to the different realities across Europe."

That is why he is calling on mid-career cancer professionals to become 'champions for change' – and calling for a change in focus from defining what should happen to equipping these champions with the knowledge and skill to make sure that it actually does.

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Reciprocity in informed consent — a fairer framework for first-in-human trials

Patients play an integral part in the clinical trial process that enables new treatments to be approved and adopted into clinical practice. Without patients, no trials can be undertaken, and thus no drugs can be approved or new standards of care established. Yet, the informed consent process in relation to trial participation indicates that patients are the risk takers in this scenario. The commitment of the trial sponsor to ensure necessary due diligence in deciphering adequate drug dose information with regards to safety and efficacy is often lacking. Is this situation fair?

What prompted this question was listening to a fascinating discussion on the ethical considerations of phase I oncology trials that unfolded at the October 2017 meeting of the Cancer Research UK Centre for Drug Development. Defining the risk–benefit criteria for participation in a phase I trial is not straightforward. Physicians act in the patient's best interest to ensure trial participants derive maximum benefit and minimum harm. While therapeutic intent is one aim of first-in-human phase I trials, it is secondary to the overall goal to determine the dose and safety of the drug being tested. To obtain a societal benefit, however, the patient in a trial should not undergo harm. Critics have suggested that trial participants offer too much for a high risk with little benefit.

How can we mitigate risk and maximise benefit? What is deemed acceptable risk and adequate gain in a situation when safety cannot be guaranteed? Early clinical safety testing standards have been established to help reduce risk. For instance, the design element and starting dose used in a phase I trial should be considerably below the dose limit likely to cause adverse events. For the first dose being tested, one strategy is to enrol one patient at a time and not on the same day as another patient to limit risk. Although dose-escalation decisions are based on observed toxicity in relation to maintaining efficacy, an inherent tension is created in the steps that are aimed at reducing risk and those that increase the dose to determine the recommended phase II dose (RP2D) in phase I trials.

Lisa Hutchinson is a Trustee of the Foundation for World Health, London, and founding Chief Editor of *Nature Reviews Clinical Oncology*

Patients must understand the pros and cons for them

Therapeutic misconception still exists around informed consent. In one survey, almost 70% of patients assumed they would benefit from a phase I trial. Consequently, what a patient understands in terms of likelihood of personal benefit may ultimately represent an unrealistic patient optimism. Therefore, the possibility of experiencing a life-threatening or severe adverse event in order to address a research question can create an uncomfortable scenario for vulnerable patients. It is important for patients to understand trial objectives and their own risk-versus-benefit gains. However, some clinical trial informed

consent forms can be up to a staggering 40 pages and are typically written in technical language that is not easy to understand. In these situations, the nuanced discussion between the patient and physician regarding personal risk–benefit might not materialise when a patient signs an informed consent form. Moreover, the doctor has to shoulder the responsibility of knowing what is relevant for the patient to know and understand in their personal situation when they are entered onto a phase I trial.

It was commented in this meeting that some companies that sponsor trials are insisting on mandatory patient biopsies in order to study how the biology of a tumour changes in response to therapeutic pressure. Whilst this stipulation is understandable and rational in light of the precision medicine era, for those with a primary or metastatic tumour located in a difficult-to-sample location (such as for some lung cancers), such expectations would border on deviating from the Hippocratic Oath of 'first do no harm'. Most patients entering phase I trials have advanced disease with a poor performance status and poor prognosis, so stipulating multiple biopsies is a big ask. Currently, the onus is on each individual patient to provide signed consent to enrol in early-phase trials. As the benefit to the patient is uncertain in such trials, the added expectation to provide tissue for molecular analysis, potentially involving repeated painful and invasive biopsies, raises considerable concern about the ethical considerations and the purpose served by informed consent.

Towards a fairer framework

Perhaps some degree of reciprocity in the informed consent process would represent a fairer situation. Detailed pharmacokinetic and pharmacodynamic analysis would better determine the minimally effective dose after which further dose escalation adds to toxicity but does not improve efficacy. This is unlikely to be the same for every patient in the phase I trial, which means a dose range should be tested in phase II trials, with the purpose of deciding how to select the right dose for the right patient. Currently, the RP2D that results from a phase I study is typically a single dose that may be associated with a toxicity level that is unacceptable, and might be many times higher than the minimally effective dose. Conversely, it might also be too low a dose for adequate efficacy, especially when subsequent trial testing is performed in an earlier disease setting.

If sponsors had to sign a commitment to perform optimisation work, it may give patients on the trial the best chance of benefit, and maximise the improvements for future patients by ensuring that when new drugs reach the market, we would have a good idea about optimum dosing and cost-effectiveness. It must be possible to achieve a consent process without a cumbersome 40-page consent form. The entire consent form should be brief, consisting of a few pages, which could include a reciprocal component overseen by an independent governing body on behalf of all patients to stipulate safeguards. Furthermore, it could provide a means of promoting an informed and nuanced discussion between doctor and patient about the pros and cons of entering the trial.

"If sponsors had to sign a commitment to perform optimisation work, it may give patients on the trial the best chance of benefit, and maximise the improvements for future patients"

This reciprocity would surely improve our existing drug development and clinical trial process to provide a more transparent, fairer framework for first-in-human and subsequent trials. In later-stage trials that assess an investigational regimen or drug, a reciprocal informed consent arrangement might ensure a greater delivery in value terms. For instance, once an agent is approved it may open a path to negotiate fairer, value-based drug pricing or dosing options, with reimbursement or significant cost-reduction opportunities to healthcare providers or patients post-approval if value is not delivered. In future trials, the responsibility of testing dose variability might enhance adherence, and the translation of research findings in the real world.

Since seamless adaptive clinical trial designs are becoming more popular, a better determination of optimal dose testing in a reciprocity framework might offer a more robust route to help mitigate excessive drug pricing and deliver true value for patients.

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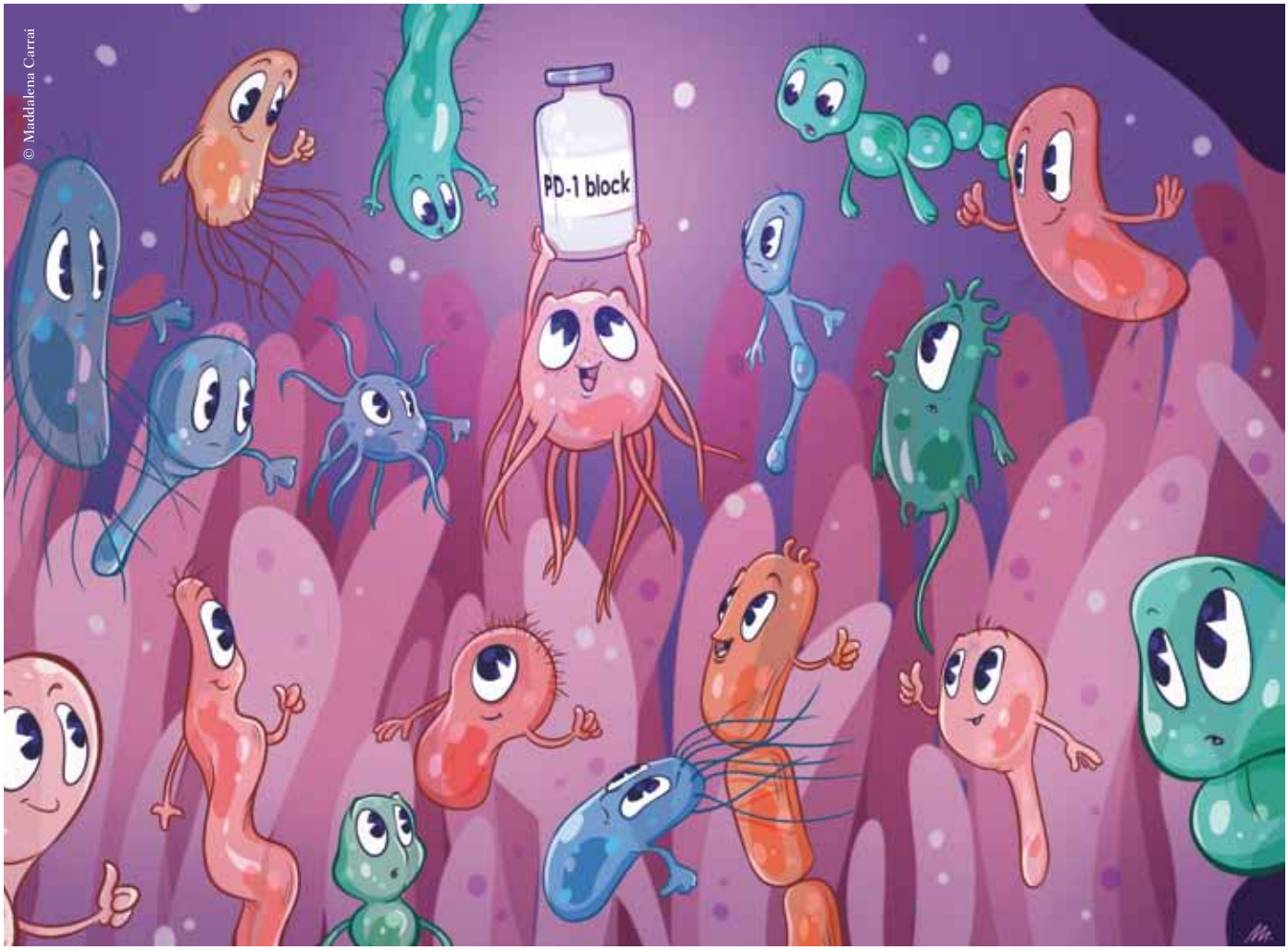


Gut response

Does benefit from immunotherapy depend on the bacteria in our intestines?

A spate of recent studies suggest that differences in population of bacteria and other micro-organisms that inhabit our intestines may be a key factor differentiating between people who respond to immune checkpoint inhibitors and those who do not. **Sophie Fessl** looks at the evidence and asks what it could mean for patients.

Accepting a course of antibiotics to clear a lung infection that has landed you in hospital might seem a no-brainer. But for the husband of patient advocate Gilliosa Spurrier-Bernard, who is trying to optimise his chances of surviving stage IV melanoma, the doctor's advice posed a serious dilemma.

The two of them had been following the growing literature showing a link between the state of the bacteria and other micro-organisms in the gut and response to immunotherapy, and they didn't want to compromise his chances.

"So when doctors wanted to give him antibiotics, we asked: Are these antibiotics really necessary? Will they affect the checkpoint inhibitor therapy?" says Gilliosa Spurrier-Bernard, who is also founder and president of the patient advocacy group Mélanome France.

"Patients are concerned that antibiotics will harm their response to checkpoint inhibitor therapy. It is their last line of therapy, and they do not want to risk their chances of a good response in an environment short on evidence," she says.

Only a minority of patients respond to immune checkpoint inhibitors, and some of these patients will stop responding eventually. Three studies published at the beginning of the year suggest that gut bacteria shape treatment response in patients treated with anti-PD-1 therapy for melanoma, non-small-cell lung cancer or renal cell carcinoma – an effect that can be replicated in mice. This may explain why not all patients respond to immune checkpoint inhibitors, and may eventually open new options to increase response rate.

The bacteria, and other micro-organisms such as archaea, fungi or protozoa, living on the internal and external surfaces of our bodies form the so-called human microbiota. Around $3x10^{13}$ bacterial cells reside in the gut alone, mostly as commensals (neither hurting nor helping the host). Some bacteria are beneficial to their host and interact with intestinal cells to prevent infestation by pathogens, synthesise vitamins, and much more – including influencing metabolic functions, inflammation, and adaptive immunity. Which bacteria and micro-organisms make up our individual microbiota is shaped by many factors, including genetics, lifestyle, birth delivery… and exposure to antibiotics.

There is a growing body of evidence to show that a dysregulation of the interaction between microbiota and host is associated with a range of diseases, from inflammatory bowel disease to diabetes and liver cirrhosis. Preclinical data from the past five years suggest that cancer will probably be added to this list, says Giorgio Trinchieri, Director of the Cancer and Inflammation Program at the US National Institutes of Health. "For the past few years, we have known from mouse models that the gut microbiota affects chemotherapy and immunotherapy. And there has been a lot of interest in these results – in the past three years, every major academic cancer conference had a session on microbiota and cancer."

First clinical data

A trio of studies published in *Science* (5 January 2018), looking at cancer patients treated with anti-PD-1 immunotherapy, suggest that patients can be divided into responders and non-responders based on the composition of their gut microbiota. Trinchieri, who was not involved in the studies, says they represent major progress in the field, "as they start putting in clinical data."

Composition of the gut microbiota differs between patients who go on to respond to anti-PD-1 therapy and those who do not

Two of the studies, by Jennifer Wargo at MD Anderson Cancer Center, Houston, Texas, and Thomas Gajewski at University of Chicago, Illinois, analysed the faecal microbiota from more than 40 patients with melanoma before treatment with anti-PD-1 therapy. The group led by Laurence Zitvogel at the Institut Gustave Roussy, Villejuif, Paris, analysed the faecal microbiota of 153 patients with non-small-cell lung cancer or renal cell carcinoma. All groups found that the composition of the gut microbiota before the start of treatment differs between patients who go on to respond to anti-PD-1 therapy and those who do not. In addition, faecal microbial analysis in all three studies identified bacteria that positively correlate with clinical outcome.

Zitvogel's group found more bacteria from the species *Akkermansia muciniphila* in the gut microbiota of patients responding to anti-PD-1 therapy, defined by either the best response according to Recist 1.1 criteria or progression-free survival for three months.

Gajewski's group identified eight

bacterial species that predict favourable response in patients with melanoma (analysed by Recist 1.1 criteria), among them *Bifidobacterium longum*. In previous work, the group had shown that the presence of *Bifidobacterium* in the intestine of mice was associated with improved immune-mediated tumour control.

The group led by Jennifer Wargo found that patients with melanoma who responded to anti-PD-1 therapy (Recist1.1 response or stable disease at 6 months) had a high relative abundance of Clostridiales, Ruminococcaceae, and *Faecalibacterium*, while non-responding patients had a high relative abundance of bacteria of the order Bacteroidales.

Mice with faecal transplants from responding patients responded better than those with transplants from non-responders

To test whether the microbiota of responding patients contains bacteria that drive anti-PD-1 response, all three groups transferred patients' faecal microbiota into germ-free mice. All studies found that these mice reproduced the phenotypes of responder and non-responder patients. When the mice were injected with cancer cells and anti-PD-1 immunotherapy, those that had received faecal transplants from responding patients showed better responses than the mice that had received faecal transplants from non-responders.

Laurence Zitvogel and her group also looked at a large cohort of patients with advanced lung, renal or urothelial cancer treated with anti-PD-1. They found that patients who had received antibiotics within two months before or one month after beginning anti-PD-1 therapy relapsed sooner. The overall survival of these patients was less than half as long as that in patients who had not received antibiotics.

Opportunities and limitations

"Oncologists and physicians are aware of these studies, and somewhat shocked and surprised by these results," says Bertrand Routy, lead author of the Zitvogel study. "But the results were validated by three independent groups. Even the most reluctant person faces the fact that the gut microbiota is key."

Trinchieri cautions, however, that the two melanoma studies used small cohorts for the more detailed analysis of bacterial species, which was done using shotgun metagenomic sequencing. Also these studies used different techniques for identifying bacterial species and different assessment methods to classify patients into responders and non-responders, making a direct comparison between the two studies difficult.

His caution is broadly echoed by Audrey Humphries, clinical research coordinator at the Department of Melanoma and Cutaneous Oncology at UCSF (University of California, San Francisco), who compared recent studies on the gut microbiota and immune checkpoint inhibitors in a review article published online in April 2018 (*Hum Vaccin Immunother* doi: 10.1080/21645515.2018.1442970).

"The weakness lies in the detail," argues Humphries. "Although several studies reveal a clear relationship between the composition of the gut microbiota and a patient's response to immunotherapy," she says, "there is not yet a standardised way to measure the correlation between gut microbiota and responses – so from how the experiment is set up to how the data is analysed varies among studies."

"This is a new and developing field," adds melanoma advocate Spurrier-Bernard. "The science is getting better and the links between gut microbiota and immune response are becoming more apparent. But these are correlations; studies have not established a causality yet."

What mechanism is at work?

While these studies demonstrate the importance of the gut microbiota in modulating patient response to immunotherapy, they also raise many important questions – most obviously the question of mechanism, which remains wide open.

As Trinchieri points out, the tumours studied are all located outside the colon, which means that the microbiota is not in direct contact with the tumour, "so it has to be an effect of distance." Patients probably respond to immunotherapy because their microbiota gives them a pre-existing immune response that is amplified by anti-PD-1 therapy, reasons Trinchieri. "The microbiota most likely primes cells in the patients for an effective immune response."

In all three studies, the tumours of mice who had received a faecal microbiota transplant from responding patients had a higher density of antitumour $CD8^+$ T cells, while tumours of mice who had received

a faecal microbiota transplant from non-responding patients had a high density of immunosuppressive $CD4^+$ T_{reg} cells. According to Routy, of the Zitvogel group, preliminary data points to an involvement of T-cell trafficking and dendritic cells. In their paper, Wargo and colleagues also argue for a model in which patients who respond to checkpoint inhibitors "have enhanced systemic and anti-tumour immune responses mediated by increased antigen presentation, and improved effector T cell function in the periphery and the tumour microenvironment."

But again, the mechanism behind this model is unknown, as Humphries points out. "It is unclear what cells or molecules are involved with how the microbiota communicate and influence the immune system. Though current research suggests that dendritic cells take part in the process."

