May-June 2015

Number 66

European School of Oncology

Learning to c

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NINETY YEARS AFTER WARBURG

The unique metabolism of cancer cells re-emerges as a therapeutic target

BAD LUCK OR BAD JUDGEMENT?

It made front page news across the world, but what does that study really tell us?

WELCOME TO THE REVOLUTION!

Researchers and patient advocates are finding better ways to work together

Per-Anders Abrahamsson

Patients want us to work as a team

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Cancerworld
Shaping the future of cancer care

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They are many, will we be too few?

KATHY REDMOND EDITOR

The message about the ticking time bomb of new cancer cases associated with our 'greying population' seems now to be well understood by policy makers, even if they don't yet have the solutions. Far less attention is being paid, however, to the 'greying' of the healthcare workforce, which could pose at least as great a threat to sustaining safe and high-quality cancer care in the coming decades.

The European Commission has predicted that, by 2020 – less than five years from now – there will be a nursing shortage of more than half a million and an overall clinical workforce shortage of nearly 1 million, rising to 2 million if long-term care and ancillary professions are taken into account.

The shortages will be more critical for certain specialties and in certain geographical areas, with an unequal distribution within and between countries. Migration of healthcare professionals will exacerbate the problem in some countries, and will pit wealthier European countries against the WHO Global Code on International Recruitment of Health Personnel, which seeks to protect the health systems of poorer nations struggling to retain their own health workers.

Some countries already face shortages of health professionals across a wide range of cancer control work, and this is likely to get worse.

Addressing the shortfall will require an urgent review of the best way to deliver the care needs, particularly for an aging patient population where multiple chronic conditions are not unusual. What roles, competencies and skill mix are needed? How can care be integrated more smoothly across different settings?

The demands on the workforce will also need reviewing. A contributing factor to the staff shortage has been the steady rise in the proportion of women in clinical roles, as women often put a higher premium on a good work–life balance.

Against this background, new ways of working will probably emerge, with a reconfiguration of roles across the multidisciplinary team, so that progressively scarce human resources can be used to best effect. The growth of new technologies will certainly have an impact on healthcare work patterns over the coming years, and this might ease the pressure on individual healthcare workers and the workforce as a whole. However, the introduction of new technologies also brings new problems in terms of skills and training requirements.

We are going to need to be creative in how we recruit and retain health professionals – a somewhat daunting task given the demanding working conditions and relatively low pay associated with some roles. Training will need to be overhauled significantly so that the new generation of health professionals will be equipped to work in a more collaborative way within an increasingly technological environment.

Concerted efforts are required to make oncology an attractive specialty for newly trained health workers. The European Commission has taken a number of actions to promote a more sustainable health workforce in Europe, but the cancer community has in general not been well engaged in these initiatives. We will need to do better if we are to ensure that the unique requirements of cancer care are taken into consideration when policy decisions about Europe's healthcare workforce are made. ■

Per-Anders Abrahamsson: patients want us to work as a team

SIMON CROMPTON

Patients look for the best treatment centres, says this leading voice in European urology. So they'll go where the specialists involved in their care work together, not where they are constantly battling over who is 'in charge'.

Per-Anders Abrahamsson is too modest to claim that, over his 11 years as Secretary General of the European Association of Urology (three as adjunct), he has succeeded in establishing urology as a specialty in Europe. That was certainly his aim, he says.

But the numbers tell a story. The EAU now has 17,000 members and the number of urologists attending the EAU's annual congress has risen threefold, to 15,000, representing all European countries. Its members now come from not just Europe, but Latin America, Oceania and South East Asia. Its journal now has the top impact factor in the field of urology and nephrology.

Abrahamsson has also been responsible for collaborative cancer initiatives – for example setting up an annual European Multidisciplinary Meeting on Urological Cancers with the European Society for Medical Oncology (ESMO) and the European Society for Radiotherapy and Oncology (ESTRO). He has been an influential researcher and opinion leader in prostate cancer.

But the territorial disputes of the cancer world have never been far away. When I meet him in Malmö – the bleak but hypnotising industrial city in southern Sweden that formed the setting for Stieg Larsson's novels and hit TV drama 'The Bridge' – the politics of cancer is much on Abrahamsson's mind.

JASON HARRIS

He is quick to point out to me – as he has many times to European politicians – that urological cancers (including prostate, kidney, bladder, testicular and penile cancers) together constitute one-third of all cancers. In a world of scarce resources and scarcer attention spans, every form of cancer must make its case for primacy.

And when I start our interview in his office at Skåne University Hospital by asking him what he'd like to talk about, he tells me that he has just returned from a meeting of the European Cancer Organisation (ECCO) in Brussels, and is worried about ESMO's recent decision to hold its own congress every year rather than continuing to collaborate with ECCO on the organisation of the biennial European Cancer Congress.

"We have to work as a team," says Abrahamsson, who is Professor of Urology at Lund University and Chairman of the urology department at Skåne. "It has been a major task for me at EAU to try and help bring all the people in cancer under the same roof."

For Abrahamsson, building a strong ECCO and getting all disciplines to work together in the interests of patients are synonymous. But the cause is made more difficult by tensions created by the increasing role of organ-specific specialties in cancer.

Turf wars between medical oncologists and urologists are a particular source of vexation for Abrahamsson. In some European countries, urologists – normally surgeons by training – play the central role in treating urological cancers, even though more and more specialise in oncology. Many see little benefit in handing control of cancer patients to medical oncologists who have less knowledge of, say, the prostate. Medical oncologists, they say, should be brought in at their request rather than co-ordinating care.

So although "working together" is an Abrahamsson mantra, achieving it in urological cancer has been fraught with difficulty in Europe. "In some countries, there is a major battle," he says.

"In Germany for example urologists are pretty well handling everything including chemotherapy, and they are not much working together with medical oncologists," he says, adding that there are urologists within EAU who want to be independent of all other specialties – not just medical oncology but areas such as imaging too. But

Abrahamsson is adamant that this is not the way forward. "It's not going to happen," he says. "You cannot do everything."

"We organ specialists have to work closely with all the other specialties involved in cancer – imaging people, radiation oncologists, medical oncologists, basic researchers, nurses – which is why I think the multidisciplinary outlook of ECCO is so important," he says. He asserts that most urologists within the EU are indeed working in a multidisciplinary fashion. "It is the only way forward, because it is what patients want."

"It is clear that surgery cannot cure everything. In urological cancers, it's all about using adjuvant and neoadjuvant radiation, and in some cases, such as testicular cancer, chemotherapy. I remember a medical student on my course dying of testicular cancer in the 1970s, but now in Norway and Sweden we cure 99% of our testicular cancer patients. This is a wonderful example of why we need to work together, and I cannot understand this ongoing fight between different organisations."

The last four years of Abrahamsson's term as Secretary General, which came to an end in March, has seen him turn his attention more and more to politics, and he jokes that his next role will be Secretary General of the United Nations. But he is hopeful the battles will end soon.

"There are dinosaurs fighting to maintain what they have on both sides, but I'm optimistic that within five years it will be history. Patient organisations like Europa Uomo are getting better organised and asking for everyone to work as a team, and we have asked politicians in Brussels to look at the same thing."

Abrahamsson doesn't have much time for dinosaurs, hierarchies or those who insist on being named as 'in charge'. He is from the Scandinavian school of open-necked informality, and proudly explains that everyone he works with at his hospital and the EAU headquarters in Arnhem, in the Netherlands, calls him Per-Anders – or even Papa Pelle, a family nickname that somehow spread. When he took over as EAU Secretary General

in 2007, he changed its military-style top-down management model to a more level, consensual structure, with four team leaders who he "trusts with everything". It was based on the structures at his own hospital. "It's more time consuming, but I totally believe in it because it's about mutual trust."

So consensual working in urological cancer makes total sense to him. And in the field of prostate cancer, it extends to supporting the spread of specialist multidisciplinary prostate cancer units – along the lines already well established for breast cancer. In 2011, the European School of Oncology promoted the concept of prostate cancer units in an article in the *European Journal of Cancer,* and set out what was involved in terms of professional education and experience. The concept revolves around two principles: every surgeon and radiotherapist who treats patients with prostate cancer must specialise in the disease; and volume equates to quality.

EAU met with ESO to discuss prostate cancer units at the EMUC meeting in Lisbon last November. "We are working together on this, and I am convinced we will sign a partnership with ESO because we have the same goals. We are def-

"There are dinosaurs fighting to maintain what they have on both sides, but I'm optimistic that it will soon be history"

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initely behind the concept of units. In many countries already, for example the UK, you now have to operate a certain number of cases a year and demonstrate follow-up and outcome to be allowed to carry out a procedure. I am convinced this is what will happen in all European countries, but it will take some time. In Germany, for example, you currently have at least 120 centres carrying out radical prostatectomy, which is not acceptable.

"If you don't have on hand a whole range of other people – including qualified pathologists, imaging people, specialised nurses, and those who can help with the side effects of treatment such as incontinence – you shouldn't be allowed to perform surgical procedures."

Again, it is pressure from patients for evidence of good outcomes that will be the main force for creating centres of excellence. "Of course they are heading for the best centres, and that's going to happen in Scandinavia, as well as the UK. That's why, in centres like our own, we are working like brothers and sisters with other disciplines."

Research into prostate cancer has been a central plank of Abrahamsson's career, continuing alongside his work as clinician and teacher. His innovative research in the 1980s and early 1990s identified new kinds of prostate cancer neuroendocrine cells and the peptides produced by them, and these were subsequently identified as promoting progression in some types of aggressive cancer. Today, there is increasing interest in neuroendocrine differentiation as a marker for prostate cancer aggression.

But it might never have happened if he'd been faster on his feet. Born in 1949, the son of a farmer and a nurse, he knew from his teens that he wasn't going to take over the family farm by the Baltic Sea, 150 km north east of Malmö. He was determined to be a Swedish version of German footballer Franz Beckenbauer, and played for a Swedish second division team. He had good ball skills and was a good header of the ball – and even today, he would be a commanding presence on a football field.

But he soon realised he wasn't fast enough to reach the top level. Influenced by his mother's vocation, he decided to enter medicine. He started medical school at Lund University, just north of Malmö, in 1970, and then in 1977 started training as a resident surgeon at a small hospital in Trelleborg on Sweden's southern tip.

Under the guidance of Arne Weiber, then President of the Swedish Society of Surgery and "a living legend" in Swedish medical circles according to Abrahamsson, he gained experience of everything from neurosurgery to delivering babies.

Work at Trelleborg also allowed him to pursue his obsession with football. He became team doctor for Trelleborg's football team – then in the Swedish third division – and stayed with them as the part-timers rose to the first division and then in 1994 defeated the British champions, Blackburn Rovers, in the UEFA Cup. He is a board member for the club, was appointed President in

He wants national screening programmes that use PSA tests in a more considered way, alongside active surveillance

A team player. Abrahamsson is President and team doctor at his local Trelleborg football club, and is pictured here with their shirt (complete with prostate cancer awareness ribbon)

2003, and is still completely obsessed: a team shirt hangs framed outside his hospital office.

But in 1980 he decided he wanted to be a urologist, not a general surgeon, and he began another residency, this time at Malmö University Hospital.

"At that time I had no clue about the technologies and new surgical techniques that would transform my specialty," says Abrahamsson. "In the early '80s, we couldn't have imagined performing shockwave or laser lithotripsy for kidney stones, and we wouldn't have dreamed about performing radical prostatectomy to cure prostate cancer. We were using oestrogens for disseminated disease, and if you were diagnosed with penile cancer it was simply amputated."

It was the urology chief at Malmö, Lars Wadström, who gave Abrahamsson the ambition to enter research, and it was his own doctoral thesis, completed in 1988, that established Abrahamsson's work on prostate neuroendocrine cells. On the basis of that, he was invited to the urology department at Rochester Medical Center in New York, becoming its laboratory director in 1991 and adjunct professor in 1993.

During his three years there, he brought in molecular biologists from all over the world, finalised 45 papers and – thanks to the influence of the department chief Abraham T K Cockett – made wide contacts in the urology world. Since then, Abrahamsson has become known for his skills as an international networker.

Returning to Malmö, however, he became dissatisfied that he could not get an appointment as a departmental chief, so began using his networking skills and giving talks about his research. At a talk in London in 1995, he met Frans Debruyne, then Secretary General of the EAU, who told him: "You are going to be Secretary General one day." Shortly after, he was asked to become a member of the scientific committee – and that is how his involvement with EAU began.

In 1998 he became chairman of the urology department at Malmö and Lund university hospitals, and then full Professor of Urology at Lund University in 2000. The two university hospitals have now merged, into Skåne University Hospital. "Now we are no longer competing against each other and we can cover all fields of expertise."

After 20 years, he is due to step down as urology chief later this year. His perspectives on the challenges of the past and the opportunities ahead have been moulded over 40 years of clinical, research, management and political experience.

In the field of prostate cancer, perhaps most striking is his view that universal screening for prostate cancer is a realistic possibility – based on taking early and, if necessary, repeated PSA readings, but not normally intervening quickly with biopsies or surgery if raised levels are found (as has become the norm).

His view is founded in research from his own department, using stored blood serum samples from 20,000 men aged 35 to 45, 900 of whom were later diagnosed with prostate cancer at the hospital. Detailed analysis indicated that low PSA levels at age 45 indicated a very low risk of prostate cancer, but levels higher than 1.5 brought increased risk later in life.

"It shows clearly that you should have a baseline reading taken when you are fairly young. If it is low, then you can wait five years before you have it again. If it is higher, you have more tests on a more regular basis," says Abrahamsson. An international randomised trial with 18 years follow-up, being coordinated from Erasmus Medical Centre, Rotterdam (the European Randomised study of Screening for Prostate Cancer or ERSPC) indicates that such procedures reduce the chance of dying from prostate cancer by up to 50% – "that's more than any breast cancer screening study has shown."

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Those wary of PSA testing say that it is an inaccurate indicator of prostate cancer, and that raised readings are often the result of other conditions or indolent tumours. It can lead to unnecessary anxiety, harmful biopsies, and unnecessary treatment, leading to incontinence and impotence. Supporters say it should be used widely because it is a better cancer marker than we have for any other type of cancer and can lead to life-saving early interventions.

Abrahamsson straddles the two camps. He wants national screening programmes that use PSA tests in a more considered way, alongside active surveillance. But he acknowledges this will require a change in attitudes to test results among clinical staff, as well as patients.

"There's a danger that, as soon as a PSA result presents a red flag, everything starts. The patient gets scared and things move very quickly. We don't want that to happen, so you need to educate patients, relatives, healthcare providers on how to proceed in a considered way. That will take time, and we cannot introduce mass screening programmes straight away. But eventually, in the future, I am convinced that testing decisions will be made on the basis of a PSA test in your 40s – unless, of course, you have a family history, in which case the need for regular testing is clear."

Abrahamsson is waiting for more results from the European randomised trials before taking the idea to policy makers. But he is about to present an award lecture on the subject at the American Urological Association meeting in New Orleans this May. The response will be interesting, given the fact that American doctors have a long history of responding to an early diagnosis of cancer with surgery rather than active surveillance.

In terms of treatments for prostate cancer, Abrahamsson has mixed feelings about the progress made. Remembering the "bloody mess" of radical prostatectomy when introduced into Sweden in 1987, he marvels at the precision of the Da Vinci robots on which surgeons today perform 500 prostatectomies a year in Malmö – and the resultant reduction in incontinence and impotence.

But for all the technological advances, progress in prostate cancer treatment is still slowed by some basic and gaping holes in research.

"Those treating prostate cancer always have the problem that there is no randomised trial comparing radiation therapy with surgery. But we have started one here in the department, genuinely randomising patients to radiation or radical prostatectomy. It has to be done. Generally, around the world, people look to Scandinavia for the best randomised trials, the landmark studies – because of our health system, but also because our patients are historically more willing to be

"There are too many super-egos among doctors, politicians, CEOs. You find them everywhere"

randomised. It's almost impossible to randomise patients in the United States."

Abrahamsson won't contemplate complete retirement. He will continue as a clinician at the hospital, and is hopeful that new-found time will allow him to pursue new research. He wants to investigate the stem-cell characteristics of cancer cells, test new combinations of treatments including chemotherapy, and find better ways of identifying the most aggressive cancers and tailoring treatments to them. His team has already begun the stem cell work in collaboration with Norman Maitland, Director of York University's Cancer Research Unit in the UK, and Jack Schalken, Director of Urology Research at Radboud University Medical Centre, the Netherlands.

But he's wondering how he's going to cope without travelling. His role with EAU takes him tens of thousands of miles each year, and he wonders whether he might be addicted to travel. He started establishing international links early in his career, traveling to Poland on several medical relief missions during martial law and the economic crisis in the 1980s (he was awarded a Red Cross medal for his work). Since then, he has travelled regularly to central and eastern European countries to give lectures – not just Poland but Russia, Serbia, Ukraine and Romania. He has been awarded honorary professorships in most of these countries.

