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OUTWITTING RESISTANCE

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A SEAT AT THE TABLE

Patient advocacy groups prepare for life on the inside track

STEPPING UP

Where cancer clinicians go to learn how to lead

Shelley Dolan

walking alongside patients

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Cancerworld

Shaping the future of cancer care

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If you want better drugs consult a PRO

KATHY REDMOND EDITOR

For many years, patient advocates have fought to have a patient perspective included in different aspects of cancer drug development and regulation, but progress to date has been slow. A number of recent developments are now showing encouraging signs of change. The European Medicines Agency (EMA) has just issued a reflection paper on patient reported outcome (PRO) measures in cancer drug regulation, with the aim of promoting an open discussion on the value of PRO data in the regulation of cancer medicines. This initiative signals a timely acknowledgement by the Agency of not only the strengthening of PRO methodology but also the need to hear from patients when evaluating a new medicine.

A PRO is a report of a patient's experience that is evaluated directly by the patient and is based on their perceptions, without external interpretation. There is growing awareness that collecting this sort of data can provide valuable evidence about the efficacy and safety of a new medicine – an important consideration given that multiple studies have shown that physicians and nurses frequently underestimate the true impact the disease and treatments have on patients.

PRO measures have the potential to provide clinically relevant information that is not captured by conventional anti-tumour efficacy and safety data; however, methodology challenges have steered European regulators away from using such data when making marketing authorisation decisions about a new medicine. Indeed, over the past decade, health-related quality of life data have rarely, if ever, swayed EMA's decisions. However, ongoing initiatives, such as the US National Cancer Institute's effort to develop a Patient Reported Outcomes version of the Common Terminology Criteria for Adverse Events grading scale (PRO-CTCAE), are starting to provide regulators with the scientifically rigorous approaches they require to be more confident about the value of PRO data.

As a consequence of these and other initiatives, patient advocates now have a unique opportunity to ensure that drug developers and regulators pay adequate attention to the patient viewpoint. A key question is whether patients are equipped to contribute at this level, which is where another important European initiative – the European Patients' Academy on Therapeutic Innovation (patientsacademy.eu) – comes into play. This September, 55 patient advocates became the first to enrol on EUPATI's 'expert-level' training, specifically tailored to building their capacity to understand and play a role in the process of researching and developing new drugs.

Equipped with the necessary expertise, advocates can play an important role in helping ensure that the cancer medicines that come to market in the future truly meet unmet need and are not unduly burdensome for patients. These initiatives are all welcome progress towards ensuring that patients are where they belong, at the centre of all our efforts. ■

Interested parties have until the end of November to provide feedback on EMA's reflection document, which can be accessed at: www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/06/WC500168852.pdf

Shelley Dolan: walking alongside patients

SIMON CROMPTON

Nurses are not the only ones who care and can nurture, support and explain things to patients who are scared and vulnerable, says pioneering cancer nurse Shelley Dolan. But they are the only health professionals to have this as their key role, and she is calling for Europe to do everything possible to empower them.

Looking at Shelley Dolan today – fresh face beaming enthusiastically as she talks about the untapped potential of her profession – it's hard to believe that 25 years ago one of Britain's most influential cancer nurses started her illustrious career as a punk rocker.

"I looked outrageous, and I was always in trouble with the senior nurses – constantly questioning whether a certain rule had to apply," she says.

But those rebellious beginnings were far from inauspicious. Dolan's youthful impatience with rules and assumptions have stood her in good stead as she has tried to widen understanding about the role of nursing in good cancer care – not just in the UK, but throughout Europe. Like her suffragette grandmother, she has refused to allow a cause she believes in to be strangled by the bonds of tradition. And far from alienating her, it has brought her to the top of her profession.

Dolan is today chief nurse at the Royal Marsden Foundation Trust – Britain's best-known specialist cancer centre, affiliated to the Institute of Cancer Research, employing 4000 staff and based on three sites in and around London. She is also clinical director for the London Cancer Alliance, an integrated cancer system looking to improve cancer outcomes and experiences in the UK's capital.

But it isn't just in the UK she is held in high esteem. Last year she received the European Oncology Nursing Society Lifetime Achievement Award, not just for her work developing the UK's largest critical care unit at the Royal Marsden, but for leading nurses to strive for better care around the world. She has

advised and lectured on nursing in many countries: she developed the first clinical leadership course for cancer nurses in South Africa, and received the Serbian People's Medal for Cancer Nursing in 2006 for her work on caring for patients in critical care.

"I want people to understand the power of nursing in cancer, and the need to liberate that power," she says. "Nursing across Europe is a major workforce and if we nurture nurses, educate them in the science, the care, the influencing and leadership skills, we could make a massive step change for the experience of people with cancer and their families. Leaders in healthcare across Europe must do everything they can do to empower nurses."

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She is aware that, as a nurse leader in the UK, she speaks from a relatively privileged position. The UK's clinical nurse specialists in cancer are graduate level nurses, normally prepared at Master's level, who are clinical experts in evidence-based nursing practice within cancer or a specialty of it. Other countries such as the United States, Australia, Belgium, Ireland and the Netherlands also have advanced practice nurses, some of whom have prescribing rights.

Highly educated in the science of treatment, but also expert in communication and personal skills, these nurses add a "different dimension" to cancer care, says Dolan. Patient outcomes are materially affected by how good the nursing is – whether it be in a clinical trial or in general care.

She is not saying that nurses are more important than any other profession in cancer care, or that nurses have attributes that other professionals do not. But they do have a unique mix of qualities. She points out that the English word "nurse" derives from the old Norse word meaning "nurture" (Dolan took an English degree while working as a senior sister in 1987).

"It means to feed and

water, grow, nourish and refresh – and nursing needs to be like this in every field. But in cancer there's a particular need to nurture, because it completely turns people's lives upside down. It's about hope – always trying to keep who a person really is at the heart of things."