A case of 'good' vs 'bad' bacteria?

The second open question is about which bacteria are most important for promoting response to anti-PD-1 therapy. All three studies showed that the gut composition differs between non-responders and responders. The researchers also identified types of bacteria suggested to be beneficial for a response to anti-PD-1 therapy. However, each study identified different 'favourable' bacteria. Why the difference?

Favourable bacteria could differ according to the type of cancer involved, or patient population, suggests Trinchieri: "The microbiota are influenced by external variables, with large geographical differences. Food, for example, influences the microbiota. So while the microbiota affects anti-PD-1 therapy, which bacteria are actually involved could differ in different places. Also, which bacteria are important could differ according to patients and tumour."

One theory suggests that it is the diversity of the gut microbiota that is important

In a recent review article, Marie Vetizou and Giorgio Trinchieri argue that "the discrepancy may in part be attributed to the small patient cohorts in geographically distant populations and different criteria for therapy response utilized in these studies," (*Cell Res* 2018, 28:263–4).

It is not even certain that a favourable response can be tied to a single bacterium, or even a specific combination of species. One theory suggests that it is the diversity of the gut microbiota that is important. "This is a huge question, and based on the current research, we suspect that the mechanism could be multifactorial," says Humphries.

"It is possible that a balance of high species diversity and an over-representation of a favourable population or species of bacteria is beneficial," though, as she points out, this is hard to measure: "How do you 'count' if, in a diverse gut, there are some bacteria that are adverse?"

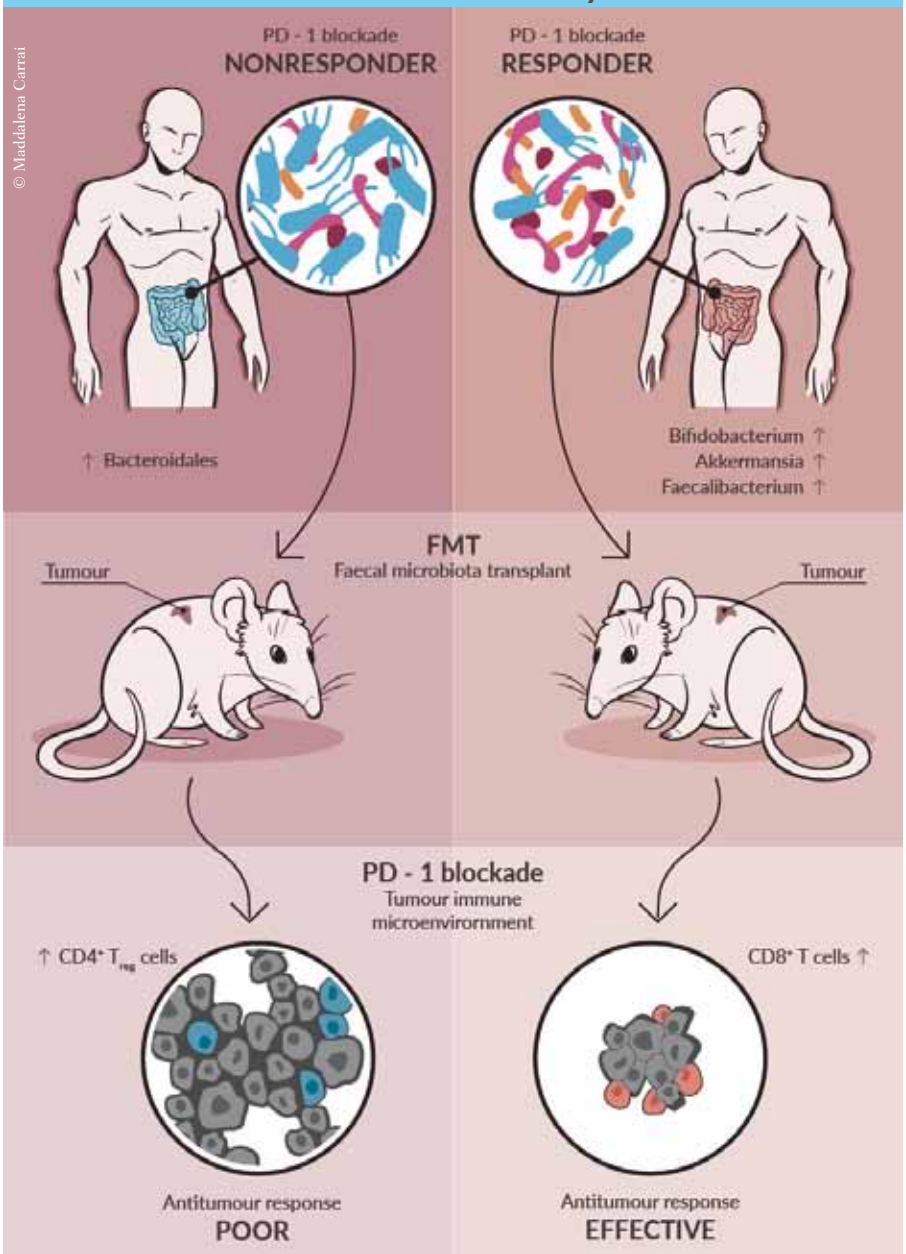
Vetizou and Trinchieri agree that the effects of the microbiota on therapy are unlikely to be due to single species, "but rather to changes in the ecology and metabolism of the gut microbiota that together affect cancer immunity. The identified species or group of species are likely biomarkers of these more complex ecological changes."

Implications for treatment and outcomes

Then comes the question of whether this new knowledge has clinical relevance. Can gut microbiota act as a biomarker to predict who will respond to therapy and eventually help select the right therapeutic option? Can the microbiota be manipulated to increase the number of patients who respond to immune checkpoint therapy? "To try to predict or induce a response, we need more data," Trinchieri cautions. Routy agrees: "Of course, the ultimate goal is to arrive at an intervention, but we are not there yet. We still have a few steps to validate before we can start to manipulate the gut microbiota of cancer patients: Which bacteria should we give to our patients? How, how often, and in which form?" Only clinical trials can provide definitive answers, and Routy, who now heads the Laboratory of Immunotherapy / Oncomicrobiome, at the University of Montréal, Canada, says he hopes to start enrolling patients in clinical trials in the next year or two. "We need to validate the importance of the gut microbiota in a larger international cohort, and develop novel biomarkers in the microbiome. But eventually, when a patient is newly diagnosed, along with a biopsy of the cancer, the microbiome will also be addressed."

Other laboratories are also planning to transfer their results from bench to bedside. Wargo's lab at the University of Texas MD Anderson Cancer Center collaborates with the Parker Institute for Cancer Immunotherapy to test the impact of anti-PD-1

Intestinal microbiota influence efficacy of PD-1 blockade



The enrichment of specific microbial populations in intestines correlates with response to PD-1 blockade in cancer patients. Faecal microbiota transplants from responders into tumour-bearing mice improved responses to anti-PD-1 therapy and correlated with increased antitumour $CD8^+$ cells in the tumours. Mice receiving faecal microbiota transplants from non-responders did not respond to anti-PD-1 therapy, and tumours had a high density of immune suppressive $CD4^+T_{reg}$ cells.

Source: C Jobin (2018) Precision medicine using microbiota. *Science* 359: 32-34.

therapy with microbiota therapy on the outcomes of patients with advanced metastatic melanoma. Gajewski and his lab are working with Evelo Biosciences to test whether giving *Bifidobacterium* with immunotherapy can increase the number of patients responding to checkpoint inhibitors. Trinchieri is collaborating closely with Hassane Zarour at the University of Pittsburgh, who is carrying out a clinical trial testing whether faecal microbiota transplant improves response to pembrolizumab in patients with PD-1 -resistant melanoma.

Implications for antibiotic use?

Although trials are only just starting, the impact of studies suggesting that gut microbiota is closely linked with response to checkpoint therapy is already starting to be felt in the clinic. In their study, Routy and Zitvogel observed that antibiotic treatment negatively affected treatment response. Does this mean doctors should change their prescribing practice?

This is a question not just doctors but also patients are now having to grapple with, says melanoma patient advocate Spurrier-Bernard. "On our forums, concerned patients are saying that they worry about taking antibiotics, or sometimes propose not taking antibiotics, because their checkpoint inhibitor therapy might not be as effective anymore. This is a problem. We say that antibiotics have saved way more lives than any immunotherapy ever will. If an antibiotic is needed, patients should not be frightened to take it."

Yet, as she points out, checkpoint inhibitors are often the last line of available therapy – and people with stage IV cancers are prepared to take

risks. "So, this is about creating a good dialogue, about honesty: patients should ask whether prescribed antibiotics will affect their checkpoint inhibitor therapy, and clinicians should be prepared to have a reasonable discussion, even if it is 'we don't know yet for sure'."

Routy echoes this concern: "Antibiotics save lives, and my biggest fear is that patients will not take antibiotics. As use of antibiotics affects the immune response, doctors should only prescribe antibiotics when they are really needed. This reinforces the importance of being thorough with antibiotic prescriptions."

Patients are also willing to experiment, adds Spurrier-Bernard: "We know that patients are already managing their diet according to what is presumed to benefit their gut flora, and also self-treating with probiotics, for which there is no real evidence yet. And people are talking about faecal microbiota transplants, for which the evidence also just isn't there yet – let alone a detailed knowledge of which compositions of gut flora are beneficial or not beneficial." Patients' biggest terror, she says, is failing to respond to, or acquiring resistance to, immunotherapy. "So they are asking what else they can do to prevent them from becoming someone who fails the treatment or gets acquired resistance. But although there is likely some amazing link between our immune system and signalling from gut bacteria, we just don't know yet what it is. At the moment, patients probably can't yet do more to help their immunotherapy response than what doctors have always advised: eat a healthy, balanced diet and continue to exercise."

Her husband is still responding to immune checkpoint inhibitors, despite having taken his prescribed course of antibiotics. "Of course, we don't want any more people dying, but we also don't want patients to do something that harms them, like trying to survive without drugs that are essential to manage their side effects and infections," says Spurrier-Bernard. "We want everyone to respond to immunotherapy, but we need much more evidence before we can say whether we can influence this by avoiding or adding other strategies."

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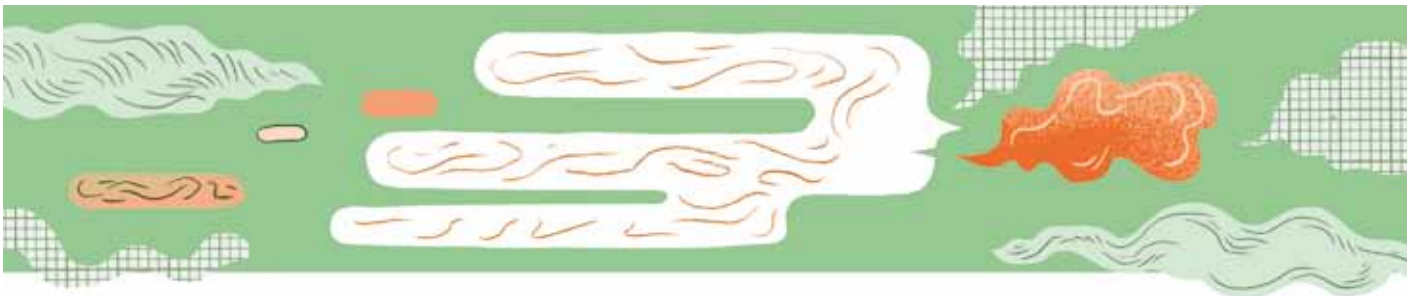

Bahadir Güllüoğlu: Driving up standards in Turkey towards the best in breast

As a young surgeon, Bahadir Güllüoğlu was drawn to specialising in breast cancer because of the opportunities that were opening up to work closely with other types of specialists, as well as with patients and their families. **Marc Beishon** talked to him about how his passion for quality, collaboration and networking is raising the standard of breast care across Turkey and the wider region.

Travelling eastwards in Europe, it is received wisdom that capacity for treating cancer decreases compared to countries such as France and Germany. This is borne out by poorer outcomes and resources, certainly in countries such as Bulgaria and Romania. But go a bit further, to Turkey – an aspiring member of the European Union – and things swing back up, which may surprise some.

This is certainly the case for breast cancer, in no small measure due to the work of Bahadir Güllüoğlu, who has helped pioneer multidisciplinary breast units in Turkey. He heads the breast centre at Marmara University Hospital, Istanbul, and is a professor at the school of medicine. His background is as a general surgeon in the 1990s following compulsory military service. It was in 1998 that he and colleagues founded the first diagnostic breast unit in Turkey – at a time when the first calls for multidisciplinary units in Europe were only just being made.

"This was a diagnostic unit, not treatment as well at this stage," says Güllüoğlu. "We had of course medical and radiation oncology in place, but for this first unit we wanted to start with diagnostic guidelines from the US and Europe, and with just three people – a pathologist, radiologist and a surgeon, which was me. We started with this because the vast majority of patients have a benign condition – 90% of patients don't have cancer, just a normal physiological change, and often just need reassurance. It was later, in 2005, that we established the other requirements for a comprehensive breast cancer unit."

Why focus on breast cancer? In the last year of his residency, in 1996, Güllüoğlu says he was much more involved in other more complex areas of surgery, such as gastrointestinal (GI). "My superiors wanted me to stay at the department, but said, 'Please don't be a general surgeon – pick a speciality, and if you can't we'll choose one for you.' After some thought, I chose not to stay with GI, but to go for breast and endocrine. It's true that GI surgery was more challenging and new laparoscopic and other techniques were coming in, and more people were interested in this,

while breast and thyroid surgery are relatively simple. In GI, you could use a lot of expensive equipment, but at that time in breast all I needed were sutures."

What attracted Güllüoğlu was a different sort of challenge: that of building patient-centred collaboration among professionals. This was something he felt he was suited for, and breast cancer was where opportunities for multidisciplinary working were opening up, as several disciplines were becoming equal partners in treatment along with surgery. In medical oncology, for example, while Güllüoğlu had long been delivering chemotherapy to patients with breast or GI cancers, oncologists were now finding their feet as a new discipline. Radiation oncologists were also playing an increasingly integral role in treating breast cancer.

What Güllüoğlu recognised is that the key work of a multidisciplinary breast unit is much more than just treating a disease – it is about human relations, communicating with colleagues and especially with patients. Of course, other cancer types have since followed breast in developing multidisciplinary approaches, but as Güllüoğlu points out, breast cancer has remained at the head of the field in terms of improvements in prognosis, thanks in large part to close international collaboration among physicians who study the biology of the disease.

This in turn has created a large community of patients and survivors who need a wide spectrum of support throughout what can be a long cancer journey – and of course they are also nearly all women, with all that entails in social and family impact, which is particularly acute in countries such as Turkey.

"I understood that the surgeon isn't the only person who can decipher codes to solve problems," he says. His idea of a team is not necessarily to have the world's best specialist in every role, but that there must be a commitment from everyone to act as mentors to replace themselves with two people who are better, and the key is to have the right people in each discipline with the all-round skills to ensure the unit develops.

The size of the problem

Breast cancer is not as prevalent in Turkey as in most of Europe. Registries currently cover half the population, and in recent years have counted an incidence of about 50 per 100,000 women, which is about half the rate in Europe and the US – although it is double the rate it used to be in Turkey in the early 1990s. One "striking finding", he mentions is that, while incidence rates were increasing up until around 2013, there is evidence they may be falling again, down to around 45 per 100,000. Another key finding regards the age of diagnosis: while in Europe around one in four or one in five cases are diagnosed in women under the age of 50, in Turkey it is about one in every two, which is important because breast cancer in younger women can be more aggressive.

"Everyone must commit to act as mentors to replace themselves with two people who are better"

Turkey does not have a national mammography screening programme, but there has been a big push in recent years to roll out early diagnosis, screening and training centres (known as KETEMs) for breast and other cancers, which offer opportunist screening. Since 2013, guidelines for breast screening recommend starting at age 40, not 50 as in most of Europe. Güllüoğlu is not in favour, arguing that there is no evidence that screening works for younger women. The rate of 'interval cancers' diagnosed between scheduled screening appointments is at least double that in older women, and breast cancers diagnosed in younger women are typically more aggressive, so local treatment is not appropriate. He cites a recent paper co-authored by leading cancer epidemiologist Philippe Autier, which examines the evidence to back this up (*Eur J Cancer* 2018, 90:34–62).

An additional problem is that younger women tend to have more dense breast tissue, which means a higher rate of recall for mammographs that are unclear. Even without these recalls, starting screening at 40 years would double the eligible population from 8 million to 16 million, which is well beyond what current capacity can handle.

Turkey is a big country with a large and growing population that will rise to about 83 million by 2023, and if it is to accommodate national invitational screening as the population ages and lifestyles become more westernised, there will be a lot of pressure on its health system.

However, breast screening rates in Turkey are still very low, at about 30%, owing to lack of awareness and resources. About one in four breast cancer patients in eastern Turkey present at an advanced stage, reflecting the lower economic development of this part of the country, and delays in treatment are common (see *Eur J Public Health* 2014, 25 1: 9–14 for a first study comparing delays with other countries). The Bahçeşehir Mammography Screening Project, a 10-year project in the Istanbul area (2009–2019), has been investigating how a population-based screening programme could work across the country. It has cut the number of breast cancers diagnosed at an advanced stage, and could be a model for other low- and middle-income countries as well as for Turkey (see *Eur J Breast Health* 2017, 13:117–122).