"I probably spent more time in these countries than some western European countries, because they wanted to catch up. It also helps that I speak Russian. But I'm always curious and I have been traveling like crazy. But I haven't seen all the countries in the world. I haven't been to Moldova!"

He got engaged to his Swedish wife – a nurse he met while teaching at a nursing school during his medical training – when they were on their first Polish relief mission together. "She has supported me all the way." Their three boys used to tell him as children that he worked too much and didn't earn enough money. One became an international lawyer, presently in Shanghai, China, another went into IT in Spain. And the other became a Swedish urologist. Abrahamsson keeps in touch with them on Skype, and there's a big screen on the wall in his office for their conversations. But twice a year, the families still get together for a week in the Swedish archipelago, sailing a Nordic 'Folk' boat, and skiing in the Alps.

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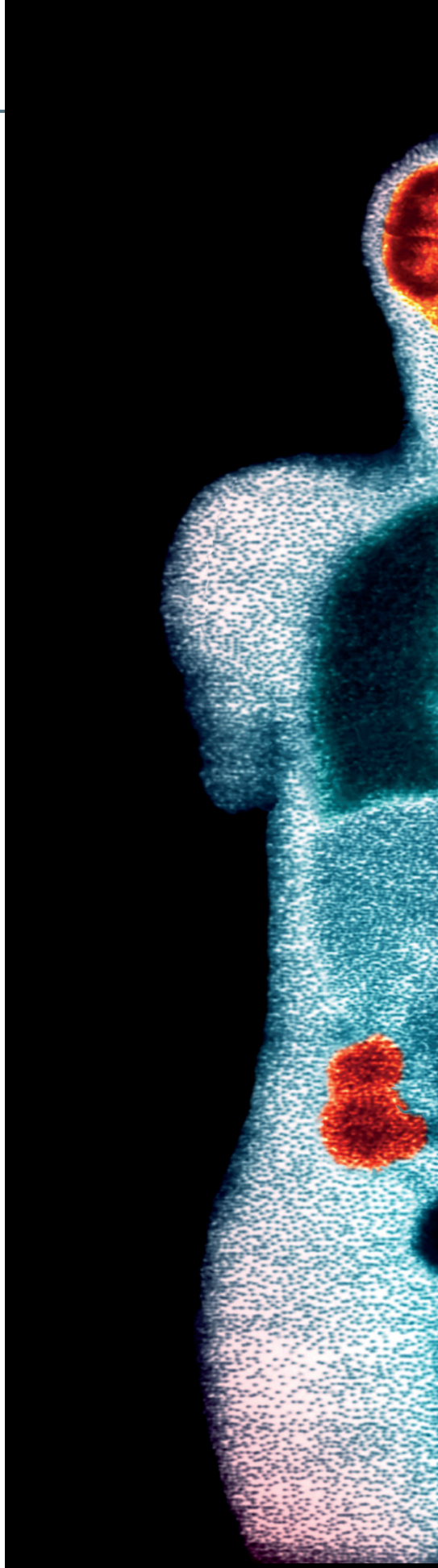
"The only real challenge in my career has been lack of time," he says. "Now, I think, if there's anything I could do in the next few years, it would be to continue to work in the international arena and offer them my experience and networks – I know so many opinion leaders in urology and oncology."

And it's here that he may need to take on the role of a United Nations-style peacemaker. "Time is so short, it's crazy. There are too many super-egos among doctors, politicians, CEOs. You find them everywhere. They have to downsize their egos. We need to sit down peacefully together, not fight each other." ■

Targeting the supply lines: metabolic approaches to killing cancer cells

MARC BEISHON

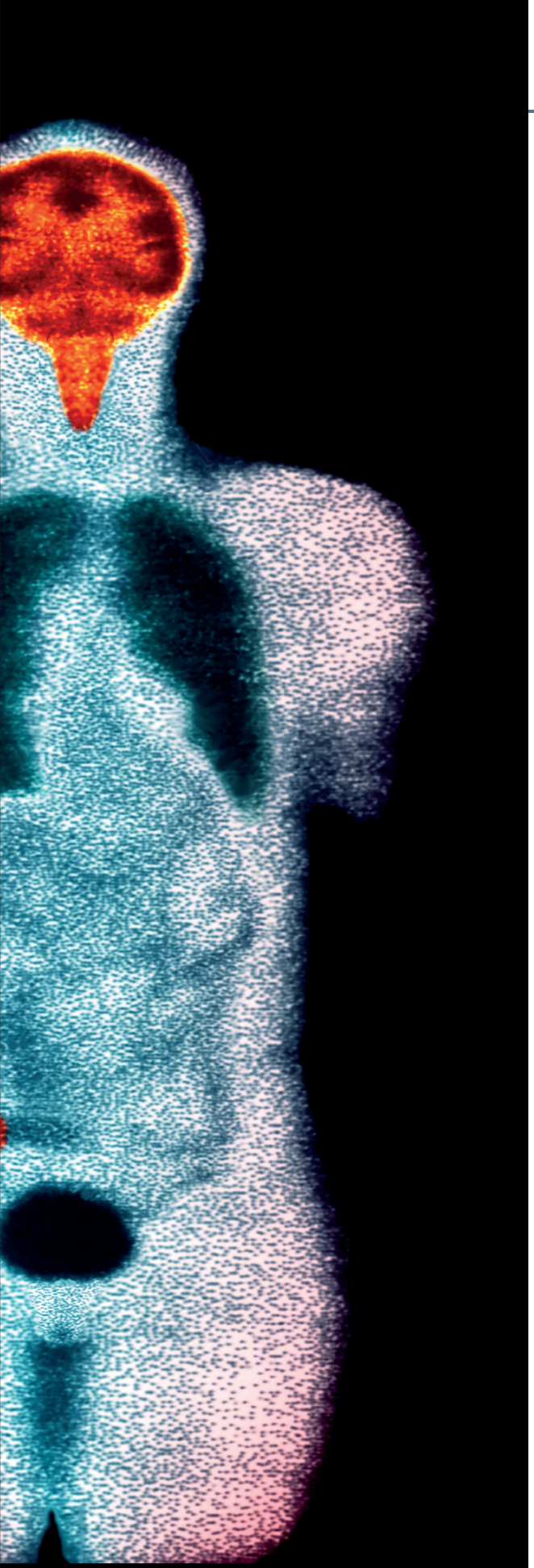


Recent years have seen a revival of interest in the unique metabolism of cancer cells. This time the focus is on the potential it offers as a target, rather than any possible causal role – but that link with obesity still needs explaining.

The association between cancer and altered cell metabolism was first highlighted by a German biochemist more than 90 years ago. Otto Warburg observed in 1924 that cancer cells process glucose – one of the body's key nutrients – into lactate, as athletes' muscles do when they run short of oxygen, but they do so even when they have sufficient oxygen. They also process glucose much faster than normal cells, which rely mostly on using mitochondria as the engine room for producing energy.

The Warburg effect, as it became known, was put forward by its proposer as the cause of cancer, resulting from the impairment of mitochondria. The effect has been widely discussed and the biology explored, but after a while the field of cancer research moved on.

Interest in the metabolism of can-



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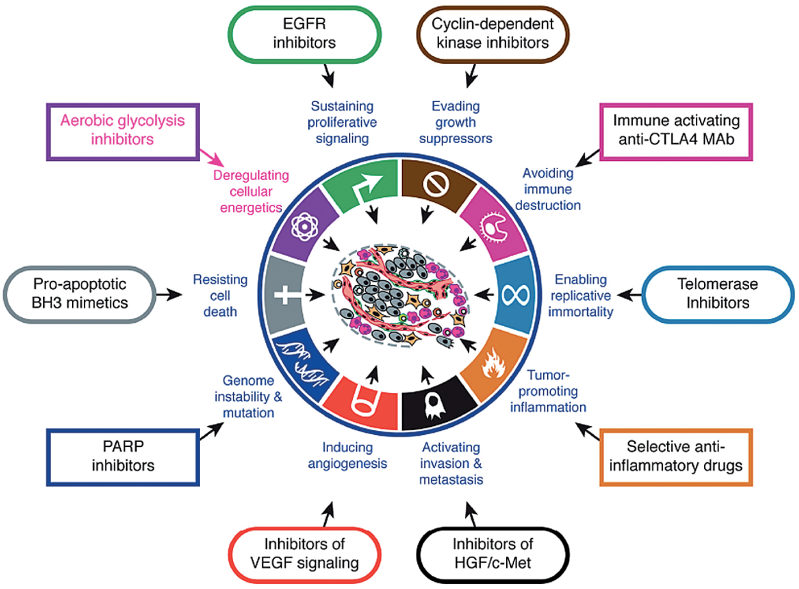


The abnormal metabolism of cancer cells was added to the "hallmarks of cancer" (*above*) in 2011, almost 90 years after Otto Warburg had first remarked on it, and 20 years after the first PET scan used the phenomenon to visualise tumour cells, like this colon cancer (*left*). Today there are a number of drugs in early trials that are designed to help kill cancer cells by exploiting their voracious appetite for glucose and other nutrients and their reliance on mutated pathways to feed their addiction

Source: D Hanahan and RA Weinberg (2011) Hallmarks of cancer: the next generation. *Cell* 144:646–674, reprinted with permission from Elsevier

cer cells revived with the advent of PET scanning using radiolabelled-glucose, in the early 1980s. This time, however, the focus was on making use of the Warburg effect to obtain images of the behaviour and spread of an individual cancer.

But despite the known metabolic actions of some of the most widely used chemotherapy drugs, such as methotrexate and 5-fluorouracil (5FU), there was little interest in addressing metabolism as a possible weak link in cancer that could be targeted. The famous 'hallmarks of cancer' paper by Douglas Hanahan and Robert Weinberg, from the year 2000, for instance, did not include metabolism.

That's all changed now, and the Warburg effect is again centre stage. And although most researchers do not believe it causes cancer, there is great interest in whether this and other metabolic changes

"Many cancer genes cross-talk with machinery that brings in glucose or amino acids"

in cancer cells might be an Achilles heel that could be targeted. Now, new knowledge about the function of cancer genes and their relationship with the way cells metabolise a range of nutrients, together with epidemiological evidence from the relationship between obesity, exercise and cancer, is fuelling a rapidly growing cancer metabolism field.

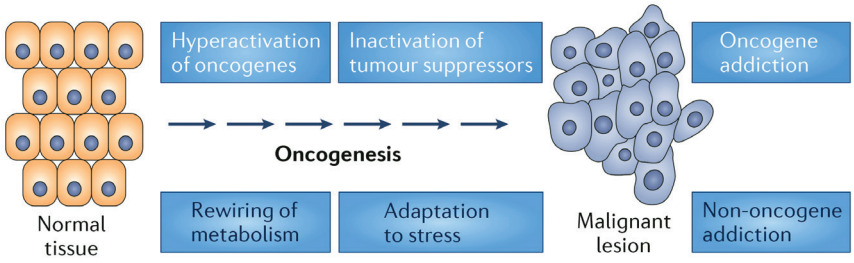
This has reached the point of dedicated international research conferences, a new journal, a growing number of investigational agents in both public and private research, and some clinical trials, in particular of the low-cost antidiabetic drug, metformin. And in 2011 Hanahan and Weinberg updated their 'hallmarks' to include abnormal metabolic pathways.

Oncogene–metabolism cross-talk

"Back in the early 1990s it was assumed we knew all about metabolic pathways of glucose and amino acids – they were set out in standard biochemistry textbooks," says Chi Van Dang, director of the Abramson Cancer Center, University of Pennsylvania, and a medical oncologist who researches cancer metabolism.

"We thought that it was only cancer genes that drive the cell cycle machinery that cause cells to replicate, and the energy part was just along for the ride and doesn't need to be regulated. But what we have found is that there are specific oncogenes that drive many other genes, including metabolic ones, rather like an orchestra conductor, both causing cells to replicate and to take in nutrients to do so."

CANCER CELLS SUMMON THE ENERGY THEY NEED



Specific oncogenes drive many other genes, including metabolic ones, both causing cells to replicate and to take in nutrients to do so

Source: L Galluzzi, O Kepp, MG Vander Heiden et al. (2013) *Nature Reviews Drug Discovery* 12:829–846, reprinted with permission

This was initially met with scepticism, he says, but it is now known that, somehow, cancer genes 'cross-talk' with metabolic pathways. It is not the case that when cancer genes send the signals that turn on the DNA replicating machinery, the energy to carry out that proliferation is there as if by magic. "Many cancer genes cross-talk with machinery that brings in glucose or amino acids," says Dang, who says a similar shift in knowledge took place with angiogenesis, where it is now known that a tumour can release hormones to grow new blood vessels to feed itself.

Dang likens the behaviour of normal cells to the way a tall building is constructed – materials such as bricks and cement have to be shipped in an orderly fashion and coordinated, or orchestrated, for growth. A normal cell has feedback loops that tell it that, if it doesn't have enough nutrients or oxygen, it won't divide, as it could make genetic mistakes. Only when conditions are right will it build up to divide in an orderly way with the least chance of a genomic error.

"In a cancer cell the same switches, instead of turning on and off, are permanently on, owing to genetic mutations, such as with the *Myc* oncogene that we study in my lab, and you have a deregulated system that continues to grow without the right nutrients. But that also creates a vulnerability, because the cells are addicted to nutrients. It's like building a wall with bricks but without cement."

Epidemiological evidence

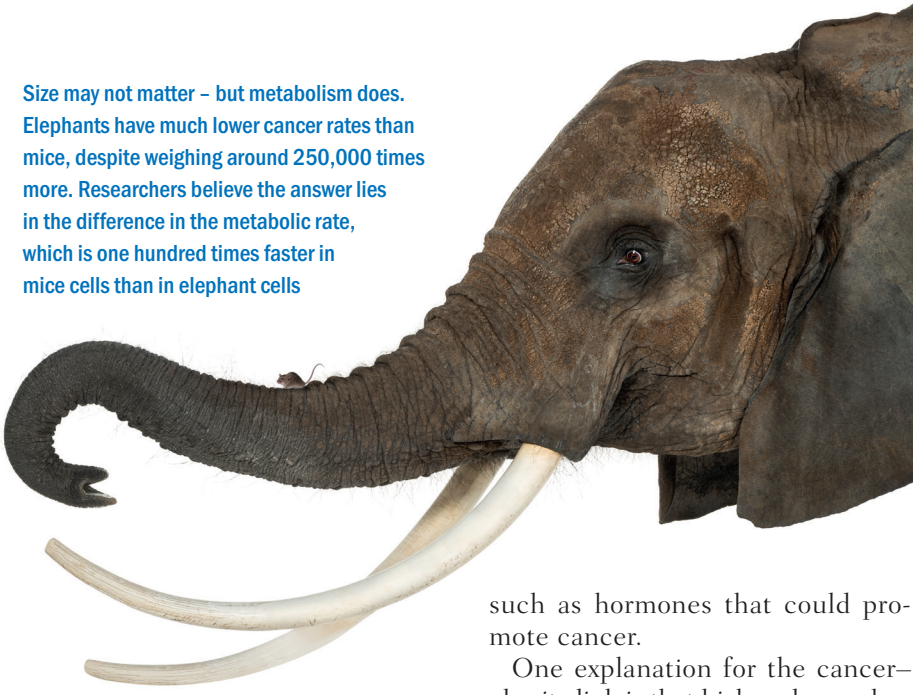
If the data from cell biology are becoming compelling, relating the knowledge to observations about animals, humans and cancer rates

adds important context about the causes of cancer. When cells divide and there are mistakes or mutations in the process, the accumulation of these mutations can lead to cancer if they permanently turn on a cancer gene.

But as Dang points out, there is a paradox about cancer in animals, named after British epidemiologist Richard Peto. Given that large animals have many cell divisions to grow to adulthood – and elephants certainly grow to a large size – it would be expected that they would also suffer from a higher cancer rate than smaller animals, such as the much-studied mouse.

"But elephants have much lower cancer rates than mice and the answer lies in the metabolic rate of their cells – mice have a rate a hundred times greater than elephants, which of course also live much longer," notes Dang. If mice are given drugs to restrict metabolism, such as metformin, which slows mitochondrial function, or rapamycin, which inhibits a growth and metabolism pathway, they live longer. "And a recent study shows that if you remove just one copy of the *Myc* gene in mice, metabolism is slowed and that can prolong their life. The interpretation is that a higher metabolic rate increases mutation rates and contributes to cancer development."

In turn this leads to the idea of 'metabolic fitness' and relationships between cancer, obesity, diet and exercise. The evidence for a link between obesity and cancer is now a given. The US National Cancer Institute, for example, projects that, by 2030, there will be 500,000 additional cancer cases in the US owing to obesity, with the risk for some cancers, such as oesophageal, pancreatic, colorectal and endometrial, increasing more than for others.