"When people with cancer are frightened and vulnerable, specialist nurses walk alongside them, and can translate the science of cancer to them. The specialist nurse gets to know the person, what is important to them, and provides a system-wide approach to getting the safest, most effective care and the best experience. The pathway through cancer can be extraordinarily confusing and battering and they can manipulate resources around the person and provide information at every stage."

So Dolan's "cause" is partly to get people to understand this special role. She's made significant headway at the Royal Marsden since she joined in 1994. In 2000, she became nurse consultant in cancer and critical care – the first nurse in the UK to be made a consultant. And as chief nurse she has successfully pressed for nurses to be put in charge of research studies as primary researchers – there are now 20 PhD-qualified nurses working at the hospital's health services research unit.

Yet getting people to understand their contribution beyond the enlightened sanctums of Britain's leading cancer hospital is a different matter.

She says that in many countries doctors can be disproportionately powerful in in-patient healthcare settings, so their beliefs about what nurses can and should do tend to predominate. That's fine if doctors have travelled widely and seen how advanced practice nursing works, but many have not. In some settings, Dolan points out, the organisational culture is simply not permissive or experimental enough to acknowledge an extended role for nursing in cancer.

"This can be bound up with societal influences," she says. "Nursing has been a predominately female profession. In many countries it emerged from religious orders and a servant culture. Now it's certainly true that there are outstanding examples in low-resourced countries of advanced practice nursing – in Africa, for example, there are amazing nurses who deliver palliative care in situations where they can't even get

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hold of any opioids. But they are not the norm in Africa, because there is the expectation that a family will provide and care for a loved one. Societal constructs do play a part."

The solution, she says, does not necessarily lie in working towards a UK-style model of advanced practice nursing in every country. "It may not be appropriate everywhere," she says. "I have been involved with European nursing for over 20 years, and I'm greatly in favour of going to other countries to look at what happens, and then bringing back the bits that fit your system."

"Nurses need to be able to fulfil their ambitions, but it's got to be right for your context. And, of course, you can't create specialist nurses overnight – you have to have the right graduate education, organisations that foster innovation and support nurses doing research and taking forward new practice."

The vital first step, she says, lies in nurses communicating their potential to policy makers. And here lies the overlap between the personal and professional challenge for nurses – because communicating the news about nursing requires confidence and courage. Dolan admits to me that she still has to steel herself to be outspoken in front of politicians. Nursing too requires a collective act of steeling.

"Even now when I'm meeting politicians or senior leaders in other countries, even though I know that I'm very experienced and fairly expert in cancer, inside I still feel like a staff nurse, and I've still got to think, oh gosh, right, I've got to do this now."

It's an interesting insight from a woman apparently at ease with the big policy world of cancer. She is on the board of the Institute of Cancer Research and the Health Research Authority, and until last year was vice chair of the UK's medicines regulatory agency. She is an executive director of the Royal Marsden's board and head of its health services research unit.

But Dolan is clearly driven to make things happen, and she believes the inspiration of others, rather than any inner confidence, has cultured her dogged refusal to be daunted by big challenges.

"The thing that I observe in people I look up to or who excite me and make me think we have to do this or that for patients or nurses is a 'can-do' attitude. I've learned that anything can be possible from all sorts of people – patients and professionals."

"It's so important that none of us are precious, or think we're the only ones that care. The patient is at the centre"

At the start there was no big plan to go into nursing. Dolan did well at school, gaining five A-levels in arts and science subjects. Seeing herself as a famous artist or actress, when she left school she started a fine arts foundation course in London. That was when she embraced the punk explosion in West London – a contrast to her "quiet and gentle" family. "I loved the political rebelliousness of it," she says.

When she was 19 her family circumstances changed and Dolan had to abandon her artistic aspirations to start earning some money as soon as possible. Unsure how to do it, she saw a nursing recruitment shop and remembering the nurses who had recently cared for her father in hospital, she decided to go in. "Nursing was quite traditional in those days and I must have looked a complete sight with my punk gear. I asked them whether I would get paid straight away, they said 'yes', and I said 'okay I'll join.' I expect they were horrified but they were fairly desperate for nurses at that time."

She started her training at William Harvey Hospital in Ashford, Kent – and immediately loved the student nurse life: it reminded her of her girls' school education. "I partied hard, worked hard, and I got told off a lot. I remember all the wards I worked on, and loved them all." At the end of three years, her final ward was intensive care and she knew it was for her: "You can care for just one patient the whole day – it's emotionally stretching, and busy, but you can devote yourself to one person. Being a rebel, the fact that there wasn't much hierarchy also probably suited me."

She rose through the ranks of her profession and moved around the UK, became senior staff nurse on various intensive care units, then a sister, and then a clinical nurse specialist. In 1992 she became lead nurse for acute medicine and ITU (intensive therapy units) at Leeds General Infirmary.

She arrived at the Royal Marsden, in the London borough of Sutton, in 1994 to take up the role of clinical nurse specialist in critical care. She hadn't seen herself arriving at a cancer hospital, but in 1993 she had taken what she thought would be a temporary job at the Marsden to be near her sister. It wasn't long before she was drawn in by the Marsden's devoted staff and the special qualities and vulnerability of its cancer patients.

One of the Marsden team provided an important early lesson in her residency in 1994: Dolan is embarrassed talking about it even now – but to her credit still uses the story in her teaching. An internationally acclaimed professor of myeloma visited her with a retinue of doctors when she was nursing a young man with leukaemia. "He was on a ventilator, and was all wired up with a pulmonary artery catheter. The professor asked me how Mr Smith was, and so I started reeling off all the different readings from the monitors – I was probably being clever, and thinking 'I know about intensive care units and you cancer guys don't.' So the professor just let me finish, and then just said very quietly without being rude: 'And how is Mr Smith?' It was such an important lesson, given to me by a doctor not a nurse, and I've never forgotten it. It's so important that none of us are precious, or think we're the only ones that care. The patient is the centre of it all."