Europa Donna's Turkish affiliate has been active in recent years raising breast cancer awareness, as have the government and the World Health Organization, and there have been events such as a 'walking for the cure' across the Bosphorus Bridge, one of the bridges famously connecting Europe and Asia across the Bosphorus straits. Improving health literacy is key to improving services Güllüoğlu believes: "If society knows what to look for, it will urge the system to go that way."

He attributes recent falls in breast cancer incidence, which is also seen in neighbouring countries, to better management of people with a genetic risk, together with improving lifestyles – healthy eating and drinking less alcohol.

Access to quality care

While awareness, screening capacity and take-up remain barriers, the good news is that there are few obstacles to accessing a specialist consultation for anyone with symptoms. "While we have a good family practitioner system, people don't need a referral – they can choose the best university clinics or private hospitals," says Güllüoğlu.

Those who do search out the hospitals with a breast cancer team will find that many are now well resourced, both in the public and private sectors. Not only are core members of the multidisciplinary team in place, but also additional types of specialist who can be in short supply in other countries, including clinical geneticists and nuclear medicine specialists. "The equipment expected in the best centres is available too, such as gamma probes for sentinel lymph node biopsy, and digital mammography. Intraoperative radiation treatment is also available, as is molecular biology in the pathology labs."

Turkey also operates reimbursement programmes for most drugs, and, as Güllüoğlu points out, the country attracts a lot of health tourism, because charges tend to be a lot lower than in some other countries. The more than 2 million Syrian refugees currently living in Turkey get access to the same healthcare as Turkish citizens, adds Güllüoğlu, with costs reimbursed by government funds. "We are certainly much better off than our neighbours such as Greece or Romania," he says. "But will it be the same in future? We don't know. And there is still a lot to do to establish breast units as externally accredited centres of excellence."

Is there a barrier to being a male doctor seeing female patients? "I've never seen a female patient who didn't see me as a doctor. We are a Muslim country, but that is a bit separate from being a Turk; it is true though that secularism is declining currently. Of course, some patients prefer female doctors, but more often they look for the best of either gender. I find also their male relations trust you as a brother and a guardian of the woman."

Güllüoğlu with a group of nurses who have just completed the breast nursing course organised by SENATURK, January 2018

Improving outcomes

Building momentum to ensure facilities and expertise are not lost, but developed further, is a key aim for Güllüoğlu. He wears a lot of 'hats', and highlights in particular being president of the Turkish Academy of Senology (SENATURK) – "It's an independent body for breast diseases, not a government institution, which we established in 2011. It comprises mostly breast surgeons, but also other professionals in the multidisciplinary team."

> **"If society knows what to look for, it will urge the system to go that way"**

SENATURK, he says, was a logical development of meetings among professionals in the Istanbul area that he and colleagues had started in 10 years ago. "Our aims are to give education to breast cancer professionals, to do both medical and social research, and to tackle quality issues – that is very important because in Turkey (and the region) there are currently no quality metrics for breast cancer diagnosis and treatment.

"We are also working on centres of excellence. But it all starts with quality guidelines, then you teach them to people, and you need input from social and clinical research – and then you can implement a centre."

SENATURK, adds Güllüoğlu, is not just for Turkey; it has collaborations with more than 20 other countries in the region, including Greece, Bulgaria, Egypt and Lebanon – there is a particularly close relationship with Egypt, at least with professional colleagues, not between governments. Other organisations he has been involved with in the region include the European Asian Society of Breast Diseases (EURAMA) and the Mediterranean Mobile University of Mastology (MANOSMED).

SENATURK organises a range of training programmes in Turkey. The one on oncoplastic surgery enrols 50 surgeons a year from the region, with the aims of improving patients' quality of life and bringing surgeons up to the same standard of care now widely available in more well-off countries.

"Historically our only outcome was survival, and we are now lucky in breast cancer in giving most women a long survival, of 10, 20 and more years. But there are consequences to the treatment, and the main issue is now quality of life and to maintain normal appearance of the breast, as long as survival is not compromised."

Specialist surgery

It has been known for some time that, in the right patients, breast conserving surgery with radiation is as effective as mastectomy, but breast reconstruction is not easy

and can have complications. Breast conserving surgery with oncoplastic techniques is preferable, but it needs training if it is to become widely practised as a standard of care. "Sometimes the breast is very big and needs a large resection. If you can decrease the size of the breast, that's good for radiation treatment and quality of life." It does, however, also require reducing the other breast. "Resection with symmetrisation gives very good outcomes as long as surgery is a mainstay of treatment," says Güllüoğlu. The aim is to offer patients "breasts without defects, not excellent breasts", and not raise expectations too high, as a paper on the oncoplastic surgery course notes (*J Breast Health* 2017, 13:46–49).

Since 2010, Güllüoğlu has been an examiner for the European Board of Surgery (part of the European Union of Medical Specialists, UEMS). There is certainly a challenge in raising standards in Europe – the pass rate of the breast exam is usually about 70%. The standard to pass is that of a junior consultant breast surgeon, but also requires knowledge of reconstruction, oncoplastics and the latest breast research. It's not a practical exam – it's oral and written and, in Güllüoğlu's view, it is the least that should be done to test surgeons. Patients should have no hesitation in asking about their surgeon's qualifications, he says.

"There are no quality metrics for breast cancer diagnosis and treatment in the region"

He is also involved with the Senological International Society and European Academy of Senology, and he co-chairs the International Istanbul Breast Cancer Conference (Breastanbul). In short, he brings a lot of networking to his country.

Nurse specialists

Another course is on breast cancer nursing. "Breast nurses are important in the team – maybe the most important as they are navigating the patients and can help relieve the queue at my door, and they provide much needed psychological and social support. They help the relatives as well as the patients. We have taken the curriculum of the European Oncology Nursing Society and set up a 14-week course, for two days a week, with teaching on one day and the second day in the hospital, in the operating theatre, on the ward, and in the radiotherapy suite and the geneticist's consulting room. At the end we test them, and if they pass they have a certificate from the university. It's the only such course in Turkey, and we have had nurses from a number of countries including Iran, as word has got around."

"We have trained nurses from a number of countries including Iran, as word has got around"

Research

One area where Turkey does lag is in international research. Güllüoğlu and colleagues have been involved in the EORTC Breast Cancer Group and in trials such as the MINDACT project for sparing adjuvant chemotherapy, and have learnt a lot. Yet there is little currently in train, at least at international level. An obstacle is that ethics committees at Turkish hospitals do not like signing off on projects where the research is not instigated locally.

Despite the general lack of progress in metastatic disease, Güllüoğlu is optimistic. "We haven't seen anything yet; we are still at the beginning of the journey. Now we talk about 'early' and 'late' breast cancer – in future we will be talking about 'good' and 'bad' disease, as we get better at targeting, and maybe we won't even need surgery anymore for some cases if we can solve the biology. It's important to look back at the trends and see the significant progress we've made with drugs such as tamoxifen and trastuzumab, and the decline in mastectomies, and of course the rise in breast units.

"When I present at conferences I refer to myself as a breast physician, not a surgeon, partly because we treat a lot of benign disease too, but also because the other disciplines such as radiation and medical oncology are playing leading roles now. Radiation oncologists can now give some primary treatments instead of surgery. But I envisage that in future we may not be dividing the team into the same specialists, but talking about multiskilled breast physicians, or such like.

There are always problems, including increasing numbers of patients, he says. "But I love my profession – I would pick being a breast physician again if not a surgeon." … Or perhaps an engineer, chemist or psychologist? Apart from all the national and international breast cancer work, Güllüoğlu is involved with projects as diverse as building a physical teaching model for breast surgery, particle-based treatment delivery, and wellbeing and psycho-oncology research, at local institutes. If it can potentially contribute to driving up quality in breast care, Güllüoğlu will embrace it.

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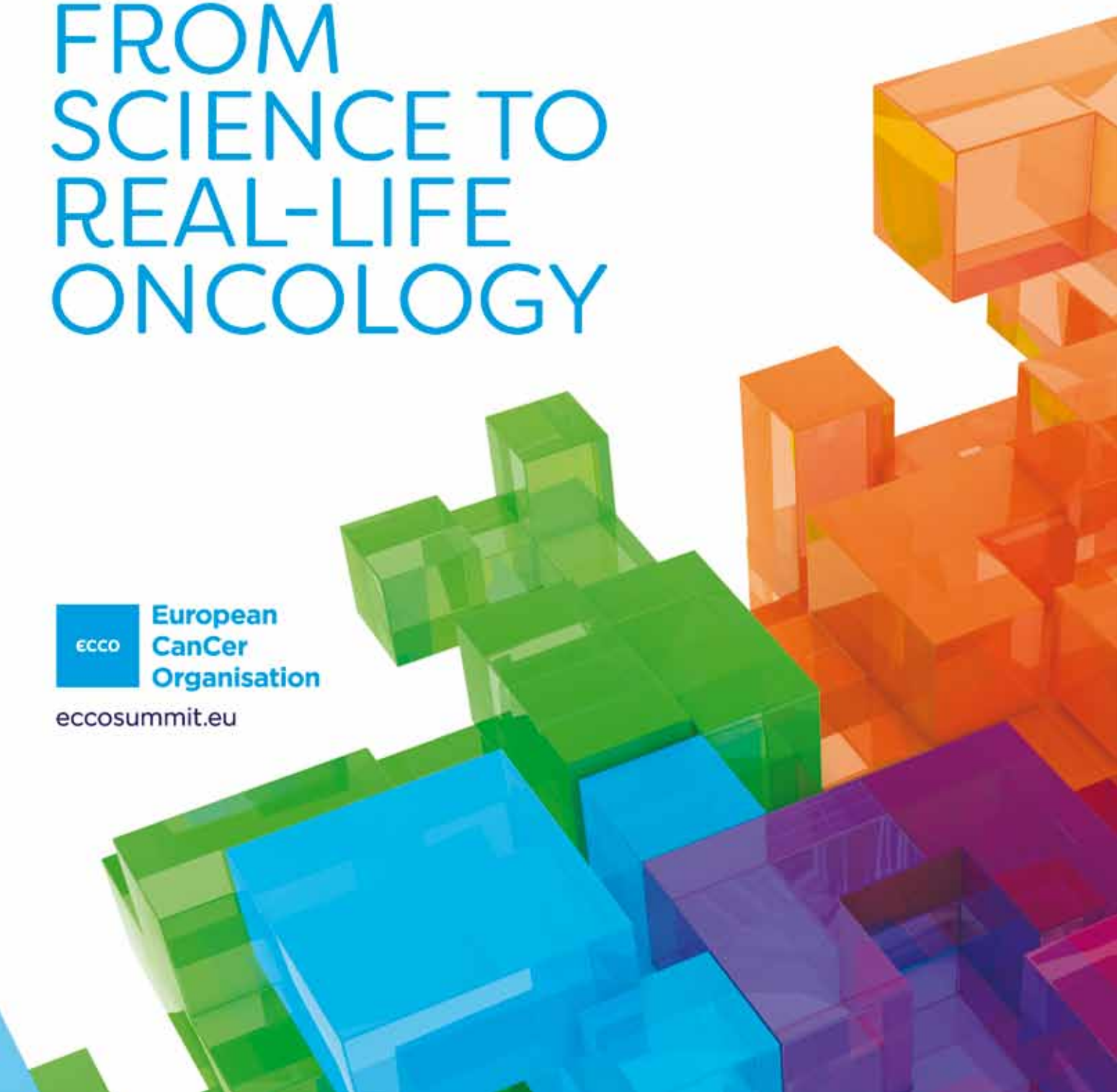

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Philip Poortmans – ECCO President (2018/2019) and head of the Department of Oncological Radiotherapy at Institut Curie, Paris

Outcomes-based healthcare –

an important opportunity for multidisciplinary care?

Cancer care in Europe must meet its good news challenges – the good news that people are living longer; scientific and medical advances are offering innovative treatment options not previously possible; and professions across the cancer care continuum are developing increasing levels of specialisation. But this good news has implications for healthcare budgets. Continued improvement in cancer care may become stalled unless the health economics challenge of cancer care is met.

Can the concept of outcomes-based healthcare provide a solution? Is it something to welcome, or should we treat it rather with healthy scepticism? It is timely for all practitioners and stakeholders in cancer care to reflect on these questions.

It is certainly true that there is misallocation of resources in cancer care. Indeed, a 2010 report by the World Health Organization estimated that 20% to 40% of all healthcare spending is wasted. It is also evident that the price tag attached to some products in cancer care, be they new medicines, medical devices, or other services, are not reasonably proportionate to the real benefit they provide over existing or alternative treatments. Furthermore, the largest investments by healthcare systems do not always go to the developments that will make the most notable differences in outcomes for the patients.

Outcomes-based healthcare therefore addresses matters of real substance. But can it deliver on its promise, and make improvements in cancer care more sustainable? Perhaps it is still too early to tell. However, as a passionate advocate for better cancer care, I can say that I *want* it to work.

Investment and spending decisions in cancer care need to be more evidence-based and less based on *ad hoc* and politicised pathways. The opportunity for improvement offered by non-commercial innovation, such as enhanced multidisciplinary and multiprofessional care and the advances of all professional specialisms, deserve to be considered as candidates for investment by health budget holders on an equal footing to propositions put forward from the commercial sector.

This is why we are putting the exploration of outcomes research, value-based healthcare and the tracking down of waste and inefficiency in cancer care at the heart of the agenda of the ECCO 2018 European Cancer Summit.

We could all usefully know more about:

- what outcomes-based healthcare really means;
- its advantages and pitfalls;
- its impact and resonance for specific areas of cancer care.

I hope you will be able to join us at the ECCO 2018 European Cancer Summit to shape the future of cancer care together!

The ECCO 2018 European Cancer Summit takes place from 7th to 9th September at the Austria Center Vienna. Information about registration and the programme is available at: www.eccosummit.eu

Mind the gap!

Who cares for patients after treatment is over?

Specialists feel responsible for their patients, but lack time to offer long-term care. Patients feel abandoned as their treatment ends, but lack resources to seek the care they need. GPs lack confidence to deal with cancer-related issues, and feel it is not their job. **Simon Crompton** asks how health systems can overcome these barriers to get cancer patients the long-term care they need to get their lives back.

The treatment is over, the cancer cured or controlled. What happens next? One, five, ten years later? For many people with cancer, 'next' is the hardest bit.

"It was this feeling that, 'I ought to be better by now,' says Kathy from the East Midlands in the UK, who finished treatment for colorectal cancer two years ago. "I've struggled lately with depression. I felt oddly guilty. It sounds bizarre, but I finally put on all the weight that I'd lost when I was ill after surgery, and everybody's saying, 'You look well, it must be so nice to be back to normal,' and it's very hard to actually say, 'No, I feel awful.'"

One reason Kathy felt awful was there was little incontinence care after she came out of hospital, and she experienced regular diarrhoea problems. "I went to see the GP, who said, 'I don't know what's going on and I can't really treat you with anything because I don't know what the hospital are doing.' It made a big hit on my quality of life because I was always scared about going out.

"There needed to be somebody who offered the support as a routine, because you're not in a very good place to go and think, 'I need some help here and I'm going to go and find out how to access it and get it myself.'"

What Kathy needed after cancer was structures recognising that treatment for a severe life-threatening illness isn't an event, but a beginning. The support needs to go on. Yet the long term has been all too rarely in the sights of cancer clinicians, researchers and funders.

There are hundreds of thousands of Kathys across Europe. Around half of those with cancer live for at least 10 years after diagnosis, and there's evidence that one in three are still struggling with physical well-being two years after discharge, and one in four have poor health over the long term. Research by the Nuffield Trust has shown that, 15 months after diagnosis, people with cancer are 60% more likely to attend accident and emergency units than the general population.

This isn't just the result of cancer, but its treatments. The late effects of treating the more common cancers, such as impotence and urinary and bowel incontinence in prostate cancer, are well documented. But there are countless others for virtually every cancer – physical, psychological, long-term, under-researched, but becoming alarmingly plain as evidence grows.

A 2016 study in the *Journal of Clinical Oncology*, for example, showed that people with multiple myeloma, non-Hodgkin lymphoma and cancers of the breast, kidney, lung/bronchus and ovary are up to 70% more likely

to develop cardiovascular disease as a result of their treatment than someone who has not been diagnosed with cancer (*JCO* 2016, 34:1122–30).

The reality of cancer long-term, then, can be a dark and mysterious place. Cancer patients making their journey into it all too often have to carry the physical and psychological burdens without support. Research from the University of Pennsylvania Abramson Cancer Center, published in 2016, found that two out of three women (65%) who had been treated for breast cancer and considered disease-free for at least three years had an unmet need for help with side effects (*Cancer Res* 2017, 77(4 Suppl):Abstract # P5-13-12).

The irony is that, while cancer is increasingly becoming a chronic disease, media and professional attention, and research and care resources, continue to coalesce around the dramatic 'cure' phase of cancer – the one-off interventions that save lives, not the measures that make the long-haul of life worth living.

As the American surgeon and author Atul Gawande recently wrote in the *New Yorker*, we may have too heroic an expectation of how medicine works. Chronic illness is commonplace and treatments have complications that require attention. "We have been poorly prepared to deal with it," he wrote. "Much of what ails us requires a more patient kind of skill."

The 'survivorship' agenda

Is the tide beginning to turn? Living with and after cancer has now become commonly known as "survivorship" – a term that doesn't go down well with all cancer patients. Some feel it implies a triumph that many don't feel, and has the same judgemental quality as "victim" and "victor". Nevertheless, survivorship is now high on the research agenda in some countries.