SHUTTERSTOCK

Size may not matter – but metabolism does. Elephants have much lower cancer rates than mice, despite weighing around 250,000 times more. Researchers believe the answer lies in the difference in the metabolic rate, which is one hundred times faster in mice cells than in elephant cells

Where's the link?

There is though no single explanation of the causal mechanisms linking people with high body mass index (BMI) and cancers – so far, molecular mechanisms are poorly understood. Dang says research is ongoing into calorific restriction, which can increase metabolic fitness – fewer nutrients can lower the metabolic rate – and factors such as hormones that could promote cancer.

One explanation for the cancer–obesity link is that higher glucose levels in overweight people are caused by insulin resistance, or a form of type 2 diabetes. "Cells cannot respond to glucose as well, so the body simply makes more insulin and an insulin-like growth factor (IGF-1), which are believed to drive cancer cells to a more aggressive state. The thinking is that it's not glucose on its own, and this model fits with a lot of data we have," he says.

A recent study adds evidence about the role of insulin. It found that postmenopausal women who are overweight but 'metabolically healthy' are not at elevated risk of breast cancer compared with women who are metabolically healthy but have a normal weight. However, women with high insulin levels have a higher breast cancer risk whether they are normal

"The interpretation is that a higher metabolic rate increases mutation rates and contributes to cancer development"

"Metabolic health may be more biologically relevant... than adiposity per se"

weight or overweight (and being overweight is in turn a risk factor for insulin resistance). The researchers suggest that "metabolic health may be more biologically relevant and more useful for breast cancer risk stratification than adiposity *per se*" (*J Cancer Res* 2015, 75:270).

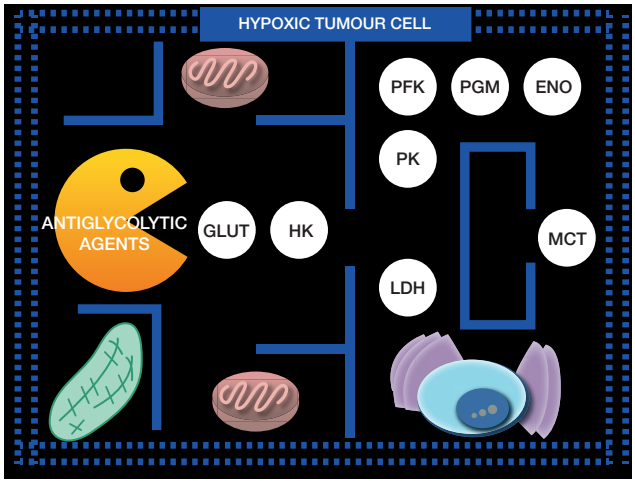
Other possible mechanisms include higher oestrogen production by fat tissue – hormones are of course implicated in several cancers – or inflammation, which can also have metabolic components. A recent special issue of *BioMed Research International* highlights a growing awareness of the link between altered cellular metabolism and the risk of developing diabetes and cancer. It includes papers that show that key pathways of fatty acid metabolism are altered in cancer, and that there is a strong prevalence of cancer in postmenopausal obese women, with associations between obesity, ovarian steroid hormones and cancer. The same issue also looks at the promise that some drugs used to treat diabetes, such as metformin, are showing as cancer therapies, and the possibility of targeting insulin growth factors.

The biochemical analysis in these papers is complex, but as Dang says, the field is simplified some-

THERAPEUTIC TARGETS AND DRUGS IN TRIALS

A number of drugs aimed at metabolic targets are now in early trials for a variety of cancers, including:

- AZD3965, a monocarboxylate transporter (MCT1) inhibitor being trialled in patients with advanced solid tumours
- DCA (dichloroacetate), a PDK1 inhibitor, being trialled in patients with recurrent malignant brain tumours, metastatic breast cancer and advanced non-small-cell lung cancer
- TCD-717, a choline kinase inhibitor being trialled in patients with advanced solid tumours
- AG-221, an isocitrate dehydrogenase (IDH) inhibitor being trialled in certain advanced solid tumours, including glioma, and with acute myeloid leukaemia and angioimmunoblastic T-cell lymphoma (AITL) with IDH mutations
- The diabetes drug metformin, being trialled for use in a number of cancer settings, including as a preventive in overweight or obese premenopausal women with metabolic disturbances, as an adjuvant in patients treated for early breast cancer, and in patients with advanced refractory colorectal cancer
- Statins, used to lower cholesterol, being trialled for use in a variety of cancers including prostate, colorectal and breast cancer, in therapeutic, preventive and adjuvant settings.



Specific modifications to the cellular metabolism that are common to most solid cancer cells offer multiple potential targets for therapeutic intervention. These include a heavy reliance on aerobic glycolysis for energy metabolism (the Warburg effect). This image shows some of the targets where progress is being made in finding and developing bioactive molecules that are able to interfere with cancer glycolysis

Source: C Granchi, D Fancelli and F Minutolo. (2014) *Bioorg Med Chem Letters* 24:4915–25

GLUT – glucose transporter, HK – hexokinase, PFK – phosphofructokinase, PK – pyruvate kinase, LDH – lactate dehydrogenase, PGM – phosphoglycerate mutase, ENO – enolase, MCT – monocarboxylate transporter

what by the fact that cells use only a small number of major nutrients – principally glucose, glutamine and fatty acids/lipids, although other substances such as acetate are also important.

One probable advantage of targeting metabolism may therefore be that approaches may extend across a range of tumours, owing to common biochemistry, although Dang points out that not all cancers are addicted to the same nutrients: "Breast cancer is addicted more to glucose, for example, and pancreatic cancer to glutamine."

Treatment opportunities

The search for therapeutic drugs is focusing particularly on the metabolic pathways by which nutrients are used by cancer cells, and enzymes in these pathways that could be inhibited. Enzymes are targeted in plenty of other drug applications, but in the cancer metabolism field, research into questions such as how enzymes operate in the glucose pathway is in its early stages.

Metformin, the drug used in diabetes to control blood sugar levels, is one of the most investigated so far in cancer metabolism. Although the exact mechanisms are still being researched, says Dang, it is known to act on an enzyme target called complex I, the first enzyme in the mitochondrial energy chain used to generate ATP (adenosine triphosphate, which every biology student knows as the key energy transfer chemical), thus slowing down the ability of cancer cells to breathe so they can't burn up nutrients.

This works because Otto Warburg's original hypothesis, that cancer cells are glycolytic and don't use mitochondria much, has been superseded by research showing that most cancer cells do, in fact, need mitochondria and do breathe oxygen. Metformin can also work against cancers by insulin control.

As metformin has been prescribed to millions of people for many years, and is known to be very safe, there are fewer obstacles to using it in clinical trials, usually in combination with chemo- or targeted therapies. "We are seeing a real biological effect from metformin in clinical trials," says Dang, and there are already data suggesting that people with diabetes who take metformin have a lower risk of developing cancer or dying from it.

Statins are another group of cheap and widely used drugs that are attracting interest for potential use against cancer, as tumours are known to need to synthesise their own cholesterol. There are now a number of trials of statins in prostate cancer, as well as retrospective analyses comparing rates of prostate cancer incidence and survival between men who have been on statins, and those who have not.

A therapeutic window

The key, as always, is to find ways of attacking cancer cells that don't harm normal cells, says Almut Schulze, a professor at the department of biochemistry and molecular biology, University of Würzburg, Germany, and co-chair of an American Association of Cancer Research (AACR) meeting on cancer and metabolism.

With metabolic approaches, one aim is to find interventions that inhibit cells' metabolic activity and their need to proliferate such that they die, while normal cells may slow down to a resting state, and are much less susceptible to this inhibition.

"The difference with targeting metabolism and using targeted therapies such as imatinib [Glivec] is that we are not attacking proteins or genes that are genetically changed in cancer cells, but other factors needed for proliferation. It's what we call non-oncogene addiction."

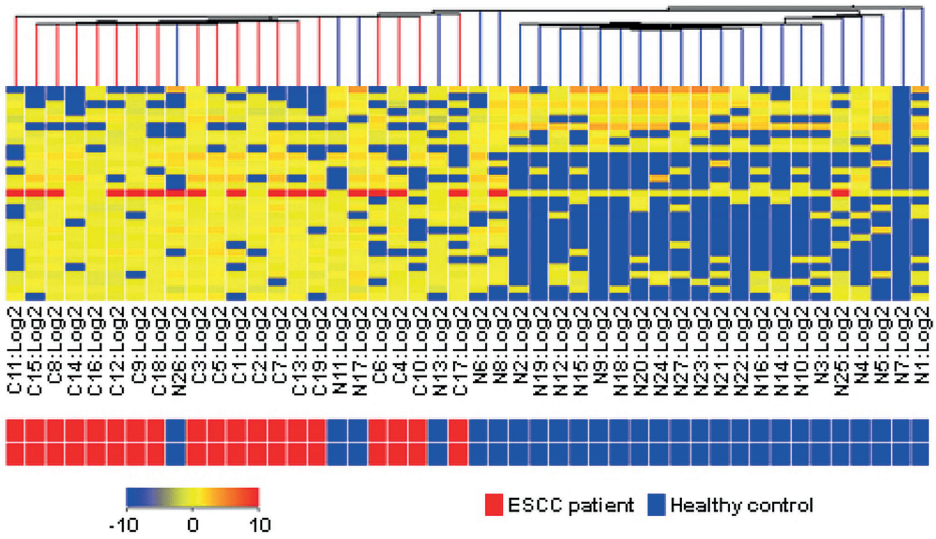
She adds that a big problem in targeting oncogenes, such as BRAF in advanced melanoma, is the rapid development of resistance. However, when people relapse there is also a change in metabolism in cells that could be addressed with new metabolic inhibitors, used in combination with existing therapies, which could be drugs or radiotherapy.

There is also a need to distinguish between the metabolism of normal proliferating cells, such as hair follicles, skin and the gut lining, and cancer cells (chemotherapy affects these normal cells as well).

Schulze's own research group, for example, is focusing on lipids, molecules that include fats and are used

One aim is to find interventions that inhibit cells' metabolic activity such that they die

BUILDING THE METABOLIC PICTURE



Metabolic profiling depicts the expression levels of metabolite markers. This image shows expression levels for 30 differential metabolic biomarkers that distinguish samples taken from patients with oesophageal squamous-cell carcinoma (ESCC – indicated by red block at the base) from those taken from healthy individuals (blue blocks at the base)

Source: R Liu, Y Peng, X Li et al (2013) *Int J Mol Sci* 14:8899–8911, reprinted with permission

Much of the research into targeting the metabolic processes of cancer cells is only now possible because of techniques such as screening genes to reveal more metabolic functions, metabolomic profiling, which can identify metabolites from abnormal pathways in cancer, and also the rise of systems biology to model metabolic processes, as they can be interconnected in a widespread network and looking at one process in isolation could be insufficient.

One important area for research is so-called whole-body metabolism, as there are limitations to using laboratory cell cultures and animal models – and that is an obvious way forward given that the very first application of the Warburg effect uses PET to highlight metabolism in cells in the body (*in vivo*), and there are now other functional imaging methods and ways to measure metabolites in people. A new paper by Jared Mayers and Matthew Vander Heiden, 'Famine versus feast: understanding the metabolism of tumors *in vivo*' sets out the stall: "Examining tumor metabolism in vivo introduces new complexities, but taking this step is crucial to gain a deeper understanding of how whole-animal physiology impacts nutrient availability, as well as to appreciate the role of tumor heterogeneity and interactions between different cell types in tissues." They make observations about how, for example, "pancreatic cancer can alter whole-body metabolism, causing new onset diabetes and cachexia in many patients"; there is "metabolic cooperation between different populations of cells within tumors" and "metabolic interactions with non-malignant tumor stromal cells can also directly influence disease progression, metastasis and redox [reduction-oxidation] status." (See *Trends Biochem Anal* 2015, 40:130–140.)

There are many papers now on cancer and metabolism, notably review style write-ups such as 'Famine versus feast', which although highly technical may also have glossaries and breakout material, a clear indication that this field is in briefing mode about current thinking (see also 'Metabolic targets for cancer therapy', *Nature Rev Drug Discovery* 2013, 12: 829–846 for another good paper). There are also plenty of recent papers that revisit and explain the Warburg effect (e.g. *Mol Biol Rep* 2015, 42:819–823).

Dang and colleagues launched a journal, *Cancer & Metabolism,* in 2013, and there are now several research conferences, such as Metabolism and Cancer, run by the American Association for Cancer Research (AACR), which will be held on 7–10 June this year in Washington DC.

"Normal cells go to rest, but the *Myc* cells die because you take away a building block"

"There is a lot of promise but we really do need some results from the first drugs now. The initial hype is over"

as building blocks in cell membranes. Normal tissues receive lipids from the blood after synthesis in the liver, she says. "But we know that tumours start synthesising lipids from sugar – what advantage is that and why don't they use blood lipids – and can we inhibit this? As most tissues don't synthesise lipids we could intervene in tumour growth without affecting other tissues too much, although the liver may be at risk from toxicity with such an agent."

Dang and colleagues, meanwhile, have demonstrated the fundamental role of the *Myc* oncogene – in a seemingly simple experiment, they put *Myc* in normal cells and then compared what happened when glucose was removed from their nutrients by doing the same with cells without the gene. "Normal cells go to rest, but the *Myc* cells die because you take away a building block and they crash from metabolic death – they try and keep up with the energy demand that their machinery needs."

There are many other targets in the various pathways under investigation, and in two main types of metabolism: bioenergetic metabolism, such as with metformin and mitochondria, and anabolic metabolism, which is about building cells, as with lipid synthesis. Hypoxia, the lack of oxygen commonly seen in tumours, is also a big factor in the metabolic picture, and it also drives angiogenesis – the promotion of blood vessels to bring in oxygen and nutrients – so there is now strong interest in the interplay between these functions.

Other enzymes under investigation include one Schulze has been involved with, which uses acetate in metabolic processes and has been found to be essential for cancer cells. "If we can disrupt it the cells can't grow," she says, adding that the work is a collaboration with AstraZeneca, while a competing study has already moved to using an investigational compound.

Dang mentions that a major advance has been made in cancers that have mutations in certain enzymes, where a drug can turn off the abnormal enzyme. There are early trials using this approach in acute myeloid leukaemia as well as preclinical data for certain brain tumours, using isocitrate dehydrogenase (IDH) metabolic enzymes.

Like most other cancer fields that are on the verge of new therapies, a lot of the activity is in the US, and specifically in the Boston area. One company that is betting on cancer metabolism is Agios, which has two IDH inhibitors at phase I and another agent entering phase II. Activity is more fragmented in Europe, but a particularly strong academic centre is the Beatson in Glasgow (where, in 1896, George Beatson made the first observation of the link between hormones and breast cancer).

It is still early days for cancer metabolism, and Dang says the data are likely to prove some parts of the thinking right but some wrong. "But it's exciting as we can probably create a whole new class of drugs – although there won't be a silver bullet as they are unlikely to work on their own." Says Schulze: "There is a lot of promise but we really do need some results from the first drugs now. The initial hype is over."

Apart from new therapies, new knowledge about metabolism also has implications for public health messaging about diet, obesity and exercise, such as with the latest dietary guidelines in the US, which have relaxed on cholesterol intake but are more strict on saturated fats and sugar.

There is low public awareness of the link between obesity and cancer, and some researchers are urging new multidisciplinary work to tackle the problem. A new term – 'adiponcosis' – has been proposed for the condition by Italian researchers (*J Clin Endocrin Metab* 2013, 98: 4664–65).

And emerging from this highly complex picture is a particularly controversial point from some researchers – that the paradigm of cancer as a genetic disease is wrong and that it is actually primarily a metabolic disease, with all recognised cancer hallmarks being 'downstream' from the "initial disturbance of cellular energy metabolism" (see Seyfried et al. *Carcinogenesis* 2013, 35:515–527). They are at least asking the age old chicken and egg question: Which comes first, cancer cells or abnormal metabolism? ■

Welcome to the revolution!

The changing role of patient advocates within research

ANNA WAGSTAFF

Patient advocates believe their input into guiding the research process is key to ensuring the right questions are investigated in the right way. Where it's been successfully tried, both sides agree there is no going back.