The unique qualities of the Marsden patients and staff cultivated her "can-do" attitude. She remembers a 22-year-old patient who needed constant respiratory support getting upset, and telling her that all he wanted to do was to marry his girlfriend so that when he died she would have the respect of a widow.

"I remember feeling 'Oh my God, this is massive, how do I deal with this?' because it was so tempting to say 'Don't be silly you'll be fine.' But I knew he also needed me to meet this honestly and not bat his request away." So, despite the technical difficulties, Dolan organised a church wedding in the intensive care unit, with wedding suits, a specially-licensed minister and a small orchestra. The groom was removed from his respiratory support for five minutes – just long enough for photographs, and beds were organised so that his new bride could stay with him overnight. The patient died two days later.

"It has always lived with me because some people at the time said it couldn't be done or it was too dangerous. But you just needed to make it happen, and we did. Throughout my clinical career I've been in intensive care nursing, where people are at their most vulnerable, and I think there has to be the belief behind everything you do that you can make things better, otherwise the whole thing becomes nihilistic. When people are broken, and you help turn that around, it is a wonderful thing. I'm inspired by people's indomitable spirit when set against something really tough."

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Recognition. Birgitte Grube (left), president of the European Oncology Nursing Society, presented Dolan with an EONS Lifetime Achievement Award, at ECCO 2013

Dolan is grateful that she has always worked in organisations that have encouraged her to be innovative, and to combine her clinical career with continuing education – first an Honours degree, then a Master's degree (in advanced practice nursing, in 1996) and then a PhD in 1996. She has pushed herself hard – and says she has frequently cursed herself for taking on too much. With two young daughters to look after at home too, she has had to find effective ways of getting things done, and fortunately finds she only needs a few hours sleep every night.

But her energy has a political source too. "With my grandmother being a suffragette, I've always had this slightly feminist, driven thing that women gave their lives so I could vote. So I think it's wrong for women like me not to engage in world events. I'll go to extraordinary lengths to vote in a local election even when the result is a foregone conclusion, and make a point of listening to the news and reading newspapers every day."

Her awareness of what's going on in the world beyond the hospital walls has an added benefit. Even though her role is now largely management, Dolan maintains contact with patients by going on weekly ward rounds, and knowing the news means she can bring the outside world

"I'm thankful for all the nurses before me and in my time who have fought for our autonomy. It hasn't been easy"

to patients, and engage them on subjects that might take away from their immediate worries.

She tells me how fundamental it is for nursing to engage people on a personal level. For the few minutes a nurse is with them, she says, a patient must believe that they are the most important person in that nurse's life. "Now that I'm in this management role, it's important that nurses feel the same way when I talk to them too. Every nurse needs to know that they are cared for." Even in conversation with a journalist like me her attentiveness is striking.

She is adamant about the need for caring management of nurses. Responding to their needs, she says, isn't just a matter of asking them to fill out questionnaires. It's about talking to them. Having belief and respect in teams translates into good care and good patient experience of care – and it stems from good leadership.

These principles apply around the world. Her international interest has spanned two decades – and she feels in her element at international cancer and nursing conferences. "I think one of the wonderful things about the European Oncology Nursing Society and other worldwide nursing networks is that every time I go to Europe and talk to other nurses, there's far more in common than our differences. We all are focused on the person with cancer and how to get the outcome and experience better."

But what about the differences? Doesn't she experience frustration from nurses in other countries, where nurses might not have the autonomy, the advanced roles and the confidence that they have in countries like the UK? "Yes I do," she says. "Nurses in the US, Australia, the UK have probably led the world in advanced practice – in the transactional sense of doing operations, putting in lines, giving intravenous drugs, prescribing and so on. Nurses in many countries feel their practice is being held back.

"So I'm very thankful about what we have, and for all the nurses before me and in my time who have fought for our autonomy. It hasn't been easy, and we're still winning some fights, losing others. You go forward and back a bit, forward and back a bit.

"So when I'm with nurses who work in places where nursing has not been able to advance so quickly, you can only try and help them to move towards autonomy when it is right for their context and society. The fact is that nursing, as a caring profession, is embedded within the society in which it works and is borne of that society." ■

Deconstructing evolution:

can number crunchers find the answer to resistance?

MARC BEISHON

Is there a logic, a pattern, a system behind the way cancer cells adapt to develop resistance to agents designed to kill them? Cancer research is calling on systems biologists to see if they can make sense of it all.

Imagine you are building a house from bricks. You can see how one brick works with another but you still have to work out how to build the house. Then imagine you have found a ruin – maybe an ancient Roman one, with bricks scattered about. How would you fit the pieces together to work out how people lived in those days? You can't reinvent the original, but you can use the number and location of the bricks to build models using a range of data sources that could give new insights into those ways of life.

That's an analogy Gordon Mills, chair of the systems biology department at the MD Anderson Cancer Center in Houston, uses to describe where we are with systems biology today. "We know an incredible amount about the pieces in cancer – all those molecules and receptors that people have been studying in exquisite depth for years. But none of them function in isolation and if you push on one the system will push right back and try and come into homeostasis.

"We have a very good idea of the wiring diagram of a basic cell – how all the pieces and pathways fit together so the cell functions as it should. In cancer we know we have hundreds of genetic aberrations in every cell that change the wiring diagram. It's that aberrant diagram, and the ability of the wiring to push back against the therapy, we are trying to tackle as we treat a cancer patient, particularly with targeted therapy."