"Much of what ails us requires a more patient kind of skill"

In the UK, moves to improve understanding of what surviving means have been led by the charity Macmillan Cancer Support, which funds the University of Southampton's Macmillan Survivorship Research Group. This year Macmillan produced a report powerfully documenting the experience of many people like Kathy (above) after cancer treatment (*Am I meant to be okay now?* Macmillan Cancer Support, October 2017).

"There is still much to do to support those who are struggling in silence or not getting the support they need," says Claire Foster, who heads the research group. "We need to make sure we are supporting those with complex needs and those who are less likely to engage with more self-directed follow-up.

"But I think we are now learning much more about quality of life after cancer treatment and recognising that many people continue to need support to manage consequences of treatment in the years beyond treatment. Important research is going on."

Foster's own research has already uncovered interesting findings about those who may need most support. For example, depression and confidence in managing illness-related problems before treatment were found to be key predictors of quality of life two years after surgery for colorectal cancer.

People who have had cancer fall down a crack between secondary and primary care

There are now Europe-wide survivorship initiatives to try to build understanding about what is experienced by cancer patients after treatment. The European Organisation for Research and Treatment of Cancer (EORTC) is developing an infrastructure to optimise long-term follow up among patients treated in clinical trials and promote data sharing. The aim is to foster scientific collaboration on long-term outcome research (see 'Gathering long-term data on what happens next', *Cancer World* Spring 2018).

And survivorship and rehabilitation was a main work package of the EU-funded Comprehensive Cancer Control Joint Action (CanCon), which ran between 2014 and 2016. This resulted in a series of recommendations for EU countries, including personalised follow-up care plans for every person emerging from cancer treatment, and more research to provide data on late effects and the cost-effectiveness of supportive care. These are to be followed up by the European Commission's newly announced Innovative Partnership Action against Cancer.

But if Europe seems finally convinced of the importance of knowing more about long-term needs, the main challenge remains: creating services and structures that actually mean something to people who are struggling in a myriad of ways after they are supposed to be 'better'.

Redesigning services and structures

Who takes responsibility for the welfare of survivors? All too often, patient accounts suggest, people who have had cancer fall down a crack between secondary and primary care. Though health systems vary across Europe, the problem seem similar: specialist care loses interest or contact after treatment is deemed successful; general practitioners feel ill-equipped to address related issues arising; and the patient ends up feeling in no-man's land.

As CanCon pointed out in its final report, lack of coordination between secondary and primary care, lack of funding, and limited capacity mean that in most countries effective long-term support remains an aspiration rather than a reality.

"There's a recognition that secondary care just can't cope any more with the increasing numbers of cancer survivors – incidence is increasing, survival is better, people have comorbidities," says Eila Watson, Professor in Supportive Care at Oxford Brookes University and Chair of the British Psychosocial Oncology Society.

Various new models are being tested. Some are led by secondary care, using phone, postal or 'self-triggering' follow up, which allows people to get back into the hospital system after discharge if they have a symptom or worry. But many countries, such as the Netherlands, Denmark and the UK, are transferring more responsibility to primary care. To some extent, this is a response to pressures on secondary care, but it also makes sense that general practice is better adapted to providing the kind of personal, 'incremental' care that Atul Gawande believes is at the heart of good medical systems.

"We definitely need systems to provide ongoing support to those who need it, and primary care is often suggested as the place where this could happen," says Eila Watson. "But at the moment, primary care does not have a structured formalised role in terms of follow-up after the diagnosis and primary treatment are over." She says she currently knows of nowhere in Europe where this is the case.

Why is this? Why is ongoing support in primary care such a problem to organise? Lack of resources, lack of professional confidence and lack of coordinated support planning seem to be significant barriers.

Netherlands: primary care/ specialist agreed care plans?

Henk van Weert, Professor of General Medical Practice at the University of Amsterdam, believes GPs are quite

capable of providing support to people who have been treated for cancer and should lead support planning. Yet his research is indicating that many GPs are reluctant to carry out follow-up care of cancer patients because they don't feel capable of dealing with many cancer-related issues – and also aren't being paid for it.

"In the Netherlands, GPs keep on seeing cancer patients, but not on a scheduled scheme," he says "They might give support to patients as normal patients, but it will be unstructured. Most GPs I know tell me that they won't start off talking to them about cancer: they say they think the patient won't like it."

Van Weert says there is no evidence that continuing to receive specialist care long after treatment is over benefits the patient. If patients feel worried about their GP's lack of specialist knowledge, the key is to reassure them that there is quick and easy access back to secondary care. In the Netherlands, it is possible to get a patient to a specialist the next day, says van Weert. "We need to end the misunderstanding that if they start going to their GP, hospital specialists won't welcome them anymore."

He wants to see support care plans agreed between primary and secondary care. But the picture is complicated by the fact that the required support needs vary so much from cancer to cancer and patient to patient. "In colorectal cancer, for example, you'll need a fairly uniform protocolised care plan, which is quite safe in the hands of a GP. In breast cancer, defining the GP role may be more difficult because there are so many different types, and lots of the therapies that go on for years."

Denmark: redefining responsibility for follow-up

In Denmark, the government has encouraged a greater role for primary care in long-term survivor support. But following a major review examining which cancers might be best suited for GP support, it became clear that cancer specialists were often reluctant to give up control. Bolette Friderichsen, a Danish GP and Board member of the Danish College of General Practitioners, says that many hospital doctors have been reluctant to lose contact with patients because of ongoing research and fear of losing out financially.

"In turn, I'm aware that many of my GP colleagues are reluctant to take up this task because they are not oncologists, and are worried about missing late effects or recurrence. We are not trained in this."

"But the important point is that we already have these patients in our waiting rooms in general practice. They have very reasonable expectations about what their family doctor should be able to provide. So whether or not we want this task, it is on our table. We might as well lift it."

She is all too aware that former cancer patients don't know where to go for help, or simply don't go any-

Drug research failing on late effects

- Only in the past 20 years have trials of cancer treatment started to evaluate the effect of treatment on long-term quality of life, as well as classical outcomes such as survival.
- A systematic evaluation of oncology drug approvals by the European Medicines Agency (EMA) in 2009–13, published in the *British Medical Journal* last year, found that most drugs entered the market without evidence of benefit on quality of life.
- A recent analysis in the *American Economic Review* concluded that pharmaceutical company investment is distorted away from studying the long-term effects of treatments.
- This year Dutch epidemiologists reported in the *British Medical Journal* that industry-funded post-marketing studies do little to improve understanding of long-term adverse effects.

where. "I hear many of my patients say, when they come out of secondary care, that they feel like a piece of meat. They say: 'I'm very grateful for the quick and competent treatment, but I saw a different person every time I went to hospital, they didn't tell me what I need to know, and I was confused. What went on? Where am I now? Am I cured?' It's almost as if they have symptoms of post-traumatic stress disorder."

It is the GP's role, she says, to be able to address this. "The comprehensive and continuous care gives us some possibilities that oncological specialists do not always have," says Friderichsen. "Of course, my patient needs to be assured that we can get help from other specialists when there is a problem. But little by little I want my patients to know that I am another kind of specialist than a hospital specialist. I am a specialist in my patients.

"At a hospital appointment, when you see a different person every time, does a woman who has had breast cancer get the chance to talk about issues to do with sex – for example, if her husband feels awkward about touching her new breast? In hospital, will they be able to spot depression coming on, or give people the opportunity to talk about feeling guilty that they are sad even though they have survived?"

World's first GP guidelines

The Danish College of General Practitioners has just completed what are believed to be the world's first guidelines for cancer follow up in general practice. Work on this has been led by Friderichsen. The aim is to give GPs more confidence in dealing with cancer. The first part addresses the need for family doctors to keep in contact with people being treated for cancer, and gives guidelines on touching base with the patient after active treatment has ended, addressing any psychosocial issues, and agreeing a personalised support plan that also takes into account the comorbidity issues. The second part is more biomedical, providing a basic oncological knowledge base with details about adverse and late effects, and guidance on early palliative treatment.

"Little by little, I want my patients to know that I am another kind of specialist. I am a specialist in my patients"

The devil of the detail, predictably, relates to how this is coordinated with secondary care. Like Henk van Weert, Friderichsen believes it is crucial that patients know they can be referred back to secondary care almost instantly if there is a hint of recurrence.

Under Danish cancer packages, former patients can get back to the hospitals and specialists that treated them before. But the responsibility of coordinating the whole of a patient's cancer journey is still fraught with difficulty.

"There are so many different models of organising services, even in a small country like Denmark," says Friderichsen. "There's a political aim of having one 'patient-responsible' doctor you always refer to in a hospital. We suggest that the family doctor works in partnership with the patient-responsible doctor in the hospital, but we have some doubts about how well the patient-responsible doctor scheme will work, because they have so many other priorities."

What if long-term supportive care were given a national priority, so that across the country structures that overarched primary and secondary care ensured that the wide-ranging physical and psychosocial needs were met?

France: extending multidisciplinarity to primary care

That is the model being aimed for in France, where survivorship care has been a focus of the National Cancer Plan, launched in 2009. According to Claudia Ferrari, head of the Care Pathways Department at the Institut National du Cancer, and one of the authors of the CanCon recommendations, finding ways to effectively coordinate survivorship care plans between primary and secondary care is key.

"We're very aware of this," says Ferrari. "Our systems are very hospital-centred at the moment. The difficulty is to link hospitals and primary care, because they function with a different logic. Hospitals are more inclined to retain what they have done, because they have their own resources, instead of sharing it with primary care."

But gradually, and step by step, things are moving forward as the national cancer plan drives the concept of survivor care plans – and crucially, according to Ferrari, allows resources to be mobilised.

New multidisciplinary platforms that include nurses, social workers, psychologists, nutritionists and other health professionals are now being established outside hospital structures to support people when they leave secondary care. A trained co-ordinator – most likely a nurse – will coordinate between primary and secondary care, ensuring there is sufficient oncology input if necessary. "We know that this kind of coordination works at hospital level, but we still have to work on coordination with the primary care professionals," says Ferrari.

To address this, the Institut National du Cancer is leading the development of a new national guide to support patients and the professionals involved in their care, as they leave secondary care, along with a framework for minimal standards in follow-up care plans. The guide will alert people to the issues that may arise after treatment, explain the need for a follow-up plan, set out healthy lifestyle issues, and provide access to patient organisations and networks of support.

Ferrari stresses that France does not yet have all the answers. But she knows that multidisciplinary teams and good co-ordination are absolutely fundamental. "We don't want patients to fall in the gaps of a very complicated system. If we are not able to create something which is simultaneously simple and effective, no one will put it into practice. So it's step by step, by hospitals and GPs in parallel."

UK: Finding a national solution

In England, as in France, the key to progress – even if slow – seems to be making what happens 'after cancer' a national policy priority. The National Cancer Survivorship Initiative was launched by the Department of Health and Macmillan Cancer Support in 2010, and researched best practice, piloted ideas, and developed recommendations which gave rise to Macmillan's Living With and Beyond Cancer Programme. This aims to improve local cancer services, with planned and tailored support for every person leaving treatment.

Various arrangements are being piloted across the UK but, as Eila Watson points out, there will not necessarily be one single national solution. "I think there's definitely a general move away from consultant-led follow-up, but I don't know if you ever get one universal way forward," she says. "You need some sort of core underpinning principles about the best way to organise services, while also recognising that you need flexibility to suit local health service set-ups. I think that nurses, whether clinical specialists or primary care practice nurses, are likely to have a key role in most arrangements."

The key to progress seems to be making what happens 'after cancer' a national policy priority

The irony is that, given the universal shortage of health resources, making long-term support personal, incremental and local requires the coarse population-based strokes of national policy. And even then, progress is too slow for many people to notice. The cracks remain, and as the personal testimony provided by the new Macmillan report testifies, sometimes it seems there will never be a way out.

"I had to find all the help myself, whether that was trying to get referrals for cognitive therapy or meditation, it was just me that was doing it," said Frances, from Leeds, who finished treatment for Hodgkin lymphoma four years ago, and found that physical problems continued, and anxiety problems were just beginning. "When I look back on that initial year, the support definitely dropped off a cliff, and the effects are lasting."

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In this Issue:

Karol Polom, Chair of EYSAC (ESSO's Young Surgeon and Alumni Club), Assistant Professor, Medical University of Gdansk, and University of Siena

Young surgeons learning to lead

Leadership skills are becoming ever more important as we attempt to navigate the increasingly complex healthcare landscape. Young surgeons across Europe are therefore joining forces through ESSO's Young Surgeon and Alumni Club (EYSAC) to foster these skills together. Junior surgeons are not alone; we are team members in our local hospitals or universities, and part of a national network of colleagues and a European movement of young surgeons sharing the belief that together we can achieve more.

We intrinsically advocate for our patients in our daily work, but when we join forces we are able to raise training standards and develop new avenues for cancer surgery across Europe. EYSAC facilitates networking between young surgeons interested in surgical oncology so we can develop partnerships, collaborate with likeminded individuals, and share our passion for what we do.

Through our peers and mentors at ESSO–EYSAC Surgical Training Hands-on Courses, we learn innovative ways to enhance our skills, improve our clinical results and overcome surgical challenges. Understanding a situation from a broad perspective and processing different approaches is part of an ever-evolving mindset. In order to embrace medical breakthroughs we must first understand that change is necessary. EYSAC capitalises on its multinational membership through our young researchers' activities by conducting European and worldwide studies.

Good leaders extend opportunities to others to enable them to move ahead. Sharing useful resources and career-advancing prospects and supporting each other can help to unlock everyone's full potential. EYSAC's social media platforms (Twitter, LinkedIn, Facebook) provide a space for young surgeons to discuss areas of interest and exchange information. Communication and cooperation improves the efficiency of the team in the theatre, and advances the wider network of surgical oncologists working towards a common goal. You will never enjoy the maximum potential of your influence until you create opportunities for others.

All surgeons already possess the attributes of a leader but *leadership* is a learned skill. Taking on progressive responsibilities and engaging in extraprofessional activities enables us to recognise these skills within ourselves, actively nurture them, and continue to develop them throughout our careers. There will come moments when our responsibilities may feel overwhelming, but with the right support and enthusiasm we can learn techniques to regulate our workload and manage our time early in our careers.

It is passion that cultivates great leaders. Leadership is not about status or title; it is about impact, influence and inspiration. Influential surgeons have the capacity to help a healthcare institution grow, to progress resident education, and to catalyse the necessary changes to improve patient outcomes.

EYSAC at ESSO38

Join us at ESSO38 on 10–12 October 2018 in Budapest, Hungary, for the following Young Surgeons and Alumni Club (EYSAC) sessions:

Education Workshop: *Virtual Reality / Artificial Reality & Training (EYSAC session)*
10 October 09:00–11:00

Young Surgeon's Mentorship Session: *Clinical Research in Surgical Oncology (EJSO session)*
10 October 12:45–14:00

Young Surgeon's Mentorship Session: *Young surgeons and their career path – "better outcomes with innovative surgery"*
11 October 12:45–14:00

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IMPORTANT DEADLINES

- Abstracts and travel grants: **6 May 2018**
- Early registration: by **17 June 2018**
- Late registration: by **23 September 2018**
- On-site registration: from **24 September 2018**

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INSIDE TRACK CONFERENCE

Hereditary mutations in cancer: the use of panels and genetic counselling

Testing for hereditary mutations that increase the risk of cancer is important for risk reduction, early detection and choice of treatment. **Ephrat Levy-Lahad** offers an overview of what we know – and what remains uncertain – about the rationale for testing, the risk implications, and how to discuss these with patients and families to enable them to make informed decisions.

This grandround was first presented by Ephrat Levy-Lahad, from the Shaare Zedek Medical Center, Jerusalem, as a live webcast for the European School of Oncology. It was edited by Susan Mayor. The webcast of this and other e-sessions can be accessed at e-eso.net.

Germline testing is carried out first for the cancer patient and second for the patient's relatives. For the patient, testing has implications for treatment. One example is the extent of surgery. If breast cancer occurred because of a genetic risk, the patient might elect to have bilateral mastectomy even if lumpectomy was sufficient for management of the cancer itself. For colon cancer, if there is a genetic predisposition, the surgeon might choose to perform a wider excision compared with non-hereditary colon cancer.

Non-surgical treatments may also be tailored, e.g. PARP inhibitors for ovarian cancer in *BRCA1/BRCA2*/Fanconi pathway carriers, or avoidance of radiotherapy in *TP53* carriers. Beyond treatment of the cancer itself, if the patient has an inherited predisposition they may be at risk for additional tumours, and these also need special surveillance and treatment. For example, a *BRCA1*

carrier with breast cancer is also at risk for ovarian cancer, and a female patient with Lynch cancer syndrome is also at risk for endometrial cancer.

The other important people in this equation are the relatives. Once we find a mutation in a patient, we can test the relatives to find out whether or not they inherited the mutation. Non-carriers in the family generally have background risk and do not require special surveillance or prevention options. Carriers have increased risk and should be given the opportunity of special surveillance and prevention.

What are gene panels?

Gene panels are essentially tests based on Next Generation Sequencing (NGS), which can test multiple genes simultaneously. There are two main types of panel:

- Tumour-, organ- or syndrome-specific, such as a colon cancer panel or the hereditary breast/ovarian panel,
- Pan-cancer panels that include all of the known hereditary predisposition genes. These include many more genes than the tumour- or syndrome-specific panels.