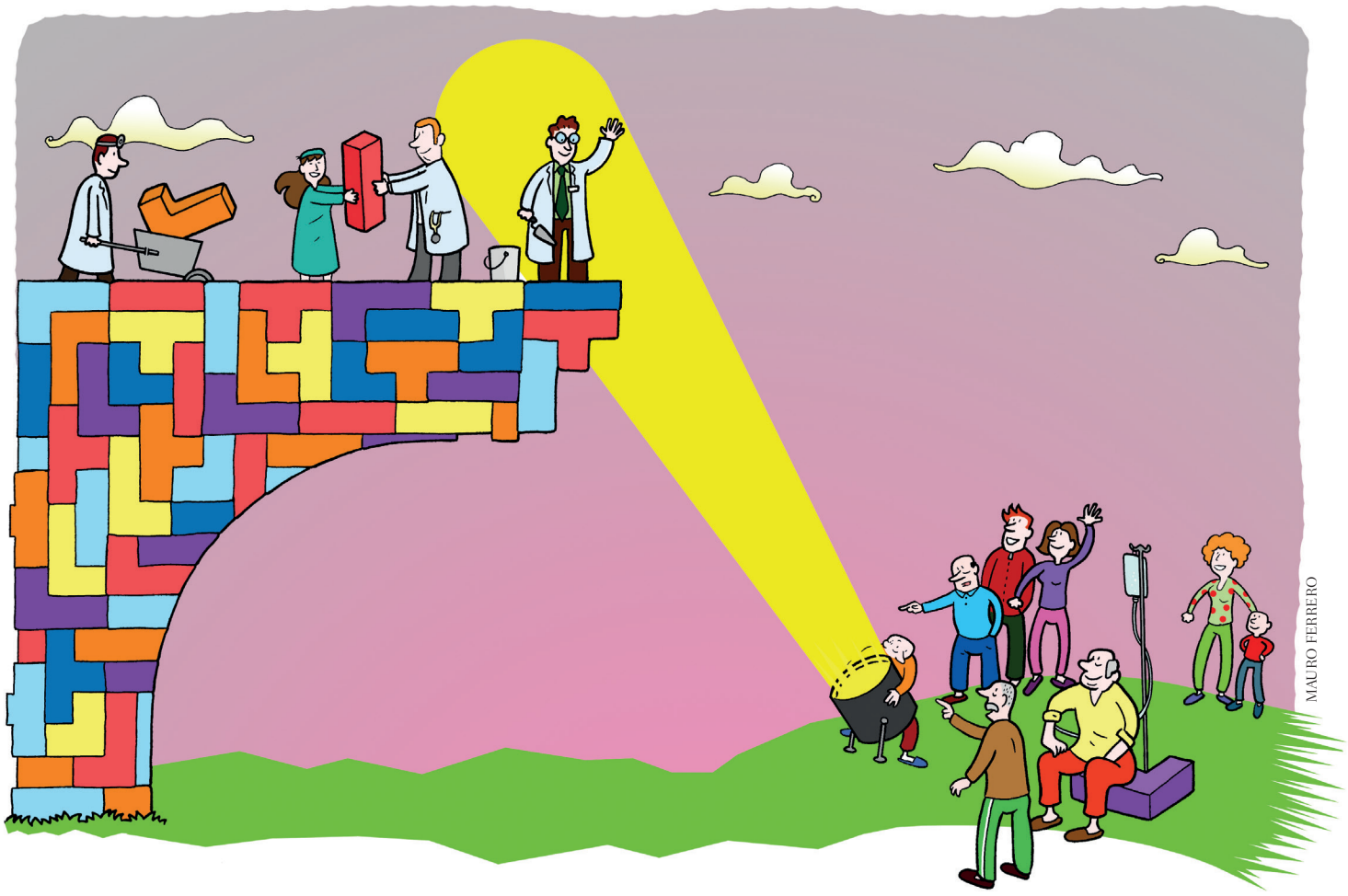
In the summer of 2011, Alessandro Liberati, a clinical statistician and founder of the Italian Cochrane group, typed "multiple myeloma" into the search function of ClinicalTrials.gov. He was looking for evidence about the best options for managing his own cancer, which had just recurred after many years in remission. He never found it.

Of the 1384 trials listed on the site, only 107 were phase II/III comparative studies, of which just over half had overall survival as an endpoint, and only 10 had it as a primary endpoint. Not one trial was the sort of head-to-head comparison of different drugs or strategies that he and his doctor could use to make informed decisions about the best treatment option.

For someone whose professional life had been dedicated to the cause of evidence-based medicine, it was a disappointing and frustrating result. But not for the first time in the course of his illness, Liberati used his experience to try to change things for the better.

In a letter published in *The Lancet* that November (vol 378, pp1777–78), only weeks before his death, he drew attention to the "mismatch between what clinical researchers do and what patients need," and called for a new research governance strategy.

The problem, he argued, is that academic researchers who should be championing head-to-head strategic phase III studies compete instead for pharmaceutical industry funding for early-phase trials, while "pharmaceutical companies avoid research that might show that new and expensive drugs are not better than another



MAURO FERRERO

comparator already on the market."

He advocated redefining the research agenda in the interests of patients, using a collaborative process that would include all stakeholders and would start from an objective analysis of existing and ongoing research.

Liberati's experience is by no means unique. Two years earlier *The Lancet* had run a damning analysis of avoidable waste in clinical research, which identified choosing the wrong question as a widespread problem, alongside duplication of existing evidence, poor study design, and a failure to publish all results promptly and in full.

The report, by Iain Chalmers, a founder of the Cochrane Collaboration, and Paul Glasziou, then head of the Oxford Centre for Evidence-based Medicine, estimated that, as a result, a staggering 85% of clinical research might be failing to contribute in any way to improving knowledge about the best strategies for treatment and care.

The evidence they cite to back their claims about "the wrong question", was drawn from a bibliographic analysis of 334 studies about the priorities of patients, clinicians and researchers for new research, and revealed some dramatic examples.

In osteoarthritis of the knee, for example, where more than 80% of randomised clinical trials were drug evaluations, only 9% of patients and clinicians saw more research on drugs as a priority; the overwhelming majority were much more interested in evidence on the value of physiotherapy and surgery.

The divergence between the priori-

ties of researchers and those of patients and clinicians, say the authors, reflect wider behaviour patterns. The vast majority of the most frequently consulted Cochrane reviews are about non-drug forms of treatment. Yet, even leaving aside commercially funded trials, the research community is highly focused on drugs.

An analysis of the controlled trials funded by the Medical Research Council and medical research charities in the UK between 1980 and 2002 showed they were substantially more likely to be drug trials when compared with trials commissioned by the National Health Service's own research and development programme, where clinicians – and increasingly patients – have a much greater input in setting the agenda.

Setting the agenda

Richard Morley, a specialist in patient and public involvement in research, based at the University of York, in the UK, sums up the problem. "Things that are generally researched are things that are important to pharmaceutical companies and researchers. And while that may be the right thing for them, those priorities are not necessarily shared by the people who are the most important – patients and professionals.

"I know that researchers have the interests of patients at heart, but they also have their own expertise and their own field of interest, and things they particularly want to pursue themselves."

For some years now Morley has been involved as a facilitator for the James Lind Alliance Priority Setting Partnership – an initiative that brings researchers together with patients and carers to define the most important research questions in a given field, very much along the lines that Liberati was calling for.

Morley says that this process brings people with different expectations, wants and needs together to talk about what is important. "It's not public and patient involvement, it's broader than that. It's about patients/carers and health professionals working together to find shared priorities. When I first started, someone sent me a tweet that said, 'Welcome to the revolution.' And it is revolutionary. It is changing the culture of research."

Last year Morley was one of two facilitators working with a group of around 20 patient advocates, clinicians and allied health professionals to set priorities for research into the treatment and care of people with brain and spinal cord tumours. This was the first time the James Lind Alliance had help set priorities for a cancer indication. The 'final top 10' questions that emerged reflected patient priorities in mitigating the stress associated with the 'ticking time bomb' of low-grade gliomas and developing evidence about lifestyle changes they can make to improve their prognosis, in addition to specific questions to do with the benefits and harms associated with different therapeutic strategies.

Designing the trials

Involving patient advocates in the research process is nothing new, but their input has traditionally been restricted to facilitating recruitment to trials.

This continues to pose a major problem in many countries. Studies, including a 2010 Cochrane review (doi:10.1002/14651858.MR000013.pub4) have shown that less than half of all trials succeed in recruiting their target number of patients.

Advocates can play an invaluable role in challenging widespread negative assumptions that researchers simply want to use patients as "guinea pigs" to experiment on for their own ends, and in encouraging patients to look for trials that could benefit them.

Researchers frequently seek patient input in drafting informed consent forms, to make them more accessible, and patient networks can be invaluable in spreading the word about which trials are recruiting.

However, patient advocates are increasingly questioning why they should act as cheerleaders for trials that have been designed without any input from the patient community.

Bettina Ryll, founder of the Melanoma Patients Network, challenges the assumption that all trials ***should*** be recruiting in the first place, because many ask questions of scant interest to patients, or ask them in the wrong way.

"It is in patients' interests that only the good trials are recruiting, not the pointless ones," she says. Indeed, she argues that "if we simply focus on making better and more relevant trials," recruitment would take care of itself Ryll was key in organising the 'Trials we want' meeting in Brussels last year, which brought doctors, researchers, pharmaceutical companies, regulators and health technology assessors to a conference led by melanoma patient advocates (see the 'The melanoma trial of the future' documentary on YouTube).

One of her slides (page 30) has been doing the rounds of cancer conferences, showing that the level of involvement of patient advocates is generally in inverse proportion to impact that they can have – by the time their advice is sought, all the important decisions have already been made. It calls on researchers not just to "do things right", but to "do the right thing".

A SHARED APPROACH TO SETTING THE RESEARCH AGENDA

Last September a group of around 20 people including patients, carers and advocates as well as clinicians, researchers and other health professionals met in London, to define the 10 priority research questions for brain and spinal cord tumours.

Participants were asked to rank their top and bottom priorities, from a shortlist of 25, explaining their reasons. The combined ranking that resulted was then fine-tuned into a consensus 'top 10' during a plenary discussion (see below).

The shortlist of 25 questions had been chosen by online voting from several hundred questions that had been gathered through surveying members of the professional and patient communities, and had been screened, using a Cochrane review-style process, to discard any that could be answered by existing evidence.

LAURA MACDONALD

Prioritising research questions for brain and spinal cord tumours

An equal voice

Kat Lewis (far left in the picture), a speech and language therapist, was impressed at how effective the priority setting process was at giving each participant an equal voice.

"It's very rare that you get patients and their representatives, family and friends in the same room as quite senior and very experienced medics, and are able to get that level of consensus," she said. "That's the real testament to the process. It doesn't always work as smoothly as it did on the day.

"There was a lot of respect for everyone else's opinion. The views of someone who is currently facing cancer or has seen someone die from it are just as valid as the view of the neurosurgeon, who is usually held up as the pinnacle of medical knowledge.

"It did get a little heated towards the end, but everyone still kept to the task of 'Let's look at the bigger picture and think about what we need here, what questions are we asking, what are we looking to get funding for?'"

She attributes the success of the exercise in large part to having clear guidance and ground rules. "Where I've seen patient involvement fail is where the remit of the patients' involvement hasn't been clear, neither side is clear about what is meant to be happening, the meeting or group has no clear directions, and everyone ends up getting frustrated because they feel that it is not really changing anything."

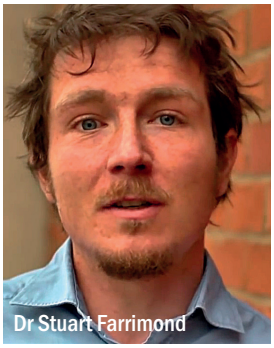
The process was facilitated by the James Lind Alliance Priority Setting Partnership and led by Robin Grant, lead for the neuro-oncology section of the Association of British Neurologists. Patient advocates were represented in the Core Group by Kathy Oliver, co-director of the International Brain Tumour Alliance.

The final top 10

1. Do **lifestyle factors** (e.g. sleep, stress, diet) influence tumour growth in people with a brain or spinal cord tumour?
2. What is the effect on prognosis of **interval scanning** to detect tumour recurrence, compared with scanning on symptomatic recurrence, in people with a brain tumour?
3. Does **earlier diagnosis** improve outcomes, compared to standard diagnosis times, in people with a brain or spinal cord tumour?
4. In **second recurrence glioblastoma**, what is the effect of further treatment on survival and quality of life, compared with best supportive care?
5. Does **earlier referral to specialist palliative care** services at diagnosis improve quality of life and survival in people with a brain or spinal cord tumour?
6. Do **molecular subtyping** techniques improve treatment selection, prediction and prognostication in people with a brain or spinal cord tumour?
7. What are the **long-term** physical and cognitive **effects of surgery and/or radiotherapy** when treating people with a brain or spinal cord tumour?
8. What is the effect of interventions to help **carers** cope with changes that occur in people with a brain or spinal cord tumour, compared with standard care?
9. What is the effect of additional strategies for managing **fatigue**, compared with standard care, in people with a brain or spinal cord tumour?
10. What is the effect of **extent of resection** on survival in people with a suspected glioma of the brain or spinal cord?

DIFFERENT PERSPECTIVES, EQUALLY VALID

Dr Stuart Farrimond can testify to the added value of including the patient perspective. He was diagnosed with a low-grade glioma midway through his training to be a general practitioner. When he was invited to participate in the priority setting exercise for brain and spinal cord tumours, he could therefore see each question from both a professional and patient perspective, and had to decide on his priorities.


Dr Stuart Farrimond

"The thing I was torn between is what is the most important from a clinical point of view, i.e. those things that are going to prolong people's life the most, and those things that affect you on a day-to-day basis," he says.

In the end he opted to give highest priority to some of the questions that he felt would be most valuable to him.

"One of the questions was: how often should we scan people who have low-grade gliomas like I have. On the surface it doesn't seem that important: Do you scan people every six months? Every year? Do you not scan? Is there another way to monitor them?

"From a doctor's point of view the answer seems obvious. The more often you scan people the better it is, because you will be able to pick up any changes sooner, so you can act sooner. But from a personal point of view, having six-monthly scans is very emotionally draining. If someone told me: 'Well actually if we only scanned you every year it would just make let's say 5% or 2% difference to your overall outcome,' that would be very useful for me to say, 'Well on balance I think I'll go down to annual scans.'

"You have the whole emotional thing that affects my wife, it affects me, it affects my family, waiting on the end of the phone to find out if it's another all clear or if your life will be turned upside down."

He also chose to prioritise the question about whether lifestyle choices can influence tumour growth.

Thinking as a medic he understands that the effects of these choices are likely to be relatively small. "So I'd say actually it's far more important that we research cutting-edge treatments, how to improve the chemotherapies that we are giving now, those will ultimately lead to a much better prognosis."

As a patient, however, he sees things differently. "When you are first diagnosed, you feel very out of control, and for many people in my situation you want to do something actively to improve your health and prognosis."

In the absence of any proper evidence, he says, he spent months looking for things he could do that might make a difference. However, eating a lot of supplements, eating certain foods, avoiding others, impacted heavily on his family's life as well as his own – and didn't stop his tumour recurring.

After that he took a more pragmatic approach. "If somebody could say, for instance, there was a supplement that has evidence for being effective, that would be a very useful thing for people in my situation to know."

He feels that the final list of 10 questions gave a fair representation of the priorities of all the groups who were there. "I thought the process was brilliant. The way you can get such a diverse group of people who all have their own agendas to come down to a list that everybody agreed on, or mostly agreed on, and that people compromised to get to, was an incredible thing."

Doing the right thing

A good example of doing the right thing comes from the UK, where patient advocate involvement has been built into the structures of the UK's National Cancer Research Institute, a strategic partnership of the main public and charitable bodies involved in cancer research.

One great advantage of the NCRI lies in its ability to promote a collaborative "portfolio" approach to setting research agendas, in place of the fragmented, competitive model that Liberati found so damaging. A commitment to train and mentor patient advocates to play a role at the heart of the process means that the patient voice is systematically heard in the identification of research questions and the development of trial proposals, often as co-applicants for research funding.

Mat Baker has been working as a patient advocate within the NCRI clinical studies group for lung cancer since shortly after his wife died of the disease five years ago. The group has responsibility for developing and managing the lung trials portfolio. Part of his role is to scrutinise trial applications, which he does from a patient perspective, ensuring they address relevant questions and are sufficiently attractive to patients to stand a good chance of achieving their recruitment goals.

"'What would motivate someone to be part of this trial?' is a question I often ask investigators. 'What would engage them?' Is it that they believe it offers an opportunity for them, or because they believe it would have the potential to improve the situation for those who come after them?

"The protocol, the purpose of the trial has to be clear and resonate and respond to the concerns of patients, either for themselves or for people who have the same conditions as themselves who will come later," he says.

EUPATI - TRAINING 100 EXPERT PATIENTS

The first cohort of 100 patient advocates who will receive training via the EUPATI project are now more than halfway through their 13-month course. They come from 21 European countries and cover a wide spectrum of conditions and diseases.

Among them is Véronique De Graeve (pictured right). A few years ago she founded NET & MEN Kanker (net-men-kanker.be), a Belgian group for people with neuroendocrine tumours and multiple endocrine neoplasia, after doctors had failed for three years to correctly diagnose a NET in her mother. She says she found the course invaluable. "As a young patient group we have to learn so much, and are confronted with such a variety of issues that all need specific knowledge.