The human body, he says, has robust mechanisms that have evolved from billions of years of life on earth to rewire itself to protect it from 'perturbations' caused by things like toxins in the environment. The problem is that this robust rewiring also comes into play when therapy is given say to hit a target such as EGFR in cancer, so that becomes a 'therapeutic liability', says Mills. It is at least one of the reasons why resistance can quickly develop to initially effective drugs, and only small and disappointing gains are seen with most new targeted therapies.

Further, as Mills describes, the traditional way of looking at single targets in a linear way – by drawing diagrams showing links between molecules and other entities – does not capture the feedback loops and regulatory processes at work in the system as whole. "The linear diagrams are qualitative in nature, whereas the systems biology approach is to put a mathematical and quantitative interpretation on what you have seen, because nothing happens in isolation and nothing is unidirectional, as high-school students learn with Michaelis-Menten kinetics [a famous enzyme reaction model]. The main point of systems is you can't look at a single piece but rather require a holistic view of the cell and the human body."

Systems biology, he adds, is about the thousands of things that happen in the steps required to generate a cancer and how they integrate with each other (and the term 'integrative biology', or indeed 'integrative systems biology', are also used to describe essentially the same field). "But the basic underlying step of why say DNA repair went wrong is not strictly systems biology – it is the many things that went wrong because of that step we are looking at," he says. It is about deciphering both the complexity of developing tumours and also their variability, or heterogeneity, which has dogged much traditional research.

What researchers are doing in cancer systems biology is taking huge amounts of data to build models that allow predictions to be made about what happens when a system is 'perturbed' by cancer or a drug, because it is only through building these models that interactions between parts can be uncovered and tested in experiments. "What happens when you build models is that 'emergent' properties arise – properties that you can't 'intuit' from the pieces alone," says Mills. "The challenge is building and testing a model that is robust enough to predict how a system will respond to perturbations, and this is why systems biology is an iterative process. We keep on using enormous and improved datasets to test concepts in experiments that arise from models. But the aim is that once you understand the system well enough, you can predict things like the bypass mechanisms and target them with therapies."

This means, he adds, that researchers could come up with new combinations of therapies, and their timing and dosing, which hit multiple targets and which could not have been tested in a conventional way as

"Looking at single targets does not capture the feedback loops and regulatory processes at work"

"I was brought up to look at one molecule at a time – this is beyond what we thought about then"

there may be no rationale for doing so, while resources for such trials are in any case severely limited. "We believe these rational combinations will be the next step in going from a transient response to targeted therapy, to durable response that will be equivalent to cures."

An example of where system biology approaches are making progress is in PI3K overactivity, associated with a number of cancers, such as triple negative breast cancer. Here, says Mills, modelling has shown that knocking out only say 60% of the activity of the pathway won't have an impact. "Instead you may need a minimum of 90% inhibition, which totally changes how you would think about implementing and dosing drugs. So you don't say, 'I need an inhibitor,' but 'I need a quantitative inhibitor.'" Further, the system has not one but at least two feedback loops, and probably more, that have to be hit, and again this is deduced from models.

Cancer system biology is furthest developed in how multiple therapies can target EGFR family members, according to Mills. "It's working out why a drug doesn't work where we will make leaps with systems biology," he adds, noting for example that in the HER2 receptor system, while a lot is known about why trastuzumab (Herceptin) works, very little is known about why it fails.

An emerging field

As a field, cancer systems biology started in earnest within molecular oncology in the past decade, with the National Cancer Institute in the US establishing the Integrative Cancer Biology Program, which "encourages the emergence of systems biology as a distinct field" and which now has 12 associated centres, and with EU programmes emphasising the importance of systems biology in collaborative efforts. Mills set up one of the first cancer departments to use the systems biology name, at MD Anderson. Since then, he says, progress has been marked by finally having the technology needed to deliver the high-quality quantitative data needed to build the models required for systems biology, and vastly improved algorithms that can deal with the large datasets.

Awareness of the need to look at cancer as a system has certainly gathered pace, as there are now dozens of systems or integrative biology departments in Europe and the US, not just looking at cancer of course, although there has been a particular focus on the problem of drug resistance and targeted therapies in cancer.

"Most important of all we are now training the next generation of people who can handle the massive amounts of information and apply it to the systems approach," says Mills. "It's a different culture – I was brought up to look at one molecule at a time in classic biochemistry programmes – this is beyond what we thought about then. Being honest, despite knowing about systems I'm nowhere near having the skill sets of some of the people we now have in training, particularly those recruited from engineering and mathematics, who we are now prioritising more than biologists."

There are any number of analogies that can be applied to systems biology, as systems behaviour is a discipline that has been applied in many other areas, such as aircraft control systems, factory production lines, city traffic systems, and other human biological systems besides cancer. But the data and modelling techniques needed in cancer has meant that it has become critical to bring in people from other disciplines, in particular physics, engineering and mathematics, to help develop the systems thinking that can work in this complex disease.