We can generally distinguish three types of gene on panels:

- Established hereditary cancer genes known to cause specific cancer syndromes. Examples include *APC* in colon cancer, *BRCA1/2* for hereditary breast/ovarian cancer and *VHL* for Von Hippel-Lindau renal cancers,
- Genes more recently identified as having strong evidence for being cancer predisposition genes, e.g. *RAD51C* for hereditary breast/ovarian cancer and *GREM1* for colon cancer.
- In the third category, which is more problematic, are genes with lesser evidence where the risk for specific cancers is unclear.

Generally speaking, there is a core list of genes included in practically all panels. These include the established hereditary cancer syndrome genes and those with strong evidence of association with specific cancer risks. However, genes with lesser evidence are more variable between panels, and there is no single consensus list of genes that are found on all panels.

Why are some genes with less evidence included on gene testing panels?

Some genes are included in panels because of 'guilt by association'. Over the last few decades it has become very clear that mutations in DNA repair genes are common causes of hereditary cancer predisposition. For example mutations in genes involved in mismatch repair such as *MLH1* and *MSH2* cause Lynch syndrome. *BRCA1/2* and *PALB2* are all part of the Fanconi anaemia pathway, which is important for homologous recombination DNA repair.

The involvement of DNA repair mutations in inherited cancer predisposition is quite logical because defects in DNA repair lead to mutation accumulation, and this is thought to lead to tumourogenesis (see figure opposite). However, the fact that a particular gene is part of a specific DNA repair pathway does not necessarily mean that mutations in this gene will be associated with a specific risk. *CHK1* or *ATR* are often included in panels, although it is, as yet, unclear whether they are associated with predisposition to cancer, and if so, for which specific cancers.

In general, we can distinguish high-risk or high-penetrance genes versus those that are associated with moderate or low risk. High-risk genes are generally associated with a relative risk for a particular cancer that his more than four times the risk in the general population. Moderate-risk genes confer a relative risk of between two and four times that in the general population. Low-risk genes have a relative risk of less than two.

There are also specific variants that can be associated with different levels of risk. For example, although *APC* and *BRCA2* are both very-high-risk genes, there are specific mutations that are associated with low risk, such as the I1307K mutation in *APC* and the polymorphic stop p.K3326X mutation in *BRCA2*. Finally, there are genes without any evidence-based risk, and so there are no guidelines on how to treat patients with mutations in these genes.

How to act on the results of a gene panel

Technically speaking, the result of a gene panel is the identification of a variant. The American College of Medical Genetics introduced a five-category – or five-tier – system that is now commonly used. Variants can be 'pathogenic' or 'likely pathogenic', in which case they are reported. They can be 'likely benign' or 'benign', in which case they are not reported.

In the middle, there is a 'black box' of variants of unknown significance (VUS), and whether or not these are reported is a matter of lab policy. Some labs report VUS and some do not.

Identification of a variant is the technical result. However, as clinicians we would like to have a 'bottom line', with a result that is either positive, indeterminate or unclear, or negative:

- A positive result is when a pathogenic or likely pathogenic mutation is identified in a high- or moderate-risk gene.
- An indeterminate result is the identification of a variant of unknown significance in a gene known to be important, or any variant in a gene with unclear significance.
- A negative result can be a true negative in the sense that the patient has no inherited predisposition. However, a negative result depends on the state of current knowledge regarding the particular genes tested. A patient with a very young age of onset or significant family history might have a genetic predisposition for their cancer, even though the particular gene has not yet been identified.

What are the pros and cons of panel testing?

The main advantages of panel testing are that it is fast and provides simultaneous testing of multiple genes. This is important, particularly if there are many genes that can cause a particular cancer or cancer syndrome. It is also helpful in time-sensitive situations, such as when a quick decision is needed on the surgical approach.

Testing gene by gene risks patients being lost to follow-up, while simultaneous testing for several genes means fewer patients will not complete testing. The cost is much cheaper, with the cost of a panel being about the same as classical sequencing of a single gene. Panels are also less syndrome-specific, which means clinicians are less dependent on family history.

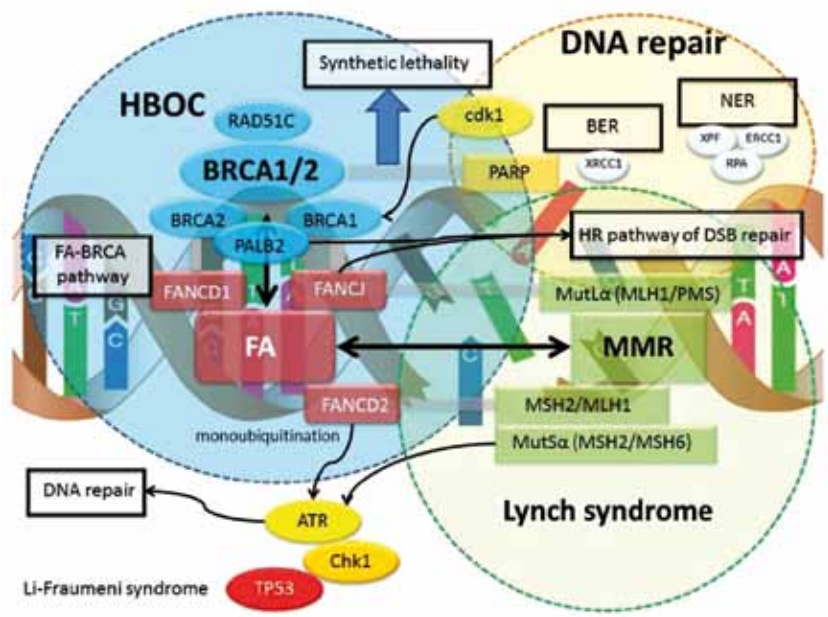
The cons of panel testing are mainly related to the fact that we can test for a lot more than we can understand, limiting interpretation of results. Some genes included in panels have limited evidence, and no guidance for clinical action.

Variations of unknown significance occur at a frequency of 10–40%, depending on the lab policy for reporting and the number of genes tested. The larger the panel, the more genes are first tested and the greater the chance of finding a variation of unknown significance.

This has significant unwanted outcomes, and often leads to over-treatment or over-screening because it is very difficult to ignore a variant once it has been identified.

An additional problem is the issue of quasi-incidental cancer mutations, which means finding a pathogenic mutation in a gene that is not related to the patient's cancer. For example, finding a Lynch syndrome mutation in a breast cancer patient may mean the Lynch mutation caused the breast cancer, but this is often unclear.

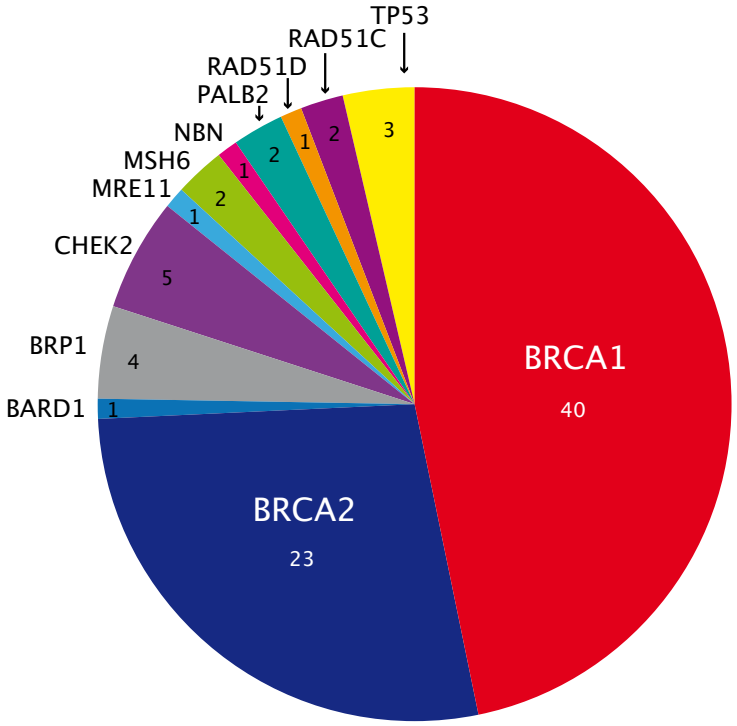
DNA repair genes in hereditary cancer



These DNA repair gene mutations are common causes of hereditary cancer predisposition

Source: H Kobayashi et al. (2013) *Oncol Rep* 30: 1019–29, republished with permission

Yield of panel testing for ovarian cancer



A prospective study of women diagnosed with ovarian cancer, not selected for family history or age, showed inherited mutations in 23% of patients, with *BRCA1/BRCA2* mutations accounting for the majority (18%)
Source: T Walsh et al (2011) *PNAS* 108: 18032–37, republished with permission

Yield of panel testing for specific cancers

Breast cancer

Breast cancer has been the most extensively studied cancer with regard to the yield of testing panels. In patients who have already tested negative for *BRCA1/BRCA2* mutations, the chance of identifying a different mutation in another gene is around 5%. In a patient who has had no genetic testing, panels including *BRCA1/BRCA2* will have a total yield of around 15%: 10% will be *BRCA1* or *BRCA2* mutations, and about 5% will be in other genes, mostly moderate-risk genes such as *ATM* and *CHEK2*. Overall, *BRCA1/BRCA2* account for most of the currently identifiable high-risk genetic predisposition for breast cancer.

Ovarian cancer

A study in ovarian cancer showed significantly higher overall yield, at over 20% (*PNAS* 2011, 108:18032–37). More than two-thirds are mutations in *BRCA1* or *BRCA2*, but there are also mutations in genes such as *TP53* and *CHEK2* (see figure above), which are not clearly linked to ovarian cancer.

One in three patients with mutations were diagnosed after the age of 60. More testing in larger numbers of individuals shows that even individuals with little family history and those of older age can have inherited mutations.

Colon cancer

The yield of panel testing for colon cancer is about 10–15%. The distribution includes more high-risk genes and fewer moderate-risk genes compared to breast cancer, with a lower predominance of particular genes and greater heterogeneity of the genes involved (*Annu Rev Genom Hum Genet* 2017, 18:201–27).

There may be more clearly pathogenic results in colon cancer, with fewer variations of unknown significance (*Gastroenterology* 2015, 149: 604–13). However, this could be a result of patient selection, as many tumours today are tested directly for mismatch repair deficiency either by microsatellite instability or immunohistochemistry for MMR proteins, such as MSH2, MSH6 or MLH1.

Perhaps panel testing is more likely in patients who have already been shown to have MMR deficiency and are, therefore, more likely to harbour inherited mutations.

Pancreatic cancer

In pancreatic cancer a recent study found that 3.5% of patients were carriers of known genes (*JCO* 2017, 35:3382–90), including 0.4% carriers of mutations in candidate genes.

Mutation distribution was somewhat different from other cancers, with *BRCA2* and *ATM* accounting for almost 70% of mutations; *BRCA1* was a much more minor player, as were *PALB2* and *MLH1*. The important message regarding pancreatic cancer is that the variants identified, although rare, are targetable. This has clear therapeutic implications for utilising PARP inhibitors (*BRCA1* and *BRCA2, ATM, PALB2*)

or immune checkpoint inhibitors (*MLH1*).

Prostate cancer

A 20-gene panel of DNA repair genes identified deleterious variants in 11.8% of men with metastatic prostate cancer (*NEJM* 2016, 375:443–53). This was much more common than the rate of 4.6% seen in men with local prostate cancer, and the 2.2% rate found in population controls from the Exome Aggregate Consortium, which assesses the frequency of variants in tens of thousands of individuals.

This is an important point, because many previous studies have only collected data on the frequency of variants in patients with cancer, without comparing their frequency to that in the general population.

The prostate cancer study also showed that age at diagnosis and family history did not significantly affect yield. The mutation distribution of prostate cancer was somewhat reminiscent of that for pancreas cancer. The major culprit was *BRCA2*, accounting for 44% of mutations; next was *ATM*, with 13%. *CHEK2* and *BRCA1* were more minor players.

Again, this has therapeutic implications, because olaparib, the oral PARP inhibitor, has been approved by the FDA as a monotherapy for previously treated, metastatic, castration-resistant prostate cancer for people with *BRCA1/2* or *ATM* mutations.

Renal cancer

Considering renal cancer as an example of a less common cancer, a 19-gene panel found that 6.1% of all renal cancer patients had a mutation (*Cancer* 2017, 123:4363–71). The most common mutations were in the *FLCN* gene (1.8%), which causes a cancer syndrome known as Birt-Hogg-Dubé.

Fumarate hydratase mutations occurred in 1.3% of patients, and the mutation rate in *VHL*, which is a canonical renal cancer gene, was only 0.2%. This could be a result of prior selection, i.e. if patients with a clear history suggestive of Von Hippel-Lindau had single-gene testing, and thus those found to have *VHL* mutations were not tested using panels.

There was a high rate of variations of unknown significance (18.4%), often in large genes or genes that have pseudogenes (genomic DNA sequences similar to normal genes but non-functional) that complicate testing, such as *TSC2* (tuberosclerosis 2 gene), *MET* and *PMS2*.

Pan-cancer panels

A 76-gene panel tested in 1,040 patients (median age 58 years) with advanced cancer showed that 17.5% had a clinically actionable mutation (*JAMA* 2017, 318:825–35); 14% had a moderate- or high-penetrance mutation. Half of these would not have been detected based on their family history, age or tumour type. Only about 4% were actionable for targeted therapy in the patients.

Regarding the distribution of mutations in this study, about 40% of mutations were either in *BRCA1* or *BRCA2*. *BRCA1* was more specific for breast and ovarian cancer, but *BRCA2* was associated with a much wider spectrum of different cancers.

Panel yield: overview

- Current studies of panels indicate a 5–15% yield overall, depending on cancer type, but some studies have detected higher rates
- Rates of variations of unknown significance are between 10% and 40%.
- Most studies do not compare mutation rates in patients against controls.
- Figures are likely to be overestimates due to ascertainment bias, because people participating in studies generally have younger than average age of onset and are often more severe cases.
- Gene distribution may be biased by previous single-gene or family-based testing.

Resources to help manage patients with a reported variant

ClinVar (short for clinical variation) is provided as a general resource by the US National Center for Biotechnology Information (ncbi.nlm.nih.gov/clinvar/). It enables searches by gene and by variants within genes, showing how the variant has been classified and the evidence for the classification.

It is becoming increasingly useful for understanding variants as more information is added. There are also gene-specific databases, including for *BRCA1*, *BRCA2* and *TP53*, and databases for Lynch syndrome and other hereditary cancers.

A number of guidelines provide information on care and follow up for patients with pathogenic or likely pathogenic variants in specific genes, in addition to prevention and surveillance guidance for relatives who are known to be carriers.

For example, the US National Comprehensive Cancer Network (NCCN) guidelines are updated annually and include recommendations regarding multiple genes, including genes for hereditary breast and ovarian cancer (including *ATM*, *BRCA1/2*, *BRIP1*, *CDH1* etc) and for colon cancer (including *APC*, with a separate recommendation for the I1307K mutation, *BMPR1A* etc).

Genetic counselling for panel testing

Genetic counselling has traditionally been given both before testing, to allow the patient an informed decision about whether to be tested, and after testing, when the results are available.

The patient should be made aware of all the ramifications of testing before they make a decision to be tested. This tends to be less of a concern for cancer patients, who are often very interested in testing, as it could impact their treatment.

Pre-test counselling

Pre-test counselling should include a discussion of the concept of inherited cancer risk and a detailed review of the pedigree, including ethnic background, overall family structure, age(s) at diagnosis and type(s) of cancer in affected family members.

It should provide information on gene mutations of interest and explain that different mutations have different cancer risk. It is not realistic to detail risks for every gene tested, but the aim should be to give an idea that some mutations are high risk, while others lead to moderate or low risk, or are of unknown risk.

Pre-test counselling should explain options and limitations of surveillance and prevention. Specific mention should be made of high-penetrance syndromes with impactful management strategies, such as *CDH1* mutations and prophylactic gastrectomy.

Patients need to know that they might be offered quite aggressive measures. We should discuss the possibility of getting uncertain results and variations of unknown significance. The implications for other family members should also be discussed.

The issues of cost and insurance coverage should be covered in countries where genetic results can influence ability to be insured. Confidentiality issues should be noted and it is essential to discuss how the patient would like to receive their results.

In terms of informed consent, a test should ideally offer the option to opt out of receiving information on variations of unknown significance, because often neither the physician nor the patient knows what to do with this result. Patients should also be offered the option not to receive information on genes that are unrelated to their cancer. However, many labs do not offer these options.

Post-test counselling

Post-test counselling has two major components: genetic issues and medical follow-up. The genetic element involves explaining the test results and the qualitative and quantitative cancer risks.

If a pathogenic or likely pathogenic mutation is found, there needs to be a discussion of the inheritance, which relatives should be tested, and how to contact relatives. If no mutation is found, there should be a discussion about whether there is still suspicion that there might be a genetic syndrome.

With regards to medical management, any early detection or risk reduction strategies should be discussed and types of therapy that might be available should be explored. There should also be a discussion of clinical trials, registries and recommendations for follow-up.

Take home messages

- Gene panels are a major advance in genetic testing, offering unbiased analysis of inherited predisposition in a timely manner and at reasonable cost.
- Panels should be chosen based on the patient's characteristics, their family history, the genes in the panel, the reporting policy on variations of unknown significance, and previous genetic testing.
- Panel yield is 5–15%, depending on the tumour type and previous genetic testing.
- Actionable outcomes are not very common, but when they occur they are important and include targeted therapy, specific surveillance and prevention, and testing of family members.

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Personalised cancer medicine: What's the evidence it works?

If we can only find out what is driving a given cancer and/or what mechanism is creating resistance to treatment, it should be possible to at least halt the progress of the tumour by blocking the driver or the cause of the resistance.