"Because of the complexity of those diseases and the need for new and better treatment options, this course is very beneficial to me. EUPATI trains you to be a competent stakeholder, to be able to communicate and engage on an equal level with all those involved in research and development."

Getting your voice heard is a particular challenge for people with rare diseases, she says. "A better informed and educated patient group gives you more power: knowledge and education opens the door to so many things. You can become a voice for what you are standing for."

EUPATI2015

Issues around recruitment are also often underplayed, he says, and sometimes not fully understood by clinical researchers. "They don't always appreciate the demands that are being placed on patients to participate or the issues that participation presents to patients. Those sorts of problems are very real, very obvious on occasion."

Mat Baker now supports other patient advocates and took the lead in developing a toolkit – a collection of resources designed to help patients and lay advocates have an impact and add value to the clinical research process (http://tinyurl.com/consumer-toolkit). The expertise accumulated by the cohort of advocates like himself, who have been involved in the clinical research process for many years, is now seen as indispensable to development of the NCRI cancer trials he says.

Since the NCRI was established in 2001, recruitment to cancer clinical trials has shot up from fewer than 1 in 25 patients to more than one in five. Mat Baker says patient advocates are now a major force trying to push those rates up further.

"My personal view is that we should be aiming to double that, to a figure approaching one in every two patients," he says, adding that the 2013 National Cancer Patient Experience Survey findings show that patients who participate in research record higher levels of satisfaction with their care. "We must therefore also have regard to the further extension of the opportunities to the benefits of participating in research."

Expert patients for Europe

Although patient advocacy groups across Europe are keen to have more say in research that affects them and the in regulatory and health technology assessment processes that determine the therapies they can access, what they lack is the opportunity.

Some major cancer charities, such as the French Ligue contre le cancer and the Dutch Cancer Society, are helping to train expert patients to have an input into the research they fund. Governments outside the UK, however, have done little to encourage or facilitate patient involvement, and advocates continue to face scepticism and about the value they can add to research, if not outright resistance.

Into the breach has stepped EUPATI,

the European Academy on Therapeutic Innovation, the brainchild of the European Patients' Forum, and funded to the tune of €10 million through the Innovative Medicines Initiative – an EU–pharmaceutical industry partnership. EUPATI aims to boost the capacity of patient advocates across Europe to play an effective role with clinical trials, on ethics committees and within regulatory processes.

The communications officer, Rob Camp, comes from the world of HIV/AIDS patient advocacy, which pioneered engaging with research thirty years ago. He explains the EUPATI strategy. "There are three levels. The first is to educate and train 100 patient experts from all over Europe in the intricacies of the research process – everything from basic research in molecular development through to post-marketing and health technology assessment."

This is done through 13-month online courses in two consecutive years, including two sets of four days spent in face-to-face meetings with the trainers, the first of which took place in Barcelona at the end of March.

These 100 'expert patients' will be the 'go-to' people for other advocates from around Europe, says Camp.

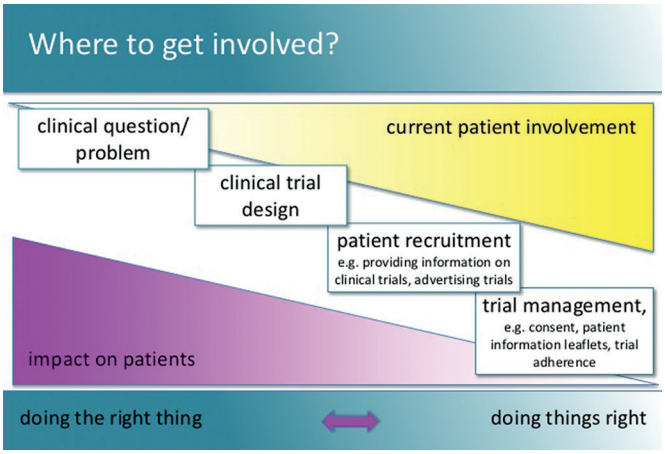
The second level of training comes in online resources that national patient advocates can use in their own countries to help patient organisations to learn more, for instance, about specifics of trials, and apply the knowledge to their needs. These resources will be available in seven languages and fine-tuned at a local level for the needs of the 12 countries involved. Though designed primarily as "training of trainers" material, says Camp, it will ultimately be accessible to anyone who registers on the site.

The third level is aimed at the largest group. "Our goal is to reach 100,000 members of the general public who are interested in one way or another about health – their own or maybe someone in their family – and want information.

"There will be a toolkit available as well as news stories and so forth, which we hope will be interesting for them as they start to negotiate their own health systems on a local level." These resources, aimed at the wider public, will also signpost people to the national advocates – the second level. "If they want to know more, they can go to the patient advocates in their countries to get more in-depth and specific information on any of the subjects they are interested in."

Doing the right thing means involving patient advocates early on, rather than asking them to help 'sell' the trial when all the important decisions have already been taken

Source: Melanoma Patients Network Europe (melanoma-patientnetworkeu.org)



A cultural revolution

Knowledge is power. However, while many patient groups will find the information and training invaluable in their quest to have a say in decisions about new research and treatments, Rob Camp accepts that information by itself is no guarantee that patient advocates gain access to the places where decisions are made. He says that this will mean opening doors on a case by case basis.

"People are still going to have to fight and knock really loudly to be let in. But at least once the door is open they will be somewhat equipped with information that will be useful for them. I think when patients start getting involved they will really become an added value to the process."

Drawing on his experience in the UK, Mat Baker advises that changing the culture to accept the full involvement of expert patients in research requires a process of learning and confidence building, which can take time and determination on all sides.

When government policies started insisting on greater public and patient involvement, he says, many in the research community were yet to be convinced, and played along with varying degrees of enthusiasm. "As the confidence and expertise of lay people has gained ground, the contribution that they make has become valued and recognised. There has been some tokenism, but also I believe there has been a process of genuine collaboration that has evolved, and where it has evolved well, the benefits are very obvious and researchers are very positive about it, and would not consider pursuing further research without having that public and patient involvement." ■

Teenagers and young adults with cancer – addressing the most important care needs

Getting cancer as a teenager or young adult can severely disrupt an important period of emotional, physical and social transition. Tailoring services to fit the particular needs of this age group can make a huge difference.

Various terms, including adolescents, youth, teenagers, young adults and young people, are all used to describe people who are neither children nor adults. In the UK, we talk about teenage and young adult (TYA) cancer care, but adolescent and young adult (AYA) care is used in Europe, the US and Australasia. The World Health Organization (WHO) defines young people as those between the ages of 10 and 24, adolescents as those between 10 and 19, and youth between 15 and 24, so the entire range is from 10 to 24 years of age. However, for the purposes of this article, we will focus on young people between the ages of 13 and 24.

Adolescence is a time of great change, challenge and culture. Young people undergo huge biological change, physically growing up and getting bigger. Going through puberty means significant hormonal changes, and there are also major changes in the brain during this period. Adolescence is also a period of gaining independence,

European School of Oncology e-grandround

The European School of Oncology presents weekly e-grandrounds which offer participants the chance to discuss a range of cutting-edge issues with leading European experts. One of these is selected for publication in each issue of *Cancer World*. In this issue, Maria Cable from Coventry University (pictured on the left) and Nicky Pettitt, Teenage Cancer Trust Lead Nurse for the West Midlands region in the UK (on the right), review the challenges in caring for teenagers and young adults with cancer, focussing on clinical care, service delivery and meeting the particular needs of this age group. Pia Riis Olsen, from Aarhus University Hospital, Aarhus, Denmark, poses questions asked by the audience during the live webcast, which was held in collaboration with the European Oncology Nursing Society (EONS).

Edited by Susan Mayor.

The recorded version of this and other e-grandrounds is available at www.e-eso.net

moving away from parents and becoming independent of them in many ways, including emotionally and financially. Relationships formed during adolescence are important, with peers and friends becoming very significant. Adolescence is also a period where sexuality is determined, and this can be a difficult time for some young people.

Most adolescents have to make important decisions about their education and careers. They also face other challenges, such as getting a driving licence. Changes going on in the world, including technology and social media, give greater freedom to young people, but also add pressure.

Question: *It is increasingly recognised that there are specific and special needs to consider in young people aged 13 to 24 who get cancer. But supportive care needs are poorly characterised for young adults aged 25 to 40, and their specific needs are left under-researched. Are there any signs of developments for these young adults who face specific challenges, some of which are similar to the younger group but which may also include having marital and family issues, young children, interrupting careers and financial problems?*

Answer: *I agree with the point raised, but current UK guidance is for people up to 24. However, age-specific challenges clearly continue above this age group. I'm not aware of any changes in UK policies that will extend the upper age limit, but in reality I'm finding that we have the opportunity to raise awareness of the special needs of this age group, and other people are starting to think about the transferable nature of some of the challenges that we have addressed in TYA cancer care.*

TYA cancer statistics

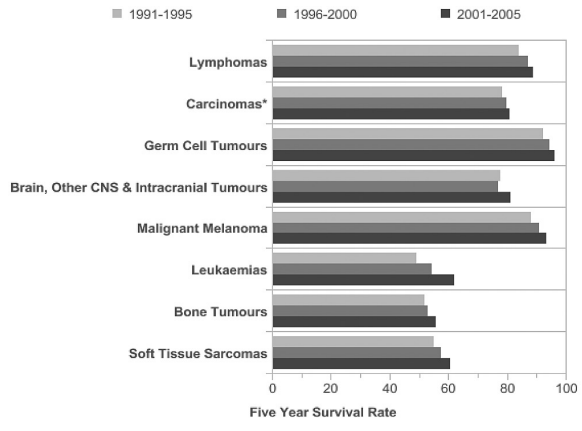
The 15- to 24-year-old age group accounts for only 1% of all new cancer registrations in the UK (all cancers apart from non-melanoma skin cancers), with slightly more males than females. The incidence of cancer in young people rose dramatically throughout the EU in the 1990s. In the last decade it stabilised among males; among females, however, the incidence continued to increase, by about 10%.

TEENAGE CANCER TRUST

The main types of cancer in teenagers and young adults in the UK are lymphomas, carcinomas, germ cell tumours, brain and CNS tumours, malignant melanomas, leukaemias, bone tumours and soft tissue sarcomas.

Some research has been done to look at the causes of these types of cancer in this age group, some of which are paediatric cancers and others adult types. Malignant melanomas are known to be associated with UV exposure, and cervical cancer, which accounts for some of the

CHANGE IN FIVE-YEAR SURVIVAL RATES FOR TEENAGE AND YOUNG ADULT CANCER PATIENTS (UK, 1991–2005)



Progress in survival for the most common cancers among teenage and young adults (ranked in order of frequency) has been painfully slow

*Excluding non-melanoma skin cancer
Source: North West Cancer Intelligence Service (NWCIS), UK; reprinted from www.cancerresearchuk.org

The Teenage Cancer Trust unit at the University College Hospital Cancer Centre in London. A place where teenagers can be teenagers

carcinomas, has a known association with the human papillomavirus. In addition, growth and hormonal factors during puberty may trigger cancers in this age group, and genetic syndromes are implicated in some cancers. Unfortunately, we are also seeing more secondary cancers due to cancer treatment during childhood.

Survival from cancer in this age group is improving. In the UK, five-year survival is now approximately 80%, with slightly higher survival in females than males. Across Europe this can range up to 92% (in Iceland). But it is important to recognise that the survival rate in the 15- to 24-year age group is significantly lower than that in children under the age of 16.

Five-year survival rates for three diagnostic periods from 1991 to 2006 in the UK are shown in the graph (*left*) They show a considerable variation in survival between different diagnostic groups, which has remained fairly consistent over the years. The most important thing to take from the graph is that survival for soft tissue sarcomas and bone tumours has not changed significantly, and is still poor.

Unfortunately, cancer remains the leading cause of death in UK teenagers and young adults after accidental death, accounting for 310 deaths in young people each year, with brain and CNS tumours being the most common causes of cancer deaths.

Survival rates are increasing, however, which is reassuring. Death rates across Europe have decreased by around 50% since the 1970s, reflecting improvements in treatments over the last 40 to 50 years.

Clinical challenges in TYA cancer

There are several challenges in TYA cancers. Survival rates for teenagers and young adults have improved less than for adults and children, and the incidence is increasing in this age group. One reason for poorer survival is limited access to clinical trials. Paediatric trials often have a cut-off age of 16 years, while adult trials start at 18, so teenagers can miss out. In the UK, at least, researchers are being encouraged to consider including teenagers and young adults in trials they are starting.

Another challenge is that many teenagers and young adults with cancer are diagnosed late, often in accident and emergency services. This is frequently because, even if they go to their GP several times, the GP may not consider the possibility that their symptoms could be caused by cancer, and assume instead that they are due to age, stress or lifestyle. In addition, young people may be reluctant to see a doctor because they themselves doubt their symptoms relate to a serious problem.

A further challenge is the small number of teenagers and young adults in cancer centres, so they don't form a coherent group. There may be just

one or two of them on an adult ward or department, or in a children's hospital, and staff may fail to see that they have different needs to children or adults. Guidance is also lacking for systematic referral pathways for young people, to clarify the steps in their programme of care. In addition, there are challenges in providing end-of-life care, whether in a hospice, hospital or at home; teenagers and young adults fall between child and adult services, and greater clarity is needed about who should look after these young people in the community.

Young people who have survived cancer can be faced with many survivorship issues: financial, emotional, physical and social. Their friends may have moved on and they have been left behind, their education has often been interrupted and they may face long-term consequences from their treatment. There may be questions as to who will continue to follow them up – will it be an adult team; if not, at what point will they transition to an adult team?

UK guidance on care of young people with cancer

The National Institute for Health and Care Excellence (NICE) issued guidance in 2005, 'Improving Outcomes in Children and Young People with Cancer', which provides clear standards for service delivery. The key principles are:

- Care is centred around principal treatment centres, supported by designated local hospitals.
- A TYA-specific multidisciplinary team works out of each group or treatment centre alongside cancer site-specific teams.
- There needs to be a TYA psychosocial team that provides an umbrella over services.
- Young people must have unhindered access to age-appropriate facilities and support, and should have choice about their care.

Very different models of care have developed across the UK, despite all following the same standards and guidance. There are multiple models for delivering a good service, in the UK and throughout Europe and Australasia. The challenges that we all face are the same, but are interpreted differently depending on the support available. Service evaluations for models that are well established and new models that are being introduced will help to guide the future.

TEENAGE CANCER TRUST

Question: *The Teenage Cancer Trust has had an enormous impact on TYA cancer care in the UK. Has the existence of this organisation also influenced health policies for TYAs?*

Answer: *The Teenage Cancer Trust and other charities have achieved a great deal in championing the needs of young adults. They have supported the building of wards and specialist units (the Teenage Cancer Trust funds 28 units), lobbied government, funded specialist staff such as clinical nurse specialists, and provided funding for activities and research to improve the care young people receive. Charities fund much of the specialist care for TYA cancer patients, which would not be provided in a stretched health service without their help.*

Question: *How can we support teenagers and adults in remote and rural areas who have limited local support?*

Answer: *I think it's about being clever with how we interpret support, using technology and engaging young people in ways other than face-to-face working, via the telephone or social media, and signposting them to alternative ideas of support. There's no definition of what age-appropriate care is, but for me it's about holistic care and supporting a young person to lead a normal life within a new normal of a cancer diagnosis. We are doing some evaluation at the moment and it has shown that not every young person gets into a teenage cancer centre. There might be ways we could look at for us to go out to the*

patients rather than them coming in to us, which just means giving them a call so we can advocate for them and to help them navigate their way through their treatment. The teenage cancer charity Canteen in Australia has just launched a new 24/7 counselling and support service for young people via the web.

Meeting TYA cancer-specific needs

Adolescence is a period of great change, and getting a cancer diagnosis impacts on every single aspect, so it's crucial that we see the adolescent first and then work with them with their new diagnosis of cancer.

We must remember what being an adolescent is like and be aware of all of these issues, some of which are detailed in the box above.

Any healthcare professional or voluntary service can support young people going through cancer, by thinking about the impact on their life trajectory and how we can support normal changes through an abnormal period.

This means, for instance, being aware of the biological changes that happen in puberty, and letting young women know that, if they've just started their periods, they may stop, or acknowledging that changes in their body might be increased or decreased.

Hormones are affected by cancer and cancer treatment in young people, and services need to make sure that the impact on fertility and growth are considered. Care and services also need to bear in mind the changes happening within the brain: behaviour, emotions, reactions and processing may not be consistent, because young people's brains are still developing.

Care also needs to include support around issues of independence, relationships, sexuality and education/employment during this critical period of growing up. This includes recognising the importance of peer support, supporting healthy sexuality and safe sex practices, and ensuring support for education and employment, which are critical in this age range. Young people may be fighting for their independence, but when they're feeling unwell they may just want to be looked after.