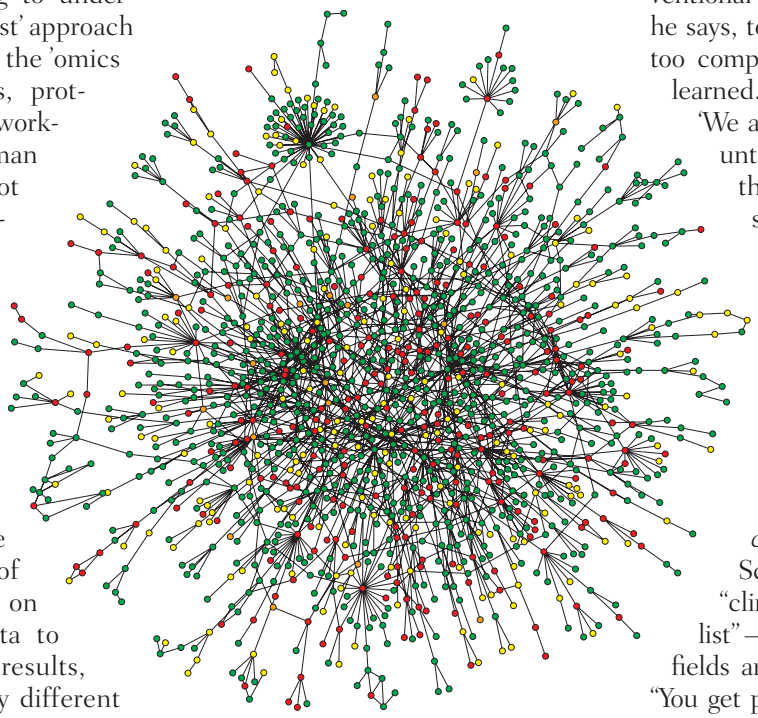
The world of big data

Jacob Scott is a good example of this new band of researchers, who are adopting a very different scientific and cultural mindset, networking with a diverse community that is now applying radical systems thinking to cancer. A practising radiation oncologist at the Moffit Cancer Center in Florida, Scott is in the middle of a PhD in mathematical oncology – a related field where systems thinkers operate – which he is doing at the University of Oxford's Wolfson Centre for Mathematical Biology. "Biologists are not typically trained in the new world of 'big data' and systems, and need to work with people who are used to this sort of data – just as people trained in big data need to work with biologists," he says.

"Systems biology is a bit of a catch-all term, but what is clear is that

more people are coming to understand that the 'reductionist' approach of progressing through all the 'omics – genomics, epigenetics, proteomics and so on – isn't working in cancer. The human genome in itself has not provided the enlightenment once thought, and the 'whack a mole' way we now keep giving lines of therapy by looking for the next mutation isn't based on a deep understanding of the systems nature of the biology."

Scott adds that there are brilliant teams of researchers working on genomics and other data to see if they can predict results, but it is a fundamentally different approach – a 'top down' one, compared with the 'bottom up' systems approach, which is to build models that explain the data. Mills concurs, saying that the prediction modelling approaches that are combining data such as genomics are mainly qualitative – again, the crucial difference in systems biology is the quantitative approach that may use the same data but in a conceptual way. "Unfortunately, though, many types of data we have today are not of sufficient quality that they will work in systems biology, which is why we, for example, have built our own proteomics platform that so far has analysed 90,000 samples just to feed our programme."



The systems approach. This network diagram shows protein–protein interactions in a yeast cell; the biology of cancer is infinitely more complex and modelling needs to take account of quantitative aspects and feedback loops

Currently the researchers in these two camps barely know how to communicate with each other, says Scott. "The papers we modellers write are often impenetrable to, say, people in the predictive genomics camp, and vice versa," he says. That may not be surprising as systems people are bringing in all sorts of models based on fields such as competition and game theory, evolution, spatial processes, patterns and much more, together with conventional biology. It's also important, he says, to create models that are not too complex, otherwise little can be learned. "We have sayings such as, 'We are never done with a model until we can no longer take anything more away,' or as Einstein said, 'A model should be as simple as possible, but no simpler.' And there is also going to be some luck involved as we try and get a balance between adding and taking things away – there is art as well as science here."

In a short article in *Lancet Oncology* (vol 13, p 236), Scott described a new type of "clinician" – the "phase i triallist" – as people coming from other fields are "turned loose" on cancer. "You get people who dream that biology can be explained by first principles – that we can build models on a chalkboard or a computer chip that can predict how a tumour will grow and evolve, how a person may live or die.

"Why not try the tools that our conservation ecologists use to manage invasive species? That macroeconomists use to understand predatory business strategists? That agronomists use to manage pest infestations?" asks Scott. "Well, these phase i triallists have, and continue to. They have hijacked the beautiful differential equation system proposed by Lotka and Volterra to understand predator–prey systems, to try to understand how the dynamic interplay between healthy and normal is

IMAGE BY HAWOONG JEONG, KAIST, KOREA

"Why not try the tools that our conservation ecologists use to manage invasive species?"

Integrating data from all the different platforms is a major challenge for enabling biological interpretation

affected by various traits or strategies. They have used Maynard Smith's evolutionary game theory to tease out the relationship between the shift to aerobic glycolysis (the Warburg shift) and cancer invasion. They have studied the prisoner's dilemma to understand cooperation between tumour cells of disparate lineage."

Collaborating across boundaries

Scott's blog, Connecting the Dots at cancerconnector.blogspot.co.uk, is a good place to experience the eclectic nature of this new community and its experimental thinking and networking events. One of the big events is scheduled for this November, organised by the European Molecular Biology Organization in Heidelberg, Germany, under the title 'From functional genomics to systems biology', which will bring together the wide spectrum of researchers who need to collaborate to make progress in systems biology. As the organisers put it: "To gain a systems level understanding of a given process, cell or organism, the current challenge is to convert these static qualitative maps [from genomics] into dynamic quantitative models of cellular processes. This rather daunting task can only be achieved through a multidisciplinary approach, which requires intensive integration of technology and thinking from basic biology, genomics, computational biology, mathematics, engineering and physics."

Simply managing a group of diverse professionals is a big challenge in itself, says Mills. He insists that everyone in his group – which comprises clinicians and nurses as well as biologists and engineers – interact with others as much as possible. There's even a designated "interaction room", but he laments that too many people lapse into emails, whereas face to face meetings – or at least video or audio calls – are essential to communication when people are from different fields and conceptual cultures, he feels.

He adds that he considers Europe to be ahead of the US in cancer systems biology, owing to centres such as Heidelberg, Oxford and others, and to projects funded by the European Commission, including the European Systems Biology Community site (community.isbe.eu), and Infrastructure for Systems Biology Europe (project.isbe.eu), and a raft of framework projects such as MODHEP (on liver cancer) and Epigenesys, described as an "ambitious EC-funded research on epigenetics advancing towards systems biology".