Cancers – particularly advanced solid tumours – are much too complex to be controlled through such precisely targeted treatments. They are too heterogeneous, and their capacity to mutate enables them to find a way around any roadblocks we can throw at them.

This argument has been going on for at least 50 years, and was brought into focus in 1984 with the classic *Cancer Research* paper by Gloria Heppner on tumour heterogeneity and its impact on therapy. Proof of principle that the personalised approach can work came in the late 1990s with trastuzumab, the first anti-cancer drug designed to block the mutations driving HER2+ breast cancers, followed by imatinib, which proved highly effective at controlling chronic myelocytic leukaemia – a blood cancer driven by a single mutation. But hopes that targeted therapies can transform advanced solid tumours into manageable chronic diseases are still a long way from being realised.

Is it just a case of giving this approach more time to define more mutations and develop more drugs to block them? Or should we be asking questions about whether we may be betting too heavily on the personalised cancer medicine paradigm, and whether we should redirect some of the research effort into areas that are more likely to deliver the big differences that everyone wants to see?

John Hickman, now an independent consultant who worked as a researcher in academia, and more recently in the pharmaceutical industry, believes we should be asking questions. In an article published in the *New England Journal of Medicine,* Hickman and his co-author questioned what evidence there is to show that the personalised cancer medicine paradigm will ever deliver big benefits to large numbers of patients, and called for a proper evaluation of the strategy "in a small number of well-designed collaborative programs" (*NEJM* 2016, 375:1289–94).

Giuseppe Curigliano, Professor of Medical Oncology at the University of Milan, and Head of the Division of Early Drug Development at the European Institute of Oncology, Milan, says that is never going to happen. He argues that new targeted medicines are proving their value in patients every day, and that treating cancers according to their molecular profile is the future.

Cancer World invited Curigliano and Hickman to debate the topic to help clarify the key differences between their two perspectives, and see if they could find any common ground.

John Hickman

Our cancer research efforts are currently invested very heavily in personalised cancer medicine, a paradigm that is based on the concept that molecular analysis of a metastatic tumour in an individual patient will allow the selection of effective drugs to control that tumour and thereby significantly prolong survival of the majority of patients undergoing this treatment. This paradigm is appealing to patients and to foundations that support cancer research, but there are strong grounds for questioning what it can deliver for the large majority of patients with advanced solid tumours either now or in the future. The cancer community has a duty to ask those questions, which is what I did with Ian Tannock in writing our *New England Journal of Medicine* article on the Limits of Personalized Cancer Medicine (*NEJM* 2016, 375:1289–94).

The essential question for personalised cancer medicine is whether any therapeutic strategy could provide cure or long-term remission despite the presence of inter- and intra-tumour heterogeneity, the heterogeneity of tumour microenvironments and the almost universal capacity of cancer cells to develop resistance, reflecting the enormous plasticity of tumour biochemistry. Two decades on from the approval of the first HER2 inhibitor trastuzumab, that question has yet to be answered.

There are high costs associated with focusing research and development resources so heavily on pursuing the personalised cancer medicine paradigm. The individual drugs are expensive, often with marginal benefit, and they are increasingly used in combinations, escalating both financial cost and toxicity. More seriously perhaps is the cost of continuing to plough resources into a strategy that has yet to show any benefit, rather than spreading the research effort across a wider range of promising avenues such as the early detection and treatment of major cancers.

To clarify the likelihood that personalised cancer medicine will be able to deliver on its initial promise, what is needed is to see a clear impact on patient survival and quality of life together with estimates of cost–benefit. This should come from a small number of well-designed collaborative research programmes. The cancer research community has a responsibility to ensure these are urgently undertaken, and transparently reported on, to ensure time and resources are not wasted pursuing a questionable strategy .

Giuseppe Curigliano

I disagree. All the achievements from the past 10 years have derived from precision medicine. ALK-amplified non-small-cell lung cancer is a good example. It is by sequencing that we discovered that target and then we developed a new generation of ALK inhibitors. The same applies to trastuzumab, gefitinib, erlotinib. It is a matter of discovery and drug development.

I also disagree completely that there is a minimal impact on survival and quality of life. If you discover an ALK amplification in a lung adenocarcinoma and you give an ALK inhibitor, you will increase the survival of the patient. And since the patient will not receive chemotherapy, you will increase also their quality of life. Before ALK inhibitors, survival was three months, and now it is three years. It's the same for BRAF-mutated melanoma. We already have in real life an achievement that completely changed the landscape of treatment over the past five years.

What we are doing now is to discover the mechanisms of resistance to these agents and to develop new agents that are more effective. The landscape from now to 10 years' time will see increased activity of targeted agents – which in my opinion will lead to improved outcomes in terms of overall and progression free survival as well as quality of life, because the new agents are less toxic.

In the future, our sequencing technology will permit a deeper analysis of genetic changes. We will discover new genetic alterations, and should look at the patient population in the future not as a general population but as niches of populations. So you will

have 5% with a PI3K mutation 2% with a BRAF alteration, 5% of patients with an HER2 mutation. Some subgroups of patients will benefit from one approach, some from another. From the sum of all the subpopulations we will capture the overall population. In this overall population you will have a single patient with his or her individual mutation profile, permitting personalised treatment

Every day there is a new mutation, a new alteration, a new biomarker being identified. We are moving from disease-oriented treatment to pathway-oriented treatment. Just think about pembrolizumab, the first cancer treatment to be approved by the FDA not for a specific cancer, but for any advanced solid tumour with flaws in genes that repair DNA. More are expected soon.

In the last 10 years, we have approved many more molecular entities in terms of new treatments than in the last 30 years.

I agree that the 3 to 5% of patients with lung adenocarcinoma carrying an ALK translocation do indeed have a prolonged survival and it is important that patients who will benefit get access to ALK inhibitors. My concern is that there are *a priori* reasons to question whether the 'ALK paradigm' will work for the majority of patients, or whether it will even deliver to ALK+ patients the long-term control or cure that they need.

I question an approach where large numbers of patients with advanced, metastatic cancers are selected for treatment with targeted agents ('basket trials') based on the presumption that a biopsy (often only a single biopsy), and genomic sequencing, will indicate that tumour's drug sensitivity. Randomised trials of this approach have yet to validate its impact on survival for the large numbers of patients involved, or to measure its cost-effectiveness. The SHIVA trial was the first reported 'basket' trial of this type, which compared standard of care against treating a variety of solid tumours based purely on their genomic profile. It proved negative, with toxicities exceeding those of standard treatment. Despite this, patients are being treated based on an unproven paradigm. There are ethical questions regarding the promotion of this type of 'personalised treatment' in the absence of data that it will be of benefit and cost-effective. Patients' expectations must be based on factual information. This approach should only be applied widely, if at all, when the results of additional randomised trials are available.

I also agree that a lot of new cancer drugs are coming on to the market, but there are questions about the evidence of benefit required for their approval, with many drugs struggling to meet the minimal criteria of efficacy defined by ESMO or ASCO.

Drugging genomic changes in cancer is not straightforward, despite your optimism. PI3KCA is an excellent example of a gene mutated in many cancers. Yet the Fathers of this field recently admitted that that the clinical results of PI3KCA inhibitors have fallen considerably short of their expectations. This struggle for efficacy is due in large part to the complex genetic evolution of tumours, which provides multiple subclonal drivers of cell proliferation and survival (see, for example, recent TracerX papers) that will thwart the effects of a single agent, or even combinations. The question is how do we respond to this emerging knowledge of extensive intra-tumour genetic heterogeneity?

The SHIVA trial is not an appropriate example. The trial was designed more than 10 years ago, using a next generation sequencing technology that was very limited, and with limited access to cancer treatments. Take a look at the recent trial of larotractenib for use in child, adolescent and adult cancer patients whose tumours test positive for the TRK fusion (*NEJM* 2018, 378:731–739).

The results showed the drug works across multiple tumour types, with a 78% response rate. That is impressive.

As for PI3KCA inhibitors, while it's true the results so far show little benefit in solid tumours, we have yet to see the results relating to alpha-selective PI3KCA kinase inhibitors, which are a different class of agent.

The answer to the problem of tumour heterogeneity and subclonal drivers is liquid biopsy. Liquid biopsies can identify, before clinical progression, subclones that are resistant to the treatment you are giving the patient, and enable you to select treatment accordingly. A good example is osimertinib, a targeted agent for non-small-cell lung cancer with the T790M mutation. The therapy is selected according to the mutation found in the liquid biopsy.

I anticipate that in future we will make the initial molecular diagnosis and select treatment using a liquid biopsy. The CancerSEEK test, which featured earlier this year in *Science* (18 January 2018), is a good example of how you can integrate several gene alterations and you can use this sort of technology not just for early detection but also to make the diagnosis.

As for the question about the level of benefit conferred by the many new cancer drugs, I don't believe that precision medicine should have to improve survival to demonstrate that it is beneficial to the patient. Some of these agents improve survival in the adjuvant setting, some in the metastatic setting have an impact on progression free survival, which is I believe a valid endpoint, and also I believe response rate is valid in some cases.

What people in the metastatic setting are asking for is not duration of life but quality of life. Of course if you have improvement in survival I would be very happy, but in a setting in which you have nothing, an improvement in progression free survival is also an achievement.

Increasing patient survival significantly is surely an important goal for the future. But, with an array of subclonal driver genes, the key question is what strategy is likely to succeed in doing this?

I don't think liquid biopsy provides a solution to addressing tumour heterogeneity. I predict that advances in this technology will merely confirm the complexity of the challenge we face. So, yes, it may be used to confirm the emergence of mutations affecting a particular targeted therapy, as in the T790M mutation in EGFR, but it may also confirm the presence of multiple subclones with their own driver genes.

The majority of cancers are not monogenic diseases, with a dependence on one driver. They are unlikely to respond to any single agent the way chronic myelocytic leukaemia does. The presence of multiple subclones, such as are reported in the TracerX study of lung cancer, therefore remains the major challenge. I agree that some targeted therapies provide responses, like the TRK inhibitor you cite. Hopefully, in these particular cases, survival will also be extended significantly, but we should be careful about assuming the ALK (or TRK) paradigms will apply more generally.

Liquid biopsy could, however, play a key role in helping us move forward towards real cures, if we focus on developing its role in the setting of early detection. The CancerSEEK test you mention uses a mixture of genetic and protein biomarker tests to assess early signs of cancer. The results were somewhat variable, but the approach is admirable.

We now need to focus on harnessing our accumulating knowledge of the genetic changes initiating cancer. Precision cancer medicine with targeted therapies (together with other interventions) will have a greater chance to deliver increases in patient survival if cancers are treated early in their evolution, when heterogeneity is limited.

I would never question the value of developing treatments that improve the quality of life of people living with incurable cancer. What I question is whether the oncology community should be focusing so heavily on personalised treatment strategies

that, on current evidence, are unlikely to deliver significant benefit for the majority of patients, and certainly not the major increases in survival that we need, nor at a price that allows the majority of patients access. A recent estimate suggests that only around 7% of patients benefit from genome-driven oncology (*JAMA Oncol* doi:10.1001/jamaoncol.2018.1660).

Oncologists have a responsibility, I believe, to pursue more promising avenues of research, in particular aimed at improving early detection. This should receive a much greater share of attention and effort.

Targeted drugs for cancer date back to trastuzumab, approved for breast cancer in 1998, and the 2001 approval of the leukaemia drug imatinib, both of which have saved many lives. So far, the FDA has approved 31 targeted therapies for various cancers, including one that is approved for use against any cancer with a particular (DNA repair) mutation. Recent basket trials indicate that a similar approach could also work for other mutations, for instance, for cancers with TRK fusion. And although TRK fusions and the DNA repair mutations occur in only a small fraction of patients with a particular cancer type, when tallied across cancers, such drugs can help many patients.

As the list of targeted drugs grows, it makes sense to test tumours with genome-wide assays. If we don't test people broadly, we will miss patients who have alterations for which there is now an approved therapy. In the trial that you mention, published in *JAMA Oncology*, 15.4% of 610,000 US patients with metastatic cancer were eligible for an FDA-approved, genome-guided drug. But they also found that, because the drugs shrink tumours in only some eligible patients, only 6.6% likely benefited. And many patients relapse after a couple of years on the drugs.

Analysis of current cancer genomic data sets suggests that we are still far from uncovering all the genetic drivers.

A major challenge for researchers working with cancer genomic data sets is their sheer size. The Cancer Genome Atlas data set alone is over a petabyte in size, with more than 575,000 files. Just to download the data using a 10-Gbit-per-second connection would take over three weeks.

Setting up a secure, compliant infrastructure of sufficient scale to store and analyse the data is technically challenging and expensive. Artificial intelligence and the new generation computing equipment will help us match human genomic with clinical data. This will overcome the logistic and economic barriers by democratising access to cancer genomics data, enabling researchers to bring their hypotheses to the data.

Despite all the criticisms, we cannot stop advances in cancer research. On 25 May 2018, the European Union General Data Protection Regulation (GDPR) took effect. It may now be possible for individual patients to become 'cancer information donors', which would allow their genomic data to be shared through specific platforms. Mechanisms for enabling such donations are being developed under the GDPR. Given appropriate informed consent systems, we could identify patients with rare molecular subtypes of cancer who could be contacted for potential participation in clinical trials appropriate for their particular cancer.

Clearly, the principles and practice of precision oncology will be accelerated by sharing data from thousands of patients with cancer. In my opinion, genomic data will have a pivotal role in precision oncology. A worthy goal will be to develop a new taxonomy of disease based on molecular pathogenesis and to demonstrate it has clinical utility in cancer treatment.

The future will be facilitating the sharing of cancer genomic and clinical data.

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Negotiating a global cancer plan:

the first two acts of a three-part drama

In recent years, a series of World Oncology Forums have brought cancer specialists together with global health organisations and national health policy makers from many countries to try to develop a global response that could do for cancer what the Global Fund does for AIDS, tuberculosis and malaria. **Anna Wagstaff** and **Richard Sullivan** sketch out how the discussion has gone so far.

CHARACTERS IN ORDER OF APPEARANCE

- Cancer specialists
- Ministers of Health from many low- and middle-income countries
- Global health bodies – (a loose coalition of governmental, non-governmental and charitable bodies involved in health and development policy and practice)

ACT 1: DEFINING THE PROBLEM

The curtain opens on a large table at which all the characters are seated. The walls are empty except for a large clock, which ticks audibly throughout the proceedings.

CANCER SPECIALISTS: Cancer is the fastest growing cause of premature death across the developing world. By 2030 it will account for 13 million deaths every year. Around 70% of cancer deaths occur in in low- and middle-income countries, and that proportion is set to rise. It is estimated to cost more than 1 trillion dollars – that's 12 zeros – every year in lost output and the cost of care, not to mention the damage it does to families deprived of breadwinners and grandmothers. It plays a role in preventing economic development in the countries that need it most. Guys you need a plan! We can't believe you're not taking this more seriously!

HEALTH MINISTERS: Are you kidding? If you haven't worked out how to prevent it or cure it, how do you expect us to? We have very little money, and we spend it where it has the greatest impact. Cancer is expensive and difficult to treat, we don't have the expertise, we don't have the equipment, and even if we did, by the time people make it to an oncologist, they're usually beyond saving.

GLOBAL HEALTH BODIES: Don't tell us we're not taking this seriously. So maybe we were wrong to have left chronic diseases off the Millennium Development Goals, but we've made up for it now. Prevention – including vaccination against cancer-causing viruses – and low-tech screening are now key elements of the Sustainable Development Goals. They feature in the Political Declaration from the UN High-Level summit on non-communicable diseases – which, by the way, most of you health ministers signed up to – and they are integral to the WHO Global Action Plan for the prevention and control of non-communicable diseases, within the context of extending universal healthcare coverage. But if you're asking for a Global Fund just for cancer, frankly we're not keen on the idea.

CANCER SPECIALISTS: We're asking for help treating the millions of people in resource-stretched countries who get diagnosed with cancer every year. OK, so cancer does share certain risk factors with diabetes and heart disease, but you know perfectly well that it's not just another 'non-communicable disease'. Cancer can strike at any age, it invariably kills if left untreated, and diagnosing and treating cancer needs infrastructure, planning and a mix of expertise that is in no way comparable with managing diabetes or heart disease. "Preventing the preventable" is of course the first line of defence, particularly to prevent smoking- and diet-related cancers. But people will still get cancer, and they will still need it detected in time, diagnosed correctly and treated or palliated. This requires surgeons, radiotherapists, medical oncologists and others with experience, expertise and adequate equipment. Are you really saying that it's not a global health priority to help governments put that in place?

GLOBAL HEALTH BODIES: Focusing on prevention makes sense for us, because it's relatively cheap, and where it works it can be very effective. And focusing on infectious diseases makes sense because

we know by and large how to do it. And focusing on tobacco makes sense because it is such a major cause of ill health – though it's fair to say that our impact has been less than we'd hoped. But the problem with cancer, as you say, is that even with the best prevention measures, it will always be with us. With the best will in the world, global aid is not the solution. India alone has a population of more than 1 billion. Pakistan, Nigeria, Myanmar, Congo all have around a million people. It's up to all you health ministers to develop sustainable services and fund them from public money. And, by the way, we'd like to point out to all you cancer specialists that lobbying for governments to invest in developing 'vertical' services for your particular disease, without reference to the many other health problems they need to address, is very unhelpful as it sucks resources away from other urgent needs.