We can't talk about young people's services without listening to what young people want. It is important that their voices are heard. The poster overleaf shows what young people want from cancer services, including: expert staff, to be treated as young people, have the opportunity to socialise, be respected as individuals, and feel comfortable and cared for in their environment.

Question: *Because the number of teenagers and young adults who have cancer is so small, maybe it is more critical to establish a special service? In our department we only have four beds for young people with cancer in a special unit for teenagers and young adults that is part of an adult ward, which offers a different approach.*

Answer: *I think if you have the right team of people and approach, you can provide a specialised service in any type of environment. The age-appropriate needs should not take precedence over the need for expert care for each young person's type of cancer. As TYA professionals, we can easily visit a neurosurgical or other specialist ward to support a young person. As a TYA champion, a lot of my role is supporting non-TYA professionals to provide age-appropriate care for young people in their care.*

SUPPORTING THE UNIQUE NEEDS OF TYA CANCER PATIENTS

Biological changes –maintaining normality through an abnormal time, impact of treatment
Hormones – fertility and growth
Brain changes – making care 'fit' young people
Independence – 'growing up and growing down'
Relationships – maintaining old and developing new
Sexuality – safe sex, 'being who I want to be'
Education/employment – providing specialist teachers, liaising with education providers, offering new opportunities for learning and development
Pressures of the modern world – social media, technology

Supporting multiprofessional working

Multiprofessional teamwork underpins good TYA cancer care. Education is very important and several organisations support this, including:

- TYAC www.tyac.org.uk (Teenage and Young Adults with Cancer) – a UK group for professionals with a useful website and educational events
- The Teenage Cancer Trust www.teenagecancertrust.org – a great support nationally and internationally in terms of developing services and sharing experiences
- ENCCA www.encca.eu (European Network for Cancer research in Children and Adolescents) and SIOPE www.siope.eu (European Society for Paediatric Oncology) – European professional and research organisations which have educational materials and are working to define and determine what TYA cancer care is
- Canteen www.canteen.org.au – an Australian charity driving TYA care

- Teen Cancer America https://teencanceramerica.org – a group founded in 2013 aiming to emulate, in some regards, what has been done in the UK
- Critical Mass http://criticalmass.org – a US group worth following on Twitter and Facebook, offering some brilliant insight into the specific needs of teenagers and young adults with cancer.

The accredited programme that we run at Coventry University, in the UK, includes an online post-graduate certificate, graduate certificate and single modules. There is also non-accredited training available as study days, online modules and short courses. SIOPE and ESMO (European Society for Medical Oncology) have e-learning materials.

Do specialist services for TYAs with cancer add value?

BRIGHTLIGHT is the first national study of young people aged 13–24 years newly diagnosed with cancer. It is currently recruiting in England, with the aim of assessing whether specialist services add value (www.brightlightstudy.com), and will follow up every newly diagnosed young person with cancer at key points in their journeys to look at their experiences up to three years from their diagnosis. It will evaluate the association between specialist treatment and TYA services in young people and the costs involved.

Summing up

The challenges of delivering age-appropriate care to teenagers and young adults with cancer include the fact that patient numbers are small and that the care they need is complex and expensive.

Young people have traditionally been treated with either children or adults, and age-appropriate units are a relatively new approach to caring for this age group.

Geography can make care delivery difficult, and we don't always know where patients are. Young people don't necessarily get into specialist services, and support and care is not always equitable. TYA cancer care is a new and emerging specialty that is not always recognised.

The take home message is to 'see the young person first and the cancer second'. This is crucial, particularly because of the age and stage of life these patients are in. Young peoples' voices are very loud and can tell a very powerful story and help lobby for change.

Small changes, such as not having an early morning routine as you would on a children's or adult ward, can make a huge difference, and are not difficult to implement. Networking with likeminded colleagues locally, sharing experience and collaborating can be very valuable. ■

What we want: what young people told Teenage Cancer Trust

impactfactor

nature REVIEWS CLINICAL ONCOLOGY

A decade of discovery in cancer genomics

KENNETH OFFIT

Over the past decade, genetic testing for rare inherited mutations, such as *BRCA1* and *BRCA2* mutations, has been successfully incorporated into clinical practice. Next-generation sequencing of cancer-susceptibility genes and entire tumour genomes has transformed cancer care and prevention. The discoveries of new cancer syndromes have raised exciting opportunities and potential liabilities for cancer-care providers seeking to incorporate genomic approaches into preventive oncology practice.

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The past decade has witnessed the incorporation of genetic testing for cancer-susceptibility syndromes into the evidence-based practice of oncology, and the emergence of 'next-generation' genome scans for cancer-risk loci. Herein, I discuss a series of seminal papers published over the past decade that described new cancer syndromes, but also raised new challenges related to informed consent, incidental findings, and the management of genetic variants of unknown significance or unproven clinical actionability.

In the 1980s and 1990s, rare but highly-penetrant cancer-predisposition genes were identified by studying cancer-prone families that demonstrate Mendelian inheritance of cancer susceptibility. These studies implicated genes, such as *BRCA1* and *BRCA2*, the DNA-mismatch-repair genes (relevant for colon cancer), *TP53* in Li–Fraumeni syndrome, and *APC* in familial adenomatous polyposis. The genetic basis of these and other syndromes had a powerful impact on the practice of preventive oncology. The incorporation of genetic testing for *BRCA* mutations in breast cancer marked one of the first applications of 'personalised' genomics in medicine, and enabled 'targeted' cancer screening, prevention and, in some cases, the ability to personalise therapies according to the patient's genetic lansdcape.[1] The translation of *BRCA* testing to clinical practice was highlighted by Domchek and colleagues[2] who showed that preventive surgery of the ovaries over a 34-year period decreased mortality in a cohort of 2,482 women with *BRCA1* or *BRCA2* mutations; compared with women who did not have salpingo-oophorectomy, women who underwent this procedure had a 60% decrease in all-cause death rates, driven by lower mortality associated with both breast and ovarian cancer.[2] In this study, the subset of women found to have occult microscopic ovarian cancer at the time of 'preventive' surgery were excluded from analysis.[2] During subsequent years, risk-reducing ovarian surgery, along with breast MRI, the option of prophylactic breast surgery, and hormonal

chemoprevention, became standard practice in preventive oncology.[1]

In the past decade it had become obvious that highly penetrant cancer genes (such as *BRCA1/2* and *MSH2*) did not account for the bulk of familial risk of the common hereditary cancers. A debate ensued regarding whether there were many common low-risk genetic variants or undiscovered rare high-risk variants, which would explain the 'missing heritability' of cancer. A pivotal paper tested the 'common variant' hypothesis using the emerging technology of 'gene chips' to assess hundreds of thousands of single nucleotide polymorphisms (SNPs).[3] In a two-stage design, 227,876 SNPs were assessed in 4,398 breast-cancer cases and 4,316 controls, identifying 30 SNPs of interest, which were further analysed in 21,860 cases and 22,578 controls.[3] The SNP that emerged as the best 'hit', which was proximal to the gene *FGFR2*, had a relative risk of around 1.2-times the baseline risk, compared with *BRCA1*, which elevated risk of early onset breast cancer by up to 40-fold.[3] Subsequent genome-wide association studies of other cancer types identified hundreds of hits near potentially causal genes, which were all statistically significant, but none of a magnitude to influence preventive management in the clinic.[4] A possible exception to this lack of clinical utility emerged from studies we performed as part of an international consortium investigating modifiers of risk in the carriers of *BRCA* mutations. In studies involving tens of thousands of *BRCA1/2* mutation carriers worldwide, panels of risk-associated SNPs could partition breast cancer risk from 20% up to 100% in *BRCA*-mutation carriers.[5] These findings will likely mark the first application of SNP-based risk profiling to inform clinical management of individuals with hereditary risk of a common cancer.

Over the second half of the past decade, a shift to identifying rare genomic variants was made possible by the emergence of next-generation sequencing (NGS) approaches. NGS involves a series of repeating sequencing reactions, performed and detected automatically, with the production of thousands to millions of simultaneous sequence reads. An immediate and obvious application of NGS was to sequence several genes at the same time. A technological *tour de force* prefigured the current era in 'cancer panel' testing. Using targeted capture and massively parallel genomic sequencing, a group at the University of Washington screened 21 candidate genes in 360 women with ovarian cancer.[6] Strikingly, 24% of these women carried germline loss-of-function mutations in genes such as *BRCA1, BRCA2, BARD1, BRIP1, CHEK2, MRE11A, MSH6, NBN, PALB2, RAD50, RAD51C*, and *TP53*.[6] Fuelled by this technological innovation, plus the equally impactful loss of patent protection for *BRCA1* and *BRCA2* sequence analysis, a plethora of commercial cancer panels flooded the oncology marketplace.

At the same time, NGS technologies were rapidly applied to studying unexplained familial cancer clusters. Over the past five years, whole-exome sequencing (WES) and whole-genome sequencing (WGS) has resulted in a renaissance in the discovery of new syndromes of cancer susceptibility (see box).

One of the early applications of this technology came from a group at the Johns Hopkins University, who applied WES of 20,661 coding genes

Cancer susceptibility syndromes*

Familial pancreatic cancer
PALB2 identified by exome sequencing; *ATM* identified by exome sequencing and WGS

Familial ovarian cancer
BRIP1 identified by WGS

Familial pheochromocytoma
MAX identified through exome sequencing

Acute myelogenous leukaemia (with Emberger syndrome)
GATA2 identified by exome sequencing

Familial Hodgkin lymphoma
NPAT identified by exome sequencing

Familial pre-B-cell acute lymphoblastic leukaemia
PAX5 identified by exome sequencing

Familial melanoma
MITF identified by WGS; *TERT* identified by targeted sequencing

Familial mesothelioma, melanoma and renal-cell cancer
BAP1 identified through exome and targeted sequencing

Hereditary mixed polyposis syndrome (HMPS)
GREM1 identified by targeted sequencing

Colorectal adenomas and colon cancer
POLE and *POLD1* identified by WGS

Familial breast cancer
XRCC2 and *FAN1* identified by exome sequencing; *PPM1D* (mosaic) by targeted sequencing

*Discovered recently by next-generation sequencing[4]
WGS – whole-genome sequencing

in a single case of familial pancreatic cancer.[7] Of 15,461 germline variants not found in the reference human genome, a deletion of four base pairs within the *PALB2* gene was discovered and tested as a pancreatic-cancer-susceptibility gene.[7] Despite this early report, we and others have failed to confirm *PALB2* as a major factor in hereditary breast–pancreas-cancer families; however, *PALB2* maintained its status as a rare breast-cancer-susceptibility gene.

Oncologists will soon be screening the inherited genomes of all patients with cancer

Another example of a new syndrome with a striking phenotype was described by Testa and colleagues in 2011,[8] on the basis of their observation of gene clustering of mesotheliomas and melanomas. Using exome sequencing strategies, germline mutations were discovered in the gene encoding *BRCA1*-associated protein-1 (*BAP1*) in two families with multiple cases of mesothelioma, and in some cases of uveal melanoma.[8] These findings built on the earlier observation of inherited germline *BAP1* mutations in uveal and cutaneous melanocytic tumours. Remarkably, this syndrome was extended by other groups to include renal-cell cancers in rare families.

In some cases the 'new' familial cancer types studied were not rare. For example, we studied families with acute lymphoblastic leukaemia, the most-common malignancy of childhood, and identified a mutation in a lymphoid-associated transcription factor, *PAX5*, in two such families,[9] with a third Israeli family more recently reported to harbour the same mutation. These 'new' cancer syndromes have redefined our notion of inherited cancer (see box, p47).

Despite these advances over the past decade, clinical interventions for these syndromes remain relatively rudimentary, and the ethical implications of these discoveries remain daunting. Risk reduction for the adult-cancer syndromes includes organ removal surgeries.[1] True genetic prevention using assisted reproductive technologies is an option oncologists should remember to discuss with their younger patients, or patient's families, taking into account ethical or religious considerations. A broader ethical debate has emerged regarding the extent to which incidental, or secondary genetic findings, termed the 'incidentalome', should be disclosed to patients. Particularly challenging for oncologists are the unexpected results of NGS analysis of tumour and normal pairs, which might include identification of genetic predispositions to non-cancer-related diseases, such as cardiac or neurological diseases.[10] A vigorous discussion is in progress regarding the potential obligations of physicians to inform individuals of incidental genetic findings.

At the same time there have been recent calls for population-based screening, –for example *BRCA* testing of all 30-year-old women worldwide. Although such requests by laboratory-based scientists have the best intentions, they overlook a more-pressing clinical reality: oncologists will soon be screening the inherited genomes of all patients with cancer. In both scenarios, population testing of healthy individuals and tumour–normal screening in patients with tumours, we must recognise what has been learnt over the past decade: not all individuals wish to know all genomic information; risks might reflect both population heterogeneity and differences in penetrance; and not all genomic information is clinically actionable. Oncology has become the 'ground zero' for a tectonic shift in paradigms regarding personalised medicine, both for targeted treatment as well as prevention based on genomic profiles. ■

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newsround

Selected reports edited by Janet Fricker

Most oncology patient requests are appropriate

■ JAMA Oncology

Patient demands or requests for tests or treatments occur in less than 10% of outpatient oncology encounters, with just 0.14% of encounters resulting in clinicians complying with inappropriate demands or requests, a recent study has found.

When surveyed, physicians often place responsibility for high medical costs on 'demanding patients', contending that the threat of malpractice suits forces them to practise defensive medicine. Little data, however, exists about the frequency of demanding patients, the clinical appropriateness of their demands, and clinician compliance.

In this study, Ezekiel Emanuel and colleagues, from the University of Pennsylvania, set out to assess how frequently patients demand or request medical tests or treatments, the types of treatment, the clinical appropriateness of demands, and how frequently clinicians comply.

Between October 2013 and June 2014, 60 clinicians (34 oncologists, 11 oncology fellows, and 15 nurse practitioners and physician assistants) from three oncology centres in Philadelphia were interviewed by trained research assistants. The interviews took place either immediately after, or at the end of, half-day clinic sessions. In interviews clinicians were asked, "During today's visit, did the patient request or demand a specific test or treatment?" A 'no' response terminated the interview, while a 'yes' response prompted a series of questions such as "on a scale from 1 to 10, how would you rate the appropriateness of the test or treatment?" Ten was extremely appropriate; while 1 was not appropriate.

The study included 5,050 patient–clinician encounters with 3,624 different patients. Results showed that 8.7% of the encounters (*n*=440) included a patient demand or request for a test, treatment, or other kind of medical intervention, such as a consultation. Healthcare professionals complied with 83.0% of requests (*n*=356), judging that 16.8% (*n*=74) were equivocal and only 11.4% (*n*=50) were clinically inappropriate. Clinicians complied with seven (out of 50) of these inappropriate demands (14%). Overall clinicians complied with inappropriate demands in seven out of 5,050 encounters (0.14%).

"At least in oncology, 'demanding patients' seem infrequent and may not account for a significant proportion of costs," conclude the authors.

Considering why patient requests 'loom large' in physicians' minds, the authors write, "Even requests for clinically appropriate interventions can suggest lack of trust in the clinician and threaten the therapeutic relationship."

In an accompanying commentary, Anthon Back, from the University of Washington, Seattle, suggests the real point is that clinicians need to stop blaming patients for being demanding. "The demanding patient myth reflects an old paradigm of patient–clinician interactions: the paternalistic physician told the patient what to do, and the patient who did not like it had to resort to a demand to cut through the physician's cloak of authority."

In the age of the worldwide web, the new dynamic is for patients to use consultations to verify what they have read, and gain from the physician's clinical experience. "It is possible that what the study ... documents is a point in the evolution of the patient–physician relationship where both sides recognize that the complexity of cancer care belies a quick fix," he writes.

■ K Gogineni, K Shuman, D Chinn et al. Patient demands and requests for cancer tests and treatments. *JAMA Oncol*, published online 12 February 2015, doi: 10.1001/jamaoncol2014.197

■ A Back. The myth of the demanding patient. *ibid* published online 12 February 2015, doi: 10.1001/jamaoncol.2014.185

Prior cancer diagnosis no reason for exclusion from lung cancer trials

■ JNCI

Among patients with stage IV lung cancer, a prior history of cancer does not cause adverse effects on clinical outcomes regardless of prior cancer stage, type or timing. The US registry analysis found that a prior cancer diagnosis did not adversely impact all-cause mortality or lung-cancer-specific mortality, with findings holding for each subgroup analysed.

In many lung cancer trials, a history of prior cancer represents a common exclusion criterion, reflecting concerns that prior cancers may affect trial conduct or outcomes. However, studies evaluating the impact of prior cancer on lung cancer outcomes have yielded conflicting results, with some show-

ing a history of previous malignancy did not have detrimental effects on survival, and others suggesting it did.