Mills and colleagues describe in detail the resources and approaches that are coming together in a paper, 'Cancer systems biology: a peek into the future?' (*Nat Rev Clin Oncol* 2014, 11:167–176). They note that integrating data from all the different platforms – such as molecular profiles of tumour samples and patient data, and projects that characterise responses to perturbing cell lines – is a major challenge for enabling biological interpretation. 'Crowdsourcing' data analysis and 'big data' projects are among the advances.

They divide cancer systems biology into several approaches. For tissue complexity, they note that understanding the diverse mechanisms at work between tumour cells and the "microenvironment" may only be solved with systems biology. Then there is heterogeneity of cells in tumours, which they suggest "may represent the greatest challenge to deliver effective personalised therapy." Again, modelling is providing insights.

Targeted therapy, in particular for breast cancer, is an area of "intense research" for systems biology, and of course also for approaches for tackling drug resistance, which Mills and colleagues see as the current greatest opportunity, provided due attention is also paid to side-effects and toxicities.

That the paper poses a question – Is it the future of patient care? – does imply there is a good deal more work to do to prove that system biology models will make major contributions in cancer. "I am worried that there may be so many perturbations or changes that happen in a cancer that each may be a unique universe in itself," says Mills. "There may be sufficient heterogeneity that we cannot developed unified models. But that doesn't mean I'm not going to try.

"For now, I can comfortably say we don't need perfect data for some of the models currently in trials that could make progress in combinations of agents that target what is really going on cancer, and how cells are likely to adapt to a drug and what we can do about targeting mechanisms of resistance."

JASON HARRIS

Communicating across the divide. Jake Scott argued the case for taking a systems modelling approach in a discussion on accelerating progress towards a cure, held at the World Oncology Forum, Lugano, 2012

Asked to mention work he considers furthest advanced, Mills modestly doesn't mention his own lab but includes Merrimack, a biotech company near Boston, US, which is developing drugs based on a systems biology approach, such as an EGFR inhibitor combining three monoclonal antibodies that was modelled to block EGFR more completely than the 95% blockage achieved by other drugs, as the "remaining 5% of activity has the potential to still provide sufficient survival signals to allow the tumour to continue to grow and propagate," the firm says. The company has resources on its website to explain systems biology, including a video from Linda Griffiths, a professor of biological and mechanical engineering at MIT, talking about her own experience with breast cancer and how insight into personalised HER2 expression led her to opt against treatment with trastuzumab.

An academic group noted by Mills is at New York University, where they are building a systems model of the brain tumour, glioblastoma, to select likely therapies. Other groups, he mentions, are assembling concepts at a molecular level that could align patients with seemingly very different diseases such as leukaemia and breast cancer, but who may benefit from similar treatments.

At Moffit, Scott, apart from practising as a radiation oncologist, is a member of the pioneering Department of Integrated Mathematical Oncology, which is led by Alexander Anderson and Robert Gatenby and in March this year was profiled in a *Newsweek* cover story, 'You can't cure what you don't understand'. He is currently working on models of metastasis, and is particularly interested in helping bring people together in systems biology; he would like to have his own lab at some point.

This field could well develop into the kind of stage seen for brilliant young researchers in 'pure' mathematics and physics, and a benchmark has been set by Franziska Michor, an Austrian who studied molecular biology and mathematics at university, gained a PhD at Harvard in evolutionary biology, and at 32 already has her own lab, which focuses on the evolutionary dynamics of cancer, at the Dana-Farber Cancer Institute. At the age of 25, she was featured as the "Isaac Newton of biology" in *Esquire*, the men's magazine.

As *Cancer World* reported recently, Larry Norton, the breast expert at Sloan Kettering in New York, and a major mathematical modeller himself, said at the Advanced Breast Cancer conference in Lisbon that the answer to cancer may well already be in the data we have, and that ramping up data sharing is now critical. Mills agrees about data sharing and says there should be little tolerance now of people sitting on resources, but he is more cautious, saying, "We have the beginning of an answer." This is a field where both quantity and quality – from many respects – are needed in equal measure. ■

Cancer and inequality: bringing the message home

Why do fewer people die of cancer in my neighbourhood than on the other side of town? Steve Buist of the *Hamilton Spectator* asked this question of his home city in southern Ontario, and used a variety of local data and sources to find answers. The story he told, using interactive maps and personal stories, won him the Best Cancer Reporter Award 2014. We reprint an edited extract.

Ask any cancer survivor and they can recall in vivid detail the day they heard the dreaded words "You've got cancer."

It's been 42 years since US president Richard Nixon launched the so-called war on cancer, and yet four decades later, with a cure as elusive as ever, cancer still scares us to the core. Is it the perverse lottery aspect of getting cancer that scares us most? The idea that you can be living your life and then – without warning, without a sign – a switch gets flipped somewhere inside your body and this ticking time bomb is lit?

Even when the link between cause and effect is clear and irrefutable, there's still a randomness to getting cancer. We all know there's a strong connection between smoking and cancer yet three out of four regular smokers will still somehow manage to escape lung cancer. Or is it cancer's lethality that scares us most? We know there's a randomness associated with that, too. Some people beat it, others die from it.

Award winner Steve Buist

But what if dying from cancer isn't as random as we believe? What if your ability to survive cancer has something to do with the size of your paycheque or the amount of education you've had?

That's what the findings of *The Spectator's* exhaustive new cancer investigation strongly suggest. Ten years of data broken down to the neighbourhood level show that poorer people in Hamilton, on average, are dying of cancer at significantly higher rates than richer people. One neighbourhood in the inner city core, for example, has a cancer death rate that's four times higher than a neighbourhood in Ancaster, the city's wealthiest suburb.