CANCER SPECIALISTS: It's not "our disease". It's the fastest growing health problem across developing countries, and the one that governments are least equipped to deal with, in part because of stigma, fatalism, and misinformation. If we hadn't spent the last ten years raising awareness about the coming epidemic, no one would be talking about it now. If we hadn't prepared policies on how to develop national integrated cancer plans, if we hadn't run pilot schemes, then governments would have no idea how to do it. And yes, cancer plans are indeed 'vertical programmes', because there's no point using primary care resources to ensure people get their cancers detected earlier if they have no access to specialised diagnostics, treatment and care.

GLOBAL HEALTH BODIES: Well we would question the value of building shiny new high-end cancer centres when time and again we've seen they are unable to put their capacity to use because by the time patients get there, it's too late to save them. Getting prevention and early detection – and palliation – has to be the starting point, and that means investing in strong primary care networks. That's why we want to prioritise 'horizontal programmes' in an effort to achieve basic universal health coverage, which the majority of people in LMIC countries still have no access to. If we're honest, we've been pretty disappointed at how little support our efforts have had from you cancer specialists.

CANCER SPECIALISTS: We'd happily play a stronger part in calls for universal health coverage so long as it includes essential cancer services, including treatment and care. Actually some of us have been leading efforts within the Noncommunicable Disease Alliance, but we won't deny we do worry that if we focus our efforts on what we have in common with heart disease and diabetes, we play to the agenda of those who argue that developing countries should essentially stick to prevention, and limit their treatment ambitions to the more simple conditions. That would mean abandoning millions of men, women and children who will be diagnosed with cancer, and we won't compromise on that.

HEALTH MINISTERS: Hey guys, guys, if we could get a word in… Look we really appreciate your concern, and we do see that cancer is a big problem in our countries, that it drains our productivity, and it causes grief and hardship in families and communities. In fact many of us have had to send family members abroad for treatment, as it happens, so if there's a realistic chance of improving options for treatment at home, we'd certainly be interested. The trouble is that we also see how expensive it is to treat. Even your industrialised western economies are struggling with the cost. So it's all very well to say it's up to us health ministers "to develop sustainable services and fund them from public money". How about you tell us exactly how we are meant to find the resources to do that.

ACT 2: IDENTIFYING SOLUTIONS

CANCER SPECIALISTS: Look it's true that a lot of the stuff used in Western health systems comes with a pretty shocking price tag, but we're not promoting that. We're talking about some essential pathology and imaging, a handful of cancer drugs on the – recently updated – WHO essential medicines list, adequate access to opioids, basic radiotherapy capacity, and investing in surgical services, which are highly cost-effective in resource-poor settings. You can't provide meaningful universal health coverage without a decent surgical service – so why not include some key cancer surgeries? What you health ministers and your governments need to be focusing on is the economic price your countries pay by not investing in cancer services. If you focus on your own cancer priorities, and make sure you get the basics right, it will pay off quite quickly and you'll reap the rewards year after year.

GLOBAL HEALTH BODIES: We'll second that. We've shown that investing in essential cancer intervention packages – which include potentially curable cancers, such as early breast, cervical and colorectal cancers as well as certain childhood cancers, depending on countries' own priorities – represent clear value in terms of lives saved and the economic payback. Just search for 'DCP3', the disease control priority setting exercise we do in conjunction with the World Bank – it's all there.

HEALTH MINISTERS: Cost-effective it may be, but that doesn't mean it is affordable.

CANCER SPECIALISTS: True. A lot of work has been done on this by health economists, and it's clear that those of you from countries at the more resource-poor end of the LMIC spectrum would need help. The Lancet Commission on Global Surgery 2030 estimates that raising surgical capacity to meet population needs would require countries in the upper-middle income bracket to raise their health spending by around 1%. That shouldn't be impossible should it? But those of you from lower-middle income and low-income countries would be looking at around 6% and 8% increase respectively, so we get that you would need a bit of help.

GLOBAL HEALTH BODIES: ... Well don't look at us.

CANCER SPECIALISTS: Well actually we are looking at you. A little over 1.5 per cent of total development assistance for health goes to all so-called non-communicable diseases, and cancer gets only a fraction of that. How can you possibly justify that?

GLOBAL HEALTH BODIES: Well perhaps you should be looking at yourselves. Around 25 billion euros a year goes into funding cancer research. Only the tiniest fraction of this goes to help LMIC countries do the research they need to develop their own cancer services. The EU's innovative medicines initiative, alone, will get a stunning 3.3 billion euros over the period 2014 to 2020. If you truly want to emulate what the global AIDS community achieved, maybe you can start by looking at their spirit of international solidarity, and allocate a decent fraction of that funding where it is needed most.

HEALTH MINISTERS: Ouch! Guys, guys, settle down. We would welcome funding to develop our cancer services from both global health aid and from cancer research funds – I mean 25 billion euros is more than the entire GDP of Paraguay!

GLOBAL HEALTH BODIES AND CANCER RESEARCH EXPERTS: And you health ministers need to look to your own responsibilities. If your governments don't prioritise spending on health, you can hardly expect us to pick up the tab. Colombia, 7.2 per cent GDP spent on health, Paraguay, 9.8 per cent – that's the sort of money that will make a sustained difference. But then Nigeria, 3.7 per cent, Sri Lanka, 3.5

per cent, Ghana 3.6 per cent... Seriously? We know that where health spending is below 4–5 per cent of GDP, or 80 to 100 dollars per capita, there's little point trying to make an integrated cancer plan work, because the health infrastructure is simply too weak to support it.

HEALTH MINISTERS: Well, looking on the bright side, all these budgeting and cost-effectiveness exercises done by DCP3 and the Lancet commission should provide us with useful ammunition to argue for more money from our finance ministers. But we'll need to convince them that we would be able to spend that money effectively. I'm not going to lie... there's more than one of us around this table who've made some rather regrettable decisions when it comes to investing in cancer care. Raise your hands if you have any linacs sitting idle in a bunker for lack of spare parts or the technical know-how to fix them...

GLOBAL HEALTH BODIES: Well if you'd just listened to us...

HEALTH MINISTERS: Actually, listening to you may have been part of the problem. Aid from you global donors often comes as a take it or leave it package. You fly in for a few weeks or months, chat to the politicians of the day, and then fly out again. And you're not very good at asking us what our needs and priorities are.

CANCER SPECIALISTS: We agree absolutely. That's why we always advise that you start by setting up reliable cancer registries so you have good data about the most problematic cancers in your countries. Only one in five countries can report reliable mortality information, and without that, you won't know what services you need to plan for and where, or whether the services you do provide are having an impact. The WHO's International Agency for Research on Cancer has a global initiative for cancer registry development and are aiming for regional hubs with consultants who can give technical assistance...

HEALTH MINISTERS: Sounds great. Where do we sign up? Is this the sort of catalytic capacity building research project that we could get help to fund?

CANCER SPECIALISTS: Sadly there's no funding stream set aside for that work at the moment. In fact IARC is still short of around 15 million dollars to fully fund their own five-year programme.

HEALTH MINISTERS: So no help set aside for the vital first step... And we're going to need a lot of help with the next bit, where we have to formulate, cost, argue for and then implement national cancer control plans that fit our overall health priorities, address our cancer priorities, and work as a coordinated, accessible, sustainable whole. It's immensely complicated. Our health departments are not used to dealing with projects this large or complex. We'll need help, and for more than just a few months. What can you offer us?

GLOBAL HEALTH BODIES: We can help plan things like vaccination pilots, or even cervical screening pilots, but we don't really advise on integrated planning and implementation of entire cancer plans.

CANCER SPECIALISTS: No we don't either. A lot of us and our institutions, offer fellowships and exchange programmes to help with particular aspects such as gynae surgery, childhood cancers, or pathology. Some groups help to adapt and pilot treatment strategies for countries with fewer resources, or poorer general health status. The UN International Atomic Energy Agency advises countries on safe and sustainable radiotherapy equipment.

HEALTH MINISTERS: Well come to that, we ourselves share specific areas of healthcare expertise with neighbouring countries. The issue here is how to stop working on isolated fragments, and develop an integrated national plan tailored to our needs and resources. We'll need to bring on board our clinicians, researchers, policy makers, administrators, accountants, lawyers, health economists, local and regional government... that's what we need help with.

CANCER SPECIALISTS: Well the Union for International Cancer Control has recently launched a scheme for big cities that could help. They are offering help with the technical, logistical, and economic aspects of pulling together a tailored integrated cancer plan for cities, with a timescale of three years of involvement – none of that fly in and fly out stuff. In return they ask for evidence that all relevant authorities including the national government are serious about investing in cancer for the long term, and are prepared to back it up with sustainable funding, and are open to working with non-governmental players – NGOs, the private sector, civic society, as appropriate.

HEALTH MINISTERS: Well that sounds like it could be an interesting offer. Where do we sign up?

CANCER SPECIALISTS: Well of course it's only for cities with one million plus populations. Four cities to start with, which have already shown some level of commitment to investing in cancer. And not the poorest. The UICC is a relatively small international advocacy agency – it's not geared up to providing that level of technical advice and assistance at a global level. But the concept could well help address some of the key challenges you health ministers have raised.

HEALTH MINISTERS: We'll need to invest in infrastructure – well building stuff is something I think we can all do. We'll need to invest in equipment – diagnostics, imaging, storage facilities, digital comms systems, operating theatres, radiotherapy equipment, drugs and vaccines, data management systems. Even with the sort of globalised centralised purchasing agreement that helped bring down the cost of AIDS therapies, and even if we can count on reaping the rewards over the coming decades, we are going to need help funding that.

GLOBAL HEALTH BODIES: We may be able to help with ideas about possible funding opportunities. We did mention in the DCP3 report the need for global initiatives to lower the costs of key inputs through large-scale commodity purchases, as well as to expand technical assistance and promote cancer research in countries that need it most. This is something we've helped with in other disease areas, and few of them have the sort of multi-billion dollar resources that are available to cancer research.

HEALTH MINISTERS: OK. We appreciate that. But then here's the real issue. Capacity building. We are talking about a major step change in every aspect of our health professional capacity – at community level, primary care, specialist care, public health, data management, administration and governance. They'd be great jobs, it would help keep talent and ability in the country, it would be a great resource for the future. No question. But it takes time and it takes money. A lot of it.

CANCER SPECIALISTS AND GLOBAL HEALTH BODIES: Yes, we get it.

HEALTH MINISTERS: Good. So can we summarise where we are? Cancer is the fastest growing health threat across the developing world. It's an economic drain and a humanitarian crisis. And if we take it seriously, make it a priority, plan properly and invest, we can make a sustainable difference that would pay off for future generations. But you're not in a position to offer us the technical advice we need to develop sustainable, tailored, integrated national cancer plans. You haven't got in place centralised large-scale commodity purchasing schemes to make key inputs more affordable. And there's no initiative to help finance the huge up-front investment this is all going to require, particularly for lower-middle-income and lower-income countries. Not exactly cancer's answer to the Global Fund to fight AIDS, tuberculosis and malaria are you? Guys you need a plan! We can't believe you're not taking this more seriously!

ACT 3 GETTING SERIOUS...

. . . Act 3 is yet to be written. How it plays out will have a dramatic impact on the lives of millions of people across the world. There are grounds for optimism. All the players want to do the right thing; between them they have the knowledge and experience required to build the global capacity to cope with the coming epidemic; they are talking to one another; and to some extent they are also listening and adjusting their perspectives. But it is hard to see the necessary political will and momentum being generated until civic society and patient advocacy add their voices. Will that be enough to galvanise the sort of streamlined global action that we've seen with AIDS, malaria and tuberculosis – technical management assistance and help with upfront financing? It's up to everyone in the cancer community to make sure it is, or this three act drama will end as a tragedy that could have been avoided.

The above script drew on discussions that took place at successive meetings of the World Oncology Forum and in other forums over the past 10–15 years.
The World Oncology Forum, convened by the European School of Oncology, brings leading cancer clinicians and researchers and global health experts together with advocates, NGOs, industry and health ministry officials to develop a coordinated approach to helping resource-poor countries build capacity to mitigate the impact of the rapid rise in the cancer burden (see WOF, at eso.net). The conclusions of the most recent World Oncology Forum (Lugano, 2017) were published in *The Lancet* (The global fight against cancer: challenges and opportunities, Franco Cavalli and Rifat Atun, *Lancet* 2018, 391:412–3). Video highlights of the 2017 World Oncology Forum, featuring contributions from a wide spectrum of voices, can be found at bit.ly/WOF2017_highlights.

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ESTRO CALENDAR OF EVENTS

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2018 LIVE COURSES

Clinical practice and implementation of image-guided stereotactic body radiotherapy
2-6 September 2018 | Porto, Portugal

Image-guided radiotherapy and chemotherapy in gynaecological cancer: focus on adaptive brachytherapy
2-6 September 2018 | Madrid, Spain

Haematological malignancies
5-8 September 2018 | Utrecht, The Netherlands

Physics for modern radiotherapy (joint course for clinicians and physicists)
9-13 September 2018 | Budapest, Hungary

Basic clinical radiobiology
15-19 September 2018 | Dublin, Ireland

Target volume determination - From imaging to margins
23-26 September 2018 | Moscow, Russia

Imaging for physicists
23-27 September 2018 | Vienna, Austria

Advanced treatment planning
23-27 September 2018 | Athens, Greece

Multidisciplinary management of head and neck oncology
30 September - 3 October 2018 | Lisbon, Portugal

Multidisciplinary management of non-melanoma skin cancer
4-6 October 2018 | Brussels,Belgium

Advanced Brachytherapy Physics
7-10 October 2018 | Valencia, Spain

Advanced technologies
7-10 October 2018 | Rajamahendravaram, India

Best practice in radiation oncology - Train the RTT (Radiation Therapists) trainers - part I
22-26 October 2018 | Vienna, Austria

Advanced technologies
28-31 October 2018 | Petaling Jaya, Malaysia

Positioning and immobilisation for radiation therapy
3-4 November 2018 | Vienna, Austria

Comprehensive quality management in radiotherapy - risk management and patient safety
4-7 November 2018 | Athens, Greece

ESTRO/ESOR multidisciplinary approach of cancer imaging
5-6 November 2018 | Rome, Italy

Accelerated partial breast irradiation
11-14 November 2018 | Brussels, Belgium

Research course in translational radiation biology and oncology
11-14 November 2018 | Florence, Italy

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2018-2019 ESTRO MEETINGS

ESTRO meets Asia 2018
7-9 December 2018
Singapore

7th ICHNO
International Congress on innovative approaches in head & neck oncology
14-16 March 2019
Barcelona, Spain

ESTRO 38
Targeting optimal care, together
26-30 April 2019
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Advanced breast cancer: What's new in treatment and care?

Despite growing precision in understanding the biology of breast cancer, progress in extending survival of people with metastatic disease remains frustratingly slow. Median survival is only about three years, having edged up only slightly in recent times, although there are signs that better care at earlier stages is reducing the numbers of advanced cases. As indicated by the updates and additions to the guidelines arising from the 4th International Consensus Conference for Advanced Breast Cancer (ABC4), which are précised below, recent progress has been in the most common subtype – ER+ (oestrogen-receptor positive), luminal advanced breast cancer.

The ABC guidelines, drawn up under the auspices of the European School of Oncology and the European Society for Medical Oncology, cover both treatment and, increasingly, quality of life factors. This is in recognition of the need to apply evidence on the holistic wellbeing of people with

Précis of the key updates and additions from ABC4

• Quality and access

MDT care for advanced disease

At ABC4, the panel added several points about the organisation of care, including that all patients should have access to a specialist breast centre that includes a nurse experienced in advanced disease. In 2015, the European Parliament adopted a declaration that added metastatic breast cancer to its call for universal breast units, and the guidelines put more pressure on services to not isolate this patient group from integrated care.

Early palliative and supportive care

The offer of survivorship and palliative care services at an early stage in care was also added to the guidelines and recommendations, together with a quality assurance programme that covers the patient journey. The key is that care pathways and quality indicators in national breast unit certification systems currently omit the metastatic stage. This will also be addressed in the forthcoming quality assurance accreditation framework from the European Commission Initiative on Breast Cancer (EIBC), due for publication in 2020, and an update of the EUSOMA (European Society of Breast Specialists) 'Requirements of a breast centre', also underway, under the auspices of the ABC Global Alliance.

QoL tools for advanced disease

Also included is a call for tools that measure health-related quality of life of advanced breast cancer patients – this is another neglected area, where oncologists' reports have tended to take precedence over patient experiences: what doctors say often does not match what patients say about side-effects. The EORTC Quality of Life and Breast Cancer Groups are working on such a scale, and it is urgently needed given the expanding range of drug combinations that are now being trialled in successive lines of therapy, and the pressure that severe side-effects can place on both the acute and community based health systems.

Biosimilars

On cost-effectiveness strong support is voiced for the use of new biosimilar drugs – a paper from the European School of Oncology this year will set out the latest issues on these, building on a paper from ESMO in 2016.

• Treatment statements

ER+ advanced breast cancer

Of the three main molecular subtypes – luminal (ER+/HER2-), HER2+, and triple negative – it is ER+ that has seen the most progress recently, and where the most impact could be seen as it is by far the most common type, at about 65% of advanced breast cancers. Two of the new statements on ER+ concern the new CDK4/6 inhibitors, two of which are approved in Europe with another on its way having gained US approval. ER+ cancer has been found to depend particularly on the CDK enzyme to grow, and the inhibitors are especially effective when combined with endocrine therapy.

However, there is no overall survival (OS) data yet for the combinations, but good evidence for progression free survival. The ABC panel has also added scores from the ESMO Magnitude of Clinical Benefit Scale to these statements to give a better guide about whether to offer them in practice. The addition of everolimus, a type of inhibitor (mTOR), to an aromatase agent also gets a statement, albeit without significant OS benefit.