In the current study David Gerber and colleagues, from the University of Texas Southwestern Medical Center, Dallas, set out to determine the prevalence and prognostic impact of prior cancers among patients with advanced lung cancer, using the Surveillance, Epidemiology, and End Results (SEER) Medicare patient registry, linked to 1991–2010 Medicare claims files.

Overall, 102,929 patients with stage IV lung cancer aged over 65 years were identified, of whom 15,170 (14.7%) had documented prior cancers. These were prostate cancer in 27.9% of patients, gastrointestinal in 15.1%, genitourinary in 14.4%, breast in 14.2%, head+neck in 7.8% , haematological in 7.7%, gynaecologic in 6.1% , and other cancers in 6.8%. Most of the cases had occurred within five years of lung cancer diagnosis.

Results showed that, in comparison to stage IV lung cancer patients without a prior history of cancer, those with a prior history had better overall survival (HR 0.93, $P<0.0001$) and lung-cancer-specific survival (HR 0.91, $P<0.0001$). Furthermore, in subset analyses according to stage, type, and timing of prior cancer, no group of patients with prior cancers had inferior survival outcomes compared with patients without prior cancers.

"Together, these findings suggest that broader inclusion in clinical trials of advanced lung cancer patients with prior cancer could be considered without impacting study outcomes," write the authors. "Such policy modifications could lead to faster accrual, higher trial completion rates, and more generalizable results, ultimately providing better treatments to more patients sooner."

There are many potential explanations, add the authors, including a healthy survivor effect, the fact that patients who have experienced cancer already are likely to engage more frequently with healthcare systems and the lead time bias. Although all cases were stage IV, those occurring after prior cancers may have been diagnosed earlier.

Concerns that exposure to prior cancer treatment renders patients less likely to tolerate experimental therapies, add the authors, can be addressed by using trial entry criteria (such as organ function, blood counts, and functional status) to screen for treatment intolerance.

■ A Laccetti, S Pruitt, L Xuan et al. Effect of prior cancer on outcomes in advanced lung cancer: implications for clinical trial eligibility and accrual. *JNCI* 5 April 2015, 107:doi:10.1093/jnci/djv002

Physical activity improves health-related quality of life

■ Journal of Cancer Survivorship

Patients with colorectal cancer who met physical activity guidelines report statistically higher levels of health-related quality of life (HRQoL) compared to patients who never or sometimes met guidelines. This Dutch study, which is the first longitudinal population-based study among survivors of colorectal cancer taking place more than two years since diagnosis, demonstrated the positive association to be consistent over time.

The number of survivors of colorectal cancer is rapidly increasing, with estimates suggesting 53% of patients diagnosed with colorectal cancer now survive more than ten years after diagnosis. Many, however, face continuing physical and psychosocial problems due to cancer and its treatment, which can have a negative impact on HRQoL. Studies have suggested that survivors meeting the public health exercise guidelines of 150 minutes or more of moderate to vigorous activity per week had better HRQoL scores than those who did not.

In the current study Olga Husson and colleagues, from the Comprehensive Cancer Centre, Eindhoven, set out to examine longitudinal relations between physical activity and HRQoL among survivors of colorectal cancer more than two years after diagnosis.

For the study, individuals diagnosed with CRC between January 2000 and June 2009, registered with the Eindhoven Cancer Registry, received a first questionnaire in December 2010 (T1), a second questionnaire in 2011 (T2) and third in 2012 (T3). HRQoL was measured by a 30-item questionnaire consisting of five functional scales, a global health status item, three symptom scales and five single symptom items. In addition, the survey included questions on the average number of hours per week participants spent walking, bicycling, gardening, housekeeping, and undertaking sports. Metabolic equivalent scores were assigned to each activity as estimates of intensity.

Response rates were 73% for the first survey (n=2,625), 83% for the second survey (n=1,643) and 82% for the third survey (n=1,458).

Altogether 82% of respondents met the Dutch physical activity guidelines of at least 150 minutes of moderate to vigorous physical activity per week at all assessment periods. Multivariate analyses showed that patients who met the physical activity guidelines scored, on average, 13.7 points higher on the global quality of life, 26.0 on physical, 24.2 on role, 9.0 on cognitive, 10.4 on emotion, and 14.8 on social functioning over time in comparison to patients not meeting the guidelines ($P<0.01$ for all).

"Our results underline the importance to focus upon training in survivorship care and strategies to get inactive cancer survivors physically active," write the authors, adding that inclusion of training programmes is still not standard in current Dutch oncology rehabilitation programmes.

"An additional barrier for supporting long-term physical activity is that most PA [physical activity] interventions are focused on short-term outcomes, while most patients will relapse into their 'old' less active behavior in the long run," write the authors.

Future physical activity interventions, they suggest, should include successful behavioural components, to increase the likelihood of long-lasting behavioural changes.

■ O Husson, F Mols, N Ezendam et al. Health-related quality of life is associated with physical activity levels among colorectal cancer survivors: a longitudinal, 3-year study of the PROFILES registry. *J Cancer Surviv* published online 9 January 2015, doi: 10.1007/s11764-014-0423-x

Study of surgical complications helps benchmark performance

■ British Journal of Cancer

A prospective multicentre UK study involving nearly 3,000 women undergoing surgery for gynaecological cancers reveals intra-operative complications occur in nearly 1 in 20 patients and postoperative complications occur in more than one in four.

Limited data have been available on surgical outcomes in gynaecological oncology, due to data collection not being standardised or structured across hospitals. To address this lack of high-quality data, Usha Menon and colleagues, from University College, London, undertook the United Kingdom Gynaecological Oncology Surgical Outcomes and Complications (UKGOSOC) study, to 'contemporaneously' capture relevant data from 10 participating UK gynaecological oncology centres.

In the study, all major surgical procedures performed in a gynaecological oncology theatre list were included, with a web-based custom-built database developed to capture data at various stages of the surgical pathway.

A surgical complication was defined as 'an undesirable and unintended result of an operation' affecting the patient that occurs as a direct result of the operation. Complications were graded I–V using the Clavien and Dindo system, based on the severity and intervention required. In addition, patients were sent follow-up letters to ensure completeness of capturing postoperative complications.

Between April 2010 and February 2012, prospective data were recorded on 2,948 major operations involving 2,910 women. In addition, patient-reported complications were available for 1,462 surgeries (68%).

Overall, 33.5% of surgeries were for ovarian, 27.8% for uterine, 7% for cervical, and 6% for vulvular cancer, with 25.6% for benign pathologies. In total, 139 of 2,948 surgeries had an intra-operative complication, giving an overall intra-operative complication rate of 4.7%. Haemorrhage accounted for 28.7% of intra-operative complications, bladder complications for 15.4%, and small bowel complications for 15.4%.

On a univariable analysis for intra-operative complications, risk was increased by previous abdominal surgery (OR 1.74), diabetes (OR 2.01) and surgical complexity (OR 8.27 for level V).

For postoperative complications there were 200 hospital-reported and 252 patient-reported grade II–V complications in 379 surgeries, resulting in an overall postoperative complication rate of 25.9%. On a univariable analysis for postoperative complications, risk was increased by diabetes (OR 1.91), previous abdominal surgery (OR 1.46), obesity (OR 1.35), duration of surgery (OR 1.50), cervical final diagnosis (OR 1.62) and vulvular final diagnosis (OR 2.02).

"Gynaecological oncology surgery is associated with considerable morbidity and our study provides much needed estimates of complication risk associated with procedures for specific cancers to counsel patients and benchmark surgical performance," write the authors. There are significant patient and surgical factors influencing risk, they add, raising the need for risk-adjusted rates for outcome comparisons.

■ R Iyer, A Gentry-Maharaj, A Nordin et al. Predictors of complications in gynaecological oncological surgery: a prospective multicentre study (UKGOSOC-UK Gynaecological Oncology Surgical Outcomes and Complications). *Br J Cancer* 3 February 2015, 112: 475–484

Elderly patients with multiple myeloma need baseline geriatric assessments

■ Blood

Frailty scores predict mortality, toxicity and treatment discontinuation in elderly multiple myeloma patients, a study from the International Myeloma Working Group reports.

"This analysis showed that a frailty score… is useful to determine the feasibility of a treatment regimen," write the authors.

Multiple myeloma predominantly affects elderly patients. More than 60% of multiple myeloma diagnoses and more than 70% of deaths occur in those aged over 65 years. Although it is well recognised that, among adults of the same age, physical and cognitive functions are highly variable, the choice of multiple myeloma treatment is currently primarily based on chronological age and performance status. In haematology, comprehensive geriatric assessments are not routinely performed for older patients, as they are considered complex and time consuming.

In the current study, Antonio Palumbo, from Azienda Ospedaliera, in Torino, Italy, and international colleagues, set out to assess the predictive role of a baseline geriatric assessment in 869 newly diagnosed elderly patients with multiple myeloma. The patients were taken from three prospective international trials involving a variety of different drug regimens that recruited patients from 72 European institutions. The trials were selected for their less strict inclusion/exclusion criteria, which allowed 30% of frail patients to be treated. Patients in the EMN01 trial were randomised to lenalidomide with either dexamethasone or cyclophosphamide-prednisone or melphalan-prednisone. Patients in the 26866138MMY2069 trial received bortezomib with either prednisone or cyclophosphamide-prednisone or with melphalan-prednisone. Patients in the IST-

CAR-506 trial received carfilzomib with cyclophosphamide-dexamethasone.

At diagnosis, a geriatric assessment had been performed to assess comorbidities, and cognitive and physical status. For the current study, an additional retrospective scoring system was undertaken, based on age, co-morbidities, and cognitive and physical conditions, to identify three groups: fit (score=0); intermediate fitness (score=1) and frail (score >2). Median age for those included in the study was 74 years, with 46% older than 75.

Results show that, at three years, overall survival was 84% for fit patients; 76% for intermediate-fitness patients (HR 1.61; *P*=0.042) and 57% for frail patients (HR 3.57; *P*<0.001). At 12 months, the cumulative incidence of grade 3 or above non-haematologic adverse events was 22.2% for fit patients, 26.4% for intermediate-fitness patients (HR 1.23; *P*=0.217) and 34% for frail patients (HR 1.74; *P*<0.001).

At 12 months the cumulative incidence of treatment discontinuation was 16.5% in fit patients, 20.8% for intermediate fitness patients (HR 1.41; *P*=0.052) and 31.2% for frail patients (HR 2.21; *P*<0.001).

"Unexpectedly, the performance status did not affect OS [overall survival], whereas the frailty status increased the risk of death by approximately 3 fold, thus confirming the need for more sophisticated evaluation of elderly patients before starting therapy," write the authors. A cut-off age of 80 years instead of 75 years, they add, should be used for the definition of frail conditions.

"Although evidence-based GA-[geriatric assessment]-tailored treatments are still lacking, fit patients could receive full-dose, triplet therapies or even more intensive approach including stem cell transplant. Intermediate-fitness patients may benefit from doublet treatments or less intense triplets. Frail patients could benefit from a gentler, reduced-dose doublet treatment or less intense triplets," suggest the authors.

■ A Palumbo, S Bringhen, M Mateos et al. Geriatric assessment predicts survival and toxicities in elderly myeloma: an International Myeloma Working Group report. *Blood* published online 27 January 2015, doi:10.1182/blood-2014-12-615187

Multidisciplinary care improves outcomes in oesophageal cancer

■ Clinical and Translational Oncology

The use of a multidisciplinary approach to clinical decision making for patients with oesophageal cancer (OC) and oesophagogastric junction cancers (OGJC) resulted in significant improvements in one- and three-year survival in patients treated with curative intent, and reductions in 30-day postoperative mortality.

Modern management of OC and OGJC requires a multidisciplinary approach involving surgeons, medical and radiation oncologists, gastroenterologists, nutritionists, radiologists, nuclear medicine specialists, pathologists and specialist nurses. It has been suggested that there may be three to four different cancer entities arising from the oesophagus, including squamous cell carcinomas (which occur in the upper- and middle-third of the oesophagus), adenocarcinoma (which occurs in the lower third), non-cardia gastric cancer (related to *Helicobacter pylori* infection), and OGJCs. In an effort to prolong survival and reduce recurrence rates in patients with OC, preoperative treatment has become the focus of interest.

In the retrospective cohort study, Maica Galán and colleagues undertook to assess the impact on outcome of different organisational approaches to clinical decision making through a review of 586 patients treated for OC and OGJC cancers at the Bellvitge University Teaching Hospital and the Catalonian Institute of Oncology, both in Barcelona. The multidisciplinary approach to clinical decision-making was implemented at the end of 2004, with all specialists holding weekly meetings to discuss and formally agree upon the therapeutic course to be followed. Patients were therefore considered over two time periods: those diagnosed in 2000–2004 (when clinical decision-making was sequentially organised by each clinical specialist); and those diagnosed in 2005–2008 (when a multidisciplinary tumour board had been set up). In total 327 patients were treated for the period of diagnosis 2000–2004; and 259 for the period 2005–2008.

Results show 30-day surgical mortality was 11.8% (*n*=9) for patients receiving sequential care in the first time period versus 2% (*n*=1) for patients receiving multidisciplinary care in the second time period (*P*=0.049). In patients undergoing surgery with curative intent (surgery plus adjuvant treatment), one-year survival was 68.4% for patients receiving sequential care versus 89.8% for patients receiving multidisciplinary care (*P*=0.006). The same group of patients had a three-year survival of 38.2% for those receiving sequential care versus 57.1% for those receiving multidisciplinary care (*P*=0.011). A multivariate analysis showed variables associated with improved survival were age, tumour stage, radical intent of treatment (surgery and radical combined chemo-radiotherapy); and therapeutic strategy.

"All things considered, these changes support an MD [multidisciplinary] approach in clinical decision-making for OC and OGJC, since it allows for better co-ordination and planning of the treatment of such patients, thanks to the fact that all relevant professionals take part in discussions focused on the specific clinical situation of the patient concerned, at a centre having the necessary facilities to offer the most appropriate treatment, whether with radical or palliative intent, in these complex cases," write the authors.

■ M Galán, L Farran, L Aliste et al. (2015) Multidisciplinary cancer care may impact on the postoperative mortality and survival of patients with oesophageal and oesophagogastric junction cancer: a retrospective cohort study. *Clin Transl Oncol* March 2015, 17:247–256

Our cancer risk is not written in the stars

If Tomasetti and Vogelstein had not used the words "bad luck" in their paper on how 'variation in cancer risk among tissues can be explained by the number of stem cell divisions', the media might not have covered the story the way they did. In this interview with *The Cancer Letter*, Bertram Kramer, head of Cancer Prevention at the US National Cancer Institute, tries to clear up some of the confusion.

The Cancer Letter (TCL): *What was your overall impression of the Tomasetti and Vogelstein paper?*

Bertram Kramer (BK): I found the paper interesting. What they did was they didn't generate any new experimental evidence, obviously. They searched the literature for reports on numbers of stem cells and number of divisions of the stem cells.

They used well-accepted concepts that the risk of mutations or number of mutations are relatively constant for a given cell division – in statistical terms, a stochastic process – that is, any given division, you don't know which gene is going to mutate, but for every given division, you can predict, relatively accurately, how many mutations are going to occur in the division. You just don't know which cell it's going to happen to. But if you have enough cells, then a statistical analysis of this stochastic process gives you, generally, a pretty good idea of how many mutations there are, and the number of mutations to be a risk factor for cancer.

TCL: *What were the authors trying to achieve in their analysis?*

BK: They took well-known concepts, went to the literature, looked for the number of stem cells in any given class of tumors or tissue type, and looked for reports of the number of divisions.

The innovation they added – actually directly plotting the number of anticipated mutations or divisions with the cancer risk – and what I found interesting was that, relative to most biological processes, they got a pretty tight correlation between the number of stem cell divisions and the risk of cancer.

The variation in cancer risk across the tumor types for which they had any data was about 65%, and that's a pretty tight correlation, in biological terms. So it fits with the existing notions of the association between mutations and cancer. I found that interesting. I think they took existing literature and results and, for the first time to my knowledge, plotted them looking for variation across cancers using that information and got a tight correlation.

So it's not conceptually different from what was, in essence, accepted, in terms of the association, but what they did was plot it graphically, and as it often happens, you get some biological input by taking existing data and graphing them.

That's what I took as particularly

THE CANCER LETTER
Inside information on cancer research and drug development

This interview was first published in ***The Cancer Letter*** (www.cancerletter.com) on 16 January 2015, and is republished with permission. The interview was conducted by Matthew Ong

The Tomasetti and Vogelstein paper, published in *Science* on January 2nd, was widely – but often inaccurately – covered in media across the world

interesting in the paper. I wouldn't have predicted that the correlation would be quite that high, and so I found it intriguing that it was. That's the good part.