The question is why? Why are poorer people dying of cancer more frequently

THE HAMILTON SPECTATOR

It's not fate, and we can do better. *The Hamilton Spectator's* Code Red: Cancer project made a powerful case for addressing the access and social injustice issues that put less educated and poorer members of their community at greater risk of cancer

PART SEVEN OF SEVEN

CANCER
A CODE RED PROJECT

THE ENEMY WITHIN CONCLUSION

PRAYING FOR A CURE

STEVE BURST
The Hamilton Spectator

ASK ANY CANCER SURVIVOR and they can recall in vivid detail the day they heard the dreaded words "You've got cancer."

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The question is why? Why are poorer people dying of cancer more frequently than richer people?

The reasons are enough to shake one's faith in this country's beloved universal health care system, long presumed to be the great equalizer that bridges the gap between the haves and the have-nots.

Disturbing continues // BA2

A higher percentage of people from impoverished neighbourhoods get, and die of, cancer than those in richer neighbourhoods. How do we address access to care, disparity and social justice?

PHOTOGRAPHY BY JOHN RENNISON AND GARY YOKOYAMA, THE HAMILTON SPECTATOR

than richer people? The reasons are enough to shake one's faith in this country's beloved universal health care system, long presumed to be the great equalizer that bridges the gap between the haves and the have-nots.

Our comprehensive analysis shows significant disparities when it comes to access and utilization of basic health services such as cancer screening programs and family physicians.

What's disturbing is that those disparities often play out along social and economic lines. When it comes to cancer screening programs for breast, cervical and colorectal cancer, people in Hamilton's poorer inner-city neighbourhoods are being screened at much lower rates than people in the richer suburbs of Ancaster, Flamborough, Dundas, Glanbrook and Stoney Creek. In some cases, the screening rates are nearly three times greater in the wealthiest neighbourhoods compared to the poorest ones.

An exclusive *Spectator* survey also shows that people in the inner-city core are three times more likely not to have a family physician and twice as likely to use walk-in clinics as their main source of health care than people in the western suburbs of Ancaster, Dundas and Flamborough. The investigation also shows that frighteningly high rates of smoking in Hamilton's inner city play a major role in the high cancer death rates that affect the city's poor.

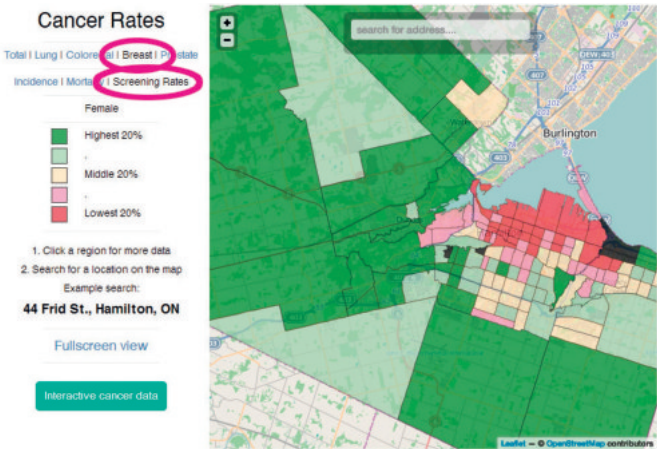
Let's start with cancer screening

Why are poorer people dying of cancer more frequently than richer people?

programs and the example of one specific inner-city neighbourhood, the chunk of downtown Hamilton between James, King, Wellington and Cannon streets. Nearly half of all adults and almost 70 per cent of children there lived in poverty, according to the 2006 census – the highest rates of poverty in the entire city.

That area also happens to have the highest cancer mortality rate in Hamilton, four times higher than an Ancaster neighbourhood that has the lowest death rate.

Now look at the cancer screening rates for that same inner-city neighbourhood. Just 29 per cent of eligible women were screened for breast cancer in 2009, the lowest proportion in Hamilton. By comparison, the highest rate was one Glanbrook neighbourhood where 75 per cent of eligible women were screened.



Just 21 per cent of eligible men were screened for colorectal cancer, and again, that was Hamilton's lowest rate.

In the best neighbourhood – again in Glanbrook – the rate was 55 per cent. When it comes to screening for cervical cancer, it's the same story. Only 34 per cent of eligible women were screened, compared to 78 per cent in one Flamborough neighbourhood.

Maybe it's just a coincidence that the neighbourhood with the highest rate of poverty and highest rate of cancer deaths also has the worst rates of screening for three common types of cancer. Or maybe it's not a coincidence at all.

Pull the camera back a little further and the same picture keeps coming into focus.

The Spectator's investigation shows the cancer death rate in the inner-city between Queen Street and Parkdale Avenue from Main Street to the waterfront was 90 per cent higher than the death rate in Ancaster, the city's wealthiest suburb. At the same time, the rates of cancer screening across the board in the inner-city are one-third lower than the rates in Ancaster.

In the core, 47 per cent of eligible women were screened for cervical cancer in 2009. In Ancaster, the rate was 68 per cent. For colorectal cancer screening, the rate in the core was 33 per cent of eligible men and 40 per cent of eligible women. In Ancaster, the rates were 48 and 54 per cent, respectively.

In every case, it's the same story. Screening rates improve as you move from areas of low income to areas of higher income. When it comes to breast cancer screening, 45 per cent of eligible women in the inner city were screened. In Ancaster, the rate was 67 per cent. If you ranked amalgamated Hamilton's 135 neighbourhoods from top to bottom for breast cancer screening, the bottom 32 neighbourhoods with the lowest rates are all found in the lower part of the former City of Hamilton.