The panel has made statements on the uncertainty of the sequence of endocrine-based therapy, and the lack of biomarkers other than the oestrogen receptor.

Pre-menopausal women

Expert opinion is given on the lack of trials in young women with ER+ advanced breast cancer, and there are strong words

advanced disease. In parallel, the wider ABC community has undertaken work on organisational and societal factors that affect metastatic patients, and this work has informed the consensus guidelines and indeed advocates are among the panel members (see Advanced Breast Cancer Goes Global, *Cancer World* Winter 2017/18).

The 4th ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC4) will be published in full in the Annals of Oncology.

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in the commentary. The recommendation is that young women should receive ovarian suppression or ablation (removal of the ovaries) and be treated in the same way as postmenopausal women and allowed to enter the same clinical trials. "Resources should not be wasted running duplicate and separate trials for pre- and postmenopausal patients," and the "ABC panel strongly advocates against unrealistic, unnecessary and sometimes expensive clinical trials requirements on contraception, with clear negative impact on quality of life, for pre-menopausal women who do not undergo suppression or ablation." A definition of what adequate ovarian function suppression means in the context of ABC has also been added, and expert opinion that the impact of therapy on fertility should be discussed with all women of childbearing age.

HER2+ and triple negative

While anti-HER2+ therapy has been key to significant survival gains, there has been little to note in the past two years, although there are two new statements that follow latest trials on patients with ER+/HER+ ABC.

Triple negative ABC continues to have few advances, but PARP inhibitors are an option (see genetic testing).

Genetic testing and precision medicine

These are mostly new sections, and include statements on genetic testing for mutations in the BCRA1/2 genes, now that the PARP inhibitors have been approved, which are an option in triple negative and luminal breast cancer associated with BRCA mutations. This currently concerns only germline (hereditary) BRCA mutations, but could in future involve other hereditary gene mutations that confer risk. The commentary also calls for high-quality genetic counselling services. BRCA mutations can also arise somatically – i.e. not via genetic inheritance – but there is no clinical relevance yet. The panel added statements against the use of certain tools that are available but not validated and so should not be used in routine clinical practice, such as next-generation multigene panels and circulating tumour DNA. Further, there is no clinical role yet for immunotherapy in advanced breast cancer.

Brain metastases

A statement on treatment of an uncommon condition, radionecrosis, has been added – it concerns an effect of using stereotactic radiotherapy that is now being seen more owing to longer survival of some patients with brain metastases from HER2+ breast cancer.

• Supportive and palliative care

Mucositis • Neuropathy • Hand & foot syndrome

The panel has added three statements on managing side-effects: on mucositis/stomatis (mouth/lip inflammation), chemotherapy induced peripheral neuropathy, and hand and foot syndrome. As the commentary notes: "When adverse events are addressed systematically and at an early stage, they often become simple and inexpensive to treat, allowing for a higher probability of continuation of the planned therapy."

• Integrative medicine

Exercise • Mindfulness • Hypnosis • Yoga • Acupuncture

Lastly, a new section has been added on what is termed 'integrative medicine' – this concerns therapies such as complementary medicines and physical exercise. It is recognised that many patients are using complementary therapies and the panel considers that some can reduce symptoms and improve quality of life. They find level I evidence in favour of physical exercise, 'mindfulness-based' stress reduction programmes, hypnosis, yoga and acupuncture. But there is evidence that some complementary medicines have no effect or can even make matters worse. Among these are antioxidants, herbs, high-dose vitamins and oxygen/ozone therapy.

Annette Berendsen

Researcher, Oncology in Primary Care

Transferring more responsibility for the care of cancer patients and survivors from specialists to general practitioners (GPs) is seen as key to coping with rising patient numbers. GPs, specialists and patients question how this can work with such a complex disease. ***Cancer World*** asked Annette Berendsen, a GP by profession, who is leading efforts to find solutions.

Cancer World: *What challenges do general practitioners (GPs) face in understanding and addressing the needs of their patients during and following cancer treatment?*

Annette Berendsen: Cancer patients are all different, there are many different types of treatment, and the problems patients are likely to encounter differ according to the therapy they have received, and now there are so many new therapies. The big challenge often voiced by GPs is that they have no idea what to expect, so they don't know how often they should see their patient or what they should be looking out for. Most importantly, it is often not clear for GPs whether the treatment is curative or palliative in intent, because this crucial information is almost never given in the letters specialists send to GPs. Usually GPs have contact with their patients after diagnosis. When patients think the treatment is curative and the GP thinks it is palliative, it can create awkward situations. We did a study on correspondence between GPs and specialists, and our hypothesis after the analysis was that these letters are not particularly meant for the person they are sent to. Specialists see it as something for their own archives, not as a means of giving GPs the information they need to provide the best care for their patient.

CW: *There's a lot of talk about shifting responsibility for follow-up care from specialists to primary care. Is that happening?*

AB: In 2011, the Dutch Cancer Society published a report on this topic. However, seven years on, it is still under discussion. Nobody has the solution. GPs say: "I'm too busy, time will be a barrier, remuneration will be a barrier." They also worry that they don't have the knowledge and skills to

take on this role, and specialists think the same. Patients also prefer hospital follow-up. So we conducted a study, focusing on patients with breast and colorectal cancer. We found that, in practice, there is a huge increase in face-to-face contact between GPs and patients after a cancer diagnosis, as well as an increase in medication prescriptions compared to a reference population. We concluded that GPs already give a lot of follow-up care to cancer patients, but it is not formalised.

Most contacts relate to side effects of therapy, for example dermatological problems from radiation or gastrointestinal problems relating to chemotherapy. Psychosocial problems are also a reason for contacting the GP, as are questions regarding lifestyle.

CW: *How well do specialists and GPs understand each other's needs and roles and work together?*

AB: This is the question I addressed in my PhD thesis. I found that GPs think they can learn from specialists, but specialists generally don't think that they can learn anything from GPs. This means specialists often have a poor understanding of the challenges GPs face, for instance, in picking up cancer symptoms when the great majority of their patients with similar symptoms do not have cancer.

Another finding was that GPs want to learn something from specialists up to a certain level, but when that is reached, another topic becomes more important. And this can be disappointing for specialists, because they like to teach GPs all the new developments.

I also found that differences in status between GPs and specialists can be a barrier to collaboration. GPs have traditionally been seen as less qualified, though that has changed a lot in recent years, at least in the Netherlands.

Remuneration and time are also important, as collaboration takes time and time is money. And familiarity is important for building effective working relationships. This is becoming a little harder now there are so many doctors who work part time.

CW: *What has to happen to ensure GPs and specialists can work well together to provide the best care for patients?*

AB: If GPs are going to take greater responsibility for caring for cancer patients, that role needs to be formalised. They will need proper protocols and guidelines that are personalised for specific groups of patients, and they will need to be properly remunerated.

If you look at care for patients with diabetes and COPD, this used to be the responsibility of secondary care, but now it is a responsibility of GPs. Clear protocols define the role of the GP and of the GP practice nurse, and spell out when the patient should be referred to secondary care and vice versa. There is nothing like that in cancer. A key reason is that cancer patients and treatments differ much more than is true for diabetes and COPD.

So we need to define subgroups of patients with cancer. For example, if you have an older patient, say 80 years old, who visits the GP every three months because of diabetes and a low-risk breast cancer diagnosis, question whether this person needs to visit the hospital often. In the case of a young cancer patient with fertility issues, by contrast, it is more obvious that they should receive care in a secondary setting.

Once we have defined subgroups, we can state who is responsible for doing what, how often GPs should see a given type of patient, what problems they should look out for, what will be reimbursed by health insurance, and so on. This is something our group at the University Medical Centre in Groningen is currently working on. In collaboration with GPs and specialists, we are trying to define such subgroups. When that work is completed, it will be possible to draw up protocols, and the remuneration will have to follow the protocols.

CW: *Is this just a Dutch initiative? Are there plans to do something at a European or international level?*

AB: Groups in the USA, Canada, Australia and Europe are doing something similar. Yet work around defining the role of GPs in providing care for cancer patients and survivors is still at an early stage. It is nowhere near as established, for instance, as research around GPs' role in early diagnosis or palliative care. If GPs are to take more responsibility for the care of cancer patients during and after treatment, as many policy makers envisage, it will need a lot more attention.

To comment on or share this interview, go to bit.ly/CW82_AnnetteBerendsen

Annette Berendsen is an Assistant Professor and head of oncology research in primary care at the Department of General Practice and Elderly Care Medicine, at the University of Groningen, The Netherlands. Her research focuses mainly on oncology during the post-diagnosis period, including the role of the GP, the role of the patient, and the continuum of care, as well as long-term effects of cancer and its treatment. She is the editor of the book '*Oncology*' for general practitioners, member of the executive committee of the Cancer and Primary Care Research International Network Ca-PRI, and convener for the WONCA (GPs international organisation) Special Interest Group on Cancer and Palliative Care.

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Art and oncology: one life

Scientist or artist? **Michael Peckham**, who is best known for his contribution to the treatment of testicular cancer and Hodgkin lymphoma, and was involved in founding the European School of Oncology, refuses to choose and has always been both. Painting and medicine have complemented one another throughout his career, as he explains.

When I decided to become a doctor, art and science were regarded as separate entities. I was already immersed in the arts and in the first years after qualifying I had doubts about continuing with medicine, not helped by having to spend two years in the army in the last batch of conscripts before military service ended. Paradoxically, being removed from the conventional career ladder was liberating. I was on my own as a medical officer to an infantry battalion and I had time to think about what I wanted to do in medicine and art. I made no distinction between a scientific and an artistic mind and I thought that the separation of artist and doctor was artificial.

Inner Man (2015) Cutaway collage

My first job at University College Hospital was in surgery and radiotherapy – then the only dedicated cancer specialty. Influenced by Gwen Hilton, the gentle and cultured head of department, I decided to specialise in oncology. My art was first shown in 1960 and I had my first solo exhibition in 1964. The paintings were abstract landscapes in oil on canvas and I was reviewed as a colourist. Around this time, I bought a book on cell proliferation and discovered how to label cells with radioactive thymidine and coat the slides with photographic film. When the film was developed, cells synthesising DNA had black grains of silver over their nuclei. Witnessing the dynamics of dividing cells was a eureka moment for me both as artist and doctor.

Subsequently, I spent two years in Paris on a Medical Research Council Fellowship working on leukaemia and lymphoma at the Institut Gustave Roussy. This was an exciting period in art, medicine, and politics – just before

Sundance (2017) Oil on canvas

the student riots of 1968. Bone marrow transplantation had been used in acute leukaemia, there were high hopes for immunotherapy, and radiation techniques had been evolved to cure Hodgkin's disease. I met Stanley Hayter, painter and print-maker, and he invited me to Atelier 17, his renowned print studio. I felt a pull between 'laboratories' in two worlds: Hayter's in Montparnasse and the cell biology laboratory a few kilometres away in Villejuif. Paris was a turning point. Science added a new dimension to my clinical work and gave fresh impetus to my art.

My paintings in the 1970s often incorporated a circle image that I thought came from diagrams of the cell division cycle, although there were other possible origins. Earlier, I had made a construction using the circular red lens of a road lamp and a cycle collage – bought by Eugene Rosenberg, the architect who designed St Thomas' Hospital – that had the title *Pit Head* after the colliery pit head wheels I knew from my youth. Later, I incorporated figures into three-dimensional collages behind a frontage rather like a stage set. One construction, *The door*, came from a poem by Miroslav Holub, doctor, immunologist, and poet, whom I had met at a haematology workshop in Prague and a poetry festival in London. In *The Root of the Matter*, he wrote lines that resonated with my concept of art: "There is poetry in everything. That/is the biggest argument/against poetry."

In 1973, I was appointed to a chair at the Royal Marsden Hospital and Institute of Cancer Research. Curative treatments for Hodgkin's disease, lymphoma, and testicular cancer were becoming a reality and my unit at Sutton was at the forefront of these advances. This was an intensely active period and I remember drafting the first paper on our use of carboplatin in Zurich airport on my way back from a lymphoma conference in Lugano. On the wards, we had seen young men dying from rapidly progressive cancer. When effective treatments were developed, the change was dramatic, and it was obvious that a transformation was underway. The human figure became more prominent in my paintings and I used colour more freely, perhaps reflecting our elation at what was being achieved on the wards.

"Many of the images I used came from my experience as an oncologist"

I made small pen drawings routinely in the notes of patients on which I marked the extent of tumour. The different visual patterns led to a staging system that helped us choose the best form of treatment. Over time, these drawings made with practical intent seemed powerfully symbolic: the figures had an imagined content related to patterns of disease scribbled into the notes on busy ward rounds. Thrity-five drawings were shown at the Royal Academy in 2004 under the title *Treatments*. An exhibition of my collages and paintings in 2017, *Balance of the Interior*, explored the human form as a zone of concealment and mappable space, notions that had their origin in the small images drawn in my clinical notes. A couple of years earlier, I had painted my own experience of the pain of post-herpetic neuralgia (*Zona*). In these paintings, the cadmium pigments that I habitually used gave way to a sombre palette of muted greys.

Many of the images I used came from my experience as an oncologist. When I looked at a person I saw the external form of a body, but I also sensed the disposition of structures under the skin and imagined cellular images and processes. Seeing past the skin became a reality with

In Movement (2017) Gouache on paper

the discovery of X-rays. It caught the imagination of artists in the early 20th century and chimed with Paul Cezanne's efforts to define an order underlying the surface of nature, as well as Alberto Giacometti's efforts to get to the essence of a head much as a physicist pursues subatomic particles. I was familiar with the human figure rendered translucent by scanning in the search for a tumour, and had a preoccupation with hidden forms linked with other strands of interest. For example, the images in my exhibition, *Philomena*, in 2013, derived from notions of concealment, detection, and metamorphosis.

In a valedictory lecture at The Hague, I compared 'seeing' in the context of a medical advance and a new departure in painting. The discovery of platinum drugs that transformed the curability of testicular cancer came serendipitously from an astute observation of the unexpected: a product interfering with bacterial growth diffusing out from platinum electrodes assumed to be chemically inert. One source of Piet Mondrian's paintings came from the way he saw fragments of sky between the branches of trees and used this to create the delineated geometric blocks of his mature paintings. Looking at the emergence of new developments in art and medicine is intriguing, although comparisons of their respective quality and importance are generally unhelpful. As John Berger asked in *A Fortunate Man: the Story of a Country Doctor*: "How does making a correct but extremely difficult diagnosis compare with painting a great canvas," and concluded that "the comparative method was absurd".

I like the idea of cumulative effort: the build-up over time that can't be replicated later when there is time and I have accumulated many small works that touch on most aspects of my experience. The painter Patrick Hayman once told me to keep my sketches as I would feed on them later. Many drawings are of the commonplace: a hospital tap, the level crossing gate I went through on my way to the hospital, a datapoint on a graph. The importance of a subject lies in its interpretation: Giorgi Morandi's bottles, Claude Monet's water lilies, and Philip Guston's boots were transformed in different ways into memorable images. My current paintings are concerned with human presence: places people have inhabited or passed through and the signs that indicate that they have been there. Although not explicit, the theme connects with notions of concealment and revelation and with issues of mortality and continuity that are of concern to both artist and physician.

Reprinted from *The Lancet*, 391 (10120), Michael Peckham, Art and oncology: one life, pp530-531. © 2018, with permission from Elsevier.
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Natural Collection (1984) Built-out collage

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CERTIFICATE OF COMPETENCE IN LYMPHOMA

FOURTH COHORT 2019-20

The European School of Oncology in co-operation with Ulm University offers a structured Certificate of Competence in Lymphoma Programme, an academically recognised curriculum of studies, which was developed with the contribution of internationally recognised physicians and scientists in the field of haemato-oncology.

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The Programme is designed for **oncologists** and **haematologists** (medical oncology, haematology, internal medicine, radiation oncology, pathology), but it is equally accessible to **graduates in natural sciences** who are engaged in the field of oncology, especially in the field of lymphoma.

ADMISSION AND DEADLINES

Admission to the Certificate of Competence in Lymphoma Programme is by competitive application only and the selection is based on the eligibility criteria and the selection procedure.
Attendance is limited to **20 participants** per cohort.
Applications for the fourth edition will open in mid-May 2018 and submission is required by the deadline of **14 September 2018**.

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Upon successful completion of the Programme, participants will obtain an **academic certificate** issued by the European School of Oncology and Ulm University assigning **14 ECTS** and a diploma supplement by Ulm University.

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THIRD COHORT 2019-20

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PROGRAMME

The Programme, which is offered on a part-time basis using blended-learning modules and seminars, is divided in **three attendance seminars** (in Austria, Portugal and Germany) and **five e-learning modules**.
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ELIGIBILITY

The Programme is designed for **physicians with experience in the field of breast cancer** (medical oncology, radiation oncology, gynaecology, senology, pathology), but it is equally accessible to graduates in **natural sciences** who are engaged in the field of breast cancer.

ADMISSION AND DEADLINES

Admission to the Certificate of Competence in Breast Cancer Programme is by competitive application only and the selection is based on eligibility criteria and the selection procedure.
Attendance is limited to **20 participants** per cohort. Applications for the third edition will open in mid-May 2018 and submission is required by the deadline of **14 September 2018**.

CERTIFICATE

Upon successful completion of the Programme, participants will obtain an **academic certificate** issued by the European School of Oncology and Ulm University assigning **13 ECTS** and a diploma supplement by Ulm University.