TCL: *What have news reports missed in their coverage of the paper's findings?*

BK: On the parts that I think may have either been misinterpreted or picked up in the press and took an extra step too far, was going beyond the actual data to some of the implications. I don't think that, given those observations, you can conclude with any confidence what would be the best strategy to decrease mortality for a given cancer.

I don't think that tells you *a priori* whether the best strategy will be screening; or the best strategy will be primary prevention; or the best strategy will be treatment. Unfortunately, you're left with the hard grunt work of testing various strategies to see which is the most effective amongst the three for decreasing mortality.

A case in point would be that they unfortunately didn't have reported evidence on stem cells or stem cell divisions from two very common cancers – prostate cancer and breast cancer – and for both of those cancers we at least have some evidence about whether or not screening works, or how effective it is, and it would have added to the paper if they had some stem cell division data on those. There have been randomized trials at least to test the inference that screening would or wouldn't work.

The next important thing, which I think was sort of missed in the press—even the paper itself says something that appears to equate that stochastic process with bad luck. I personally think that the use of the phrase 'bad luck' can be easily misinterpreted. Stochastic processes have a crisp scientific definition, but 'bad luck' doesn't. The lay public may interpret incorrectly in this case, in my opinion, that 'bad luck' simply means "it's in the stars, it's your fate, there's nothing you can do about it." And 'bad luck' is not equivalent to random mutations in a stochastic process.

TCL: *What would be a good analogy?*

BK: Let's say you're dealing with traffic patterns. The heavier the traffic, the more accidents there are going to be. There is a tight correlation between the

'Bad luck' means to most people, 'nothing you can do about it, you are meant to have cancer'

number of cars on the roads and the number of accidents, but that doesn't mean that it's pure bad luck if you have an accident.

Statisticians can predict that, for a given road at a given time and given road conditions, there's going to be a certain risk and a certain number of accidents. And the correlation almost certainly is going to be very tight, but that doesn't mean that the individual car driver has no control, and might as well give up because whether they have an accident is purely bad luck. They can choose to drive differently.

So aggressive drivers are at a higher risk than slower or safer drivers. And the same is true for speed limits. It's well known and it has been well described that for every mile per hour that you raise the speed limit, or every five or 10 miles per hour, the rate of mortalities or fatalities can go up.

But that doesn't mean for an individual driver, it's just pure bad luck. Because individual drivers and individual cars have a different risk of traffic fatality depending on how they drive, even if they're driving at the same speed in the same speed zone.

The other thing which was not picked up by most of the press was that the correlation they were even looking at, leaving aside the issue of cause and effect, because this isn't even designed to determine cause and effect – they were looking at classes of tumors.

They lined up 31 classes of tumors, and they found out that the correlation was surprisingly high, and I found that interesting. But they were not looking at risk of individual tumors. Even if it were true that two-thirds of the variability among tumor types is associated with the number of stem cell divisions, it doesn't mean that two-thirds of all cancers are predetermined.

Let's say you have an extremely common tumor and 10 extremely rare tumors, and you plot the number of stem cell divisions for those 11 tumors. The 11 tumors may line up very nicely along that diagonal line, that is, they fit a pattern that, across tumor types, there is a pretty tight association between stem cell divisions and cancer risk.

But remember, the most common tumor accounts for most of the cancers. And if that most common tumor is attributable in large measure to a known environmental carcinogen, then the overwhelming majority of cancers, individual cancers, will be preventable. And so a clear case in point would be lung cancer, which we know that 90% of lung cancers are probably attributable to smoking and preventable if people don't smoke at all.

And yet there are many, many rare tumors for which we don't have any known environmental cause, and even in the aggregate, if you add them all up, they don't come anywhere close to the number of lung cancers.

So just one simple preventive intervention would prevent the overwhelming majority of all those cancers even if the association tells you that, across cancer types, two-thirds are due to the stochastic process of mutation.

Let's say there were only five cases of every other cancer type there is, and they added up to a total of 200 cases a year, and there were 150,000 cases a year of lung cancer, 90% of which were attributable to smoking, then the overwhelming majority of individual cancers would be preventable, even if a regression curve tells you that across cancer classes, there is a pretty tight correlation with stochastic processes.

And in this case, let's take lung cancer, which we know 90% are preventable by no smoking, and skin cancer, especially non-melanoma skin cancer – which is more common than all the other cancers combined, including lung cancer – and we know that non-melanoma skin cancers are largely preventable by avoiding intensive sun overexposure, the biggest risk factor for non-melanoma skin cancer.

The number of non-melanoma skin cancers just completely outweighs all other cancers combined. And so, even though skin cancer fits on that regression line, and is part of the pattern of cancer types, sun avoidance would still prevent an inordinately large number of total cancers in the country.

Unfortunately, the term 'bad luck' got picked in a number of news outlets. Just the term 'bad luck' can be misleading. 'Bad luck' just means, to most people, "nothing you can do about it, you are meant to have cancer."

And since the term was – for the sake of simplicity or I would say, over-simplicity – equated with a more precise statistical phenomenon, stochastic risk, that led to the sense that, "Gee, there's not much you can do about cancer, it's just all in the stars." That has an unfortunate connotation, and I think that was the biggest error of translation of the results.

Lawmakers, and physicians, by the way, and health professionals and the lay

public often respond to news articles, and if they are misinterpreted, then it can lead to policy decisions, which are obviously made on behalf of the lay public.

TCL: *Do you have any other observations that you'd like to highlight?*

BK: Another thing I wanted to point out that I found interesting in Figure 1 of the paper – the correlation seems good relative to many biological phenomenon. One thing I took from it, and it wasn't emphasized in the article, is that you can sort of visually look at the vertical distance between any given individual cancers on that regression line.

The further it is away from the regression line, the more that one could suspect that there is something going on, if it is cause and effect, there's something additional going on that explains the higher incidences for the curves that are well above the line. And sure enough, that fits the pattern very nicely, so it's interesting to look at.

The best example is lung cancer. When you look at lung cancer (smokers) and lung cancer (nonsmokers), there is a very large vertical difference between those. So lung cancer (smokers) as you'd expect, the point is way above that regression line.

And the same is true, for example, for HPV head and neck cancer and other cancers, and hepatitis B liver cancer is way above the line relative to the rest of liver cancer. It fits that one would say, "Gee, the further vertically the point is from the line, especially if it's north of the line, the more may be going on, over and above the stochastic random process."

That is one indicator that something else might be going on: how far above, vertically, the regression line, a given point is. That's not pure, it's very rough, but nevertheless, if you look at some of the points, they fit that pattern.

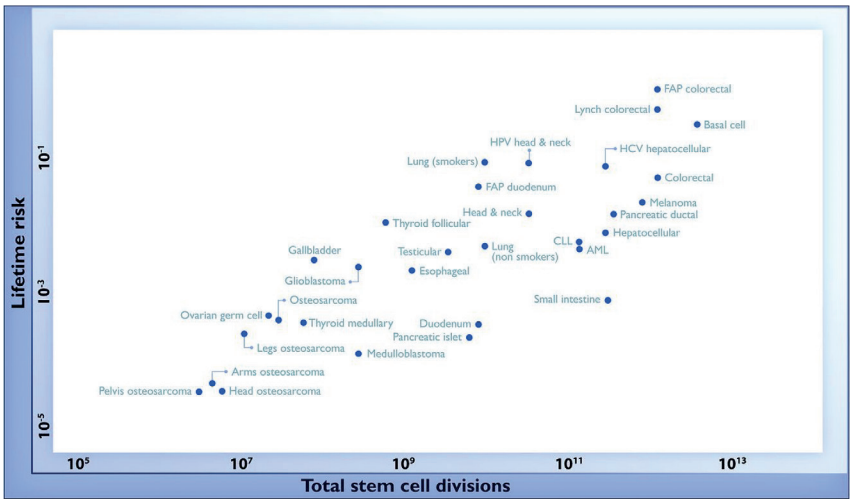
General colorectal cancer is right on the regression line, but those with a genetic predisposition (FAP) for colorectal cancer are way above that regression line vertically. Each of those points that are very far away from the line seems to fit that pattern.

Now, always, an environmental carcinogen, you have to be very cautious before you say, it must be an environmental carcinogen. A case in point is thyroid follicular cancer – the incidence may be driven by screening for thyroid cancer and screening tests are much better at picking up thyroid follicular than other forms of thyroid cancer. So all it means is that the incidence is considerably higher than you have expected simply based on the formula of stem cells and number of divisions.

I think that we can be pretty confident that there are some causative reasons for the vertical difference. Certainly, we can be confident in the case of smoking and lung cancer. That's a well-established causative factor. I think we can be confident in the case of HPV infections for head and neck cancer. We're pretty confident that that's causative.

In the case of thyroid follicular cancer, I think the weight of evidence is that screening increases the risk of thyroid cancer even if there are no known new carcinogens. And I think there is a large body of evidence that some of the incidence, and sometimes a large measure of incidence in some cancers, is attributable to screening and overdiagnosis, such as picking up very indolent, non-life-threatening cancers just by simply dipping into a reservoir of silent, non-progressive tumors with a screening test. ■

FIGURE 1: THE DATA AT THE HEART OF THE DEBATE



The relationship between the number of stem cell divisions in the lifetime of a given tissue and the lifetime risk of cancer in that tissue

FAP – familial adenomatous polyposis, HCV – hepatitis C virus, HPV – human papillomavirus, CLL, chronic lymphocytic leukaemia, AML – acute myeloid leukaemia

Source: C Tomasetti and B Vogelstein. (2015) Variation in cancer risk among tissues can be explained by the number of stem cell divisions. *Science* 347:78–81, reprinted by permission from AAAS

International collaboration and the importance of *eubiosia*

A shared sense of the value of helping people with incurable cancers achieve lives worth living has driven doctors to collaborate across borders for decades. An oncologist shares his experiences from the Cold War to the present day.

STEPHAN TANNEBERGER

For a new generation of oncologists, oncology is the pursuit of individualised medicine and targeted therapies; however, the concept of individualised cancer chemotherapy is one that I have followed since 1964. Even then, I was part of a group of oncologists who were convinced that each tumour had an individual biology requiring patient-tailored treatment.[1,2] It remains important to understand that sometimes the things that can help patients the most are not found in modern technology or expensive new agents. Sometimes it takes imagination and collaboration, beyond international borders, to open up one's perspective on how important individualisation can be.

The 1970s were a time of international conflicts and the height of the Cold War. This was also a time of two Germanys. Despite this, international collaborations blossomed. More than other professionals, even then, oncologists understood the meaning of human suffering, and we understood that striving for peace also afforded the best chance to make progress against cancer. It is epitomised by an event in Moscow. It was close to midnight, and sitting together on a staircase were Nikolai Blokhin, then the director of the All-Union Cancer Centre of Moscow, and John Higginson, an American

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who was then the director of the International Agency for Research on Cancer in Lyon, France. Between them was a bottle of vodka.

"Why can't we go together, Nikolai?" asked Dr Higginson.

"I do not understand," said Professor Blokhin.

Then, with a glass in their hands, they toasted: *"Na sdorowje"* – "To health," in Russian.

It was the 1970s, and I was flying from Berlin to Bologna, Italy, to give a lecture at an Italian cancer conference. As I entered the conference building, I ran into my colleague Franco Pannuti, who had come up the staircase.

"Do you know what the term '*eubiosia*' means?" he asked. No greeting at first, just this question.

When I did not answer, he followed quickly with a warm greeting, *"Abraccio!"* and proceeded to explain himself. "'*Eubiosia*' means 'no more pain.' It means dignity in life until the last moment of life." After a few seconds, he continued, "Right now, we cannot prevent all of our patients from dying of cancer, but we can offer incurable patients *eubiosia* as a good alternative to euthanasia [or 'good death']."

It was the notion of respect for life, well known

"We can offer incurable patients *eubiosia* as a good alternative to euthanasia"

"I cannot begin to describe the privilege of caring for thousands of patients in their homes"

to me from the great German Albert Schweitzer, and now with a new interpretation in Italy. Following the meeting, I found myself again immersed in my usual German life; however, the concept of *eubiosia* remained with me. I found myself aligned with my friend Franco and his newly founded organisation, the Associazione Nazionale Tumori (ANT), unified by his moral call to oncology, despite our separation by the Cold War.

As the 1990s set in, the notion of *eubiosia* resurfaced in my life. It was the end of the Cold War, after the fall of the Berlin Wall. Despite this, the German authorities showed little interest in unifying the cancer efforts of Heidelberg and Berlin, which might have helped raise the prominence of oncology not only in Germany but worldwide. Ultimately, there was no chance to work for *eubiosia* in Berlin. Fortunately, I had other options, including an invitation to come to Bologna, which I accepted as a chance to work for *eubiosia* in Italy and in the rest of the world.

With my move to Bologna, I switched my focus in oncology. I closed my laboratory and stopped doing clinical trials. Instead, I became a clinician, and I started seeing cancer patients in their homes. We aimed to embrace *eubiosia* in clinical practice by treating patients in the 'hospital at home.' With this new focus, I was responsible for quality control of what became a rapidly growing service. I realised then that *eubiosia* should not be confined to Italy: *eubiosia* is a human right for all the world.[3] With this belief, we started projects in other countries, including India, Bangladesh, and Albania. I have done this now for more than 20 years, and I cannot begin to describe the privilege of caring for thousands of patients in their homes, across countries and cultures.

Two experiences come to mind in describing *eubiosia* as practised. The first experience occurred while visiting a 70-year-old woman with advanced breast cancer who was living in Bologna. She was receiving chemotherapy and suffered treatment-related toxicities including alopecia and neuropathic problems that made walking difficult. In the initial consult, I was informed, "She has painful bone metastases and lives alone. Indeed, she prefers to stay at home." At our initial encounter, she looked relaxed, spoke with a little bit of optimism, and moved energetically, although requiring some help.

I asked her, "How do you feel? It must not be easy living alone and having pain."

"You are right, but I am doing well," she said. "Fortunately, I have my friend."

"Your friend?" I asked. I assumed she meant a family member or somebody who lived close to her.

After a short moment, she answered, "Yes, my friend. Do you want to see him?"

I was astonished. There was no one else here, and the apartment was so small that it was impossible that someone could be hiding. Then I saw a cardboard box on the table.

She reached for the box and opened it. "Look!" she said. Inside the box sat a small sparrow. She continued, "He flew to my balcony one day, this small bird. He was sick, perhaps a cat tried to kill him, but with care and all of my love, he got better. Now we are together."

I was awestruck. "How long has he been with you?" I asked.

"About a year now," she informed me. It was clear that she loved him and that he brought her comfort – ***eubiosia*** through bird companionship. With that, a wonderful idea was born. Pets for our patients. Perhaps they may derive as much comfort from a pet as with any drug we can administer. This hypothesis would not be easy to test, but why not try? I have learned that this is not an isolated event, and many more positive experiences have been witnessed.[4]

The second experience took place in India, where I have worked with CanSupport.[5] The day was very hot (46°C, or 115°F), but we were too busy to relax. My colleague Harmala Gupta and I were seeing patients in a poor part of Delhi. Our patient was lying in bed, but to our surprise, the bed was on the street, surrounded by more than 10 people – members of the family, friends, and

some children playing. Close to the bed were placed two armchairs, reserved for honoured guests. We approached and, with a short clap by the patient's wife, all guests dispersed.

I was shocked to see how the patient was living, but he was at peace: he had achieved *eubiosia*. He was surrounded by his family; literally, all seven were around him. Despite not having any formal education, the family was skilled at caring for the patient. Family members attended to his hygiene and followed the local doctor's recommendations, including administration of intramuscular injections. It demonstrated to me how important the family is for comfort and what a resource it can be, particularly in resource-poor regions. Certainly, calling on a family that is ready and willing to aid a patient is less costly than building new hospitals. Is it possible to achieve *eubiosia* in a cost-efficient and ethical manner? My experience shows that perhaps the role of the family is a concept that should be better evaluated.

SHUTTERSTOCK

Although we are living in the 21st century, only about 25% of those with cancer can access the global resources that are available. No doubt, globalisation of the war against cancer will cost money. Health budgets have to be increased. Although pessimists will say that this is not possible, such comments have not stopped oncologists from fighting for their patients anywhere in the world, and should not stop them now. Although we live in a world of military and financial globalisation, it is just as important that we strive for a world composed of peace and health that is globally realised.[6]

The call of the oncologist is to improve quality of life, and to do so, we can look beyond technology and expensive medications; these may not be necessary for our patients to achieve *eubiosia*. What can make as much of a difference are simple gestures of companionship, family, and knowing that we – our community of oncologists – are there for our patients and that we care. Perhaps the concept of 'hospital at home' is not one that will be readily embraced, but the point – guaranteeing access – is one that should not be controversial. Maybe oncologists should learn of the wonderful collaborations that took place during the Cold War as we face our future: *Na sdorowje!* ■

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