Ontario's target for breast cancer screening is 70 per cent of women ages 50 and older. Only three of Hamilton's 135 neighbourhoods have attained that level, according to the data provided to *The Spectator* by Cancer Care Ontario. It's taken over 15 years to even get that close to the target, said Dr Bill Evans, recently retired head of the Juravinski Cancer Centre. "Why is that?" Evans asks, then answers. "Well, we keep doing the same thing over and over again. "We promote it in *Chatelaine* magazine," he said, speaking about breast cancer screening programs. "Guess what? The folks down in north Hamilton aren't reading *Chatelaine*."

The disparities in screening rates are another sign of the strong connection between health outcomes and social factors, Evans noted. "It goes back to an awareness of what are the healthy behaviours, including going for screening, having your Pap tests, having your colorectal screening and breast screening," Evans said. "All of those things are partly determined by your level of knowledge and

Screening rates improve as you move from areas of low income to areas of higher income

understanding. "If you're in less well-off circumstances, you might not know those things or you might not know how to find them or you can't afford to get to them," he added.

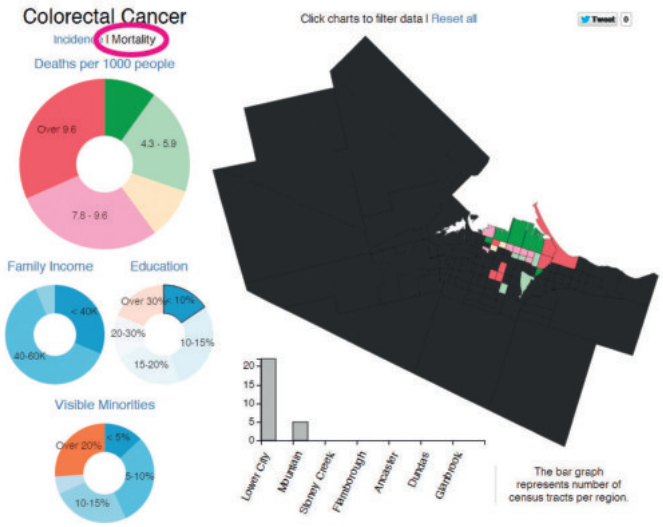
It's important to note screening programs don't change the incidence of cancer. But they should ultimately improve the outcomes for those who are screened and found to have cancer. "As you keep going in the breast screening program, you expect that you're going to pick up smaller and smaller cancers," said Carol Rand, director of systemic treatment and regional cancer programs at Juravinski. "That's the definition of being a good screening program. "You're not a good screening program if you're just picking up great big cancers," she said. "People are already well advanced at that point."

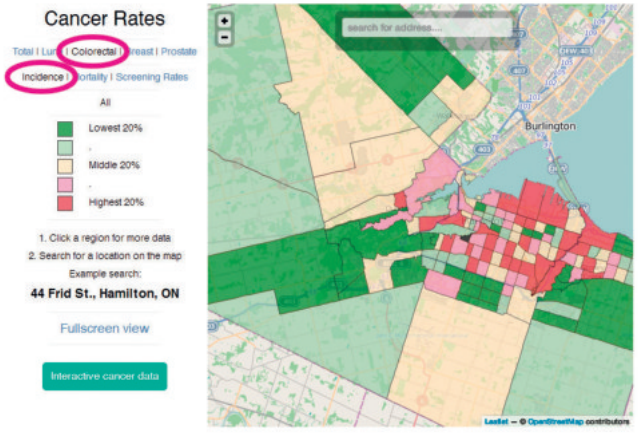
Shawn Forbes is a colorectal surgeon specializing in cancer at the Juravinski centre. Originally from Thunder Bay, Forbes came to Hamilton to attend McMaster's medical school then decided to stick around. He has no shortage of work here, that's for sure. Between 2000 and 2009, about 3,250 people in Hamilton were diagnosed with colorectal cancer, and more than 1,400 people died of the disease.

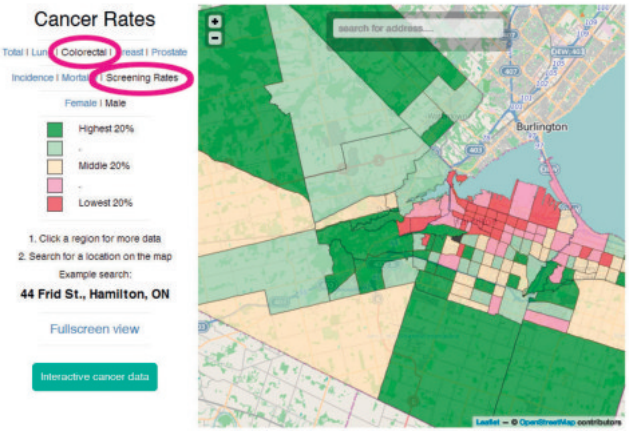
DATA MAPPING THE NEIGHBOURHOOD

Steve Buist's Code Red Cancer series combined traditional print journalism with an interactive website http://thespec-codered.com/cancer/ where readers can find searchable colour-coded maps showing the variations in rates of deaths, new cases, and screening across neighbourhoods in and around the city of Hamilton in Ontario, for the four most common types of cancer.

This is the story they tell for colorectal cancer. People living in neighbourhoods coloured red are more than twice as likely to die of this disease than those living in areas coloured green. This reflects in part lifestyle-related differences in the risk of getting the disease, but also differences in attending screening and accessing high-quality healthcare.







Gently, patiently and persistently, she is trying to persuade people to get screened for cancer

The *Spectator's* landmark cancer analysis shows there's a notable income gradient in colorectal cancer mortality rates across Hamilton. The death rate from colorectal cancer in Hamilton's east end between Parkdale Avenue and the Stoney Creek border was about 80 per cent higher than the colorectal death rate in Flamborough. The numbers are sobering, Forbes said.

"The way our health care system is set up is a universal system and everybody should have equal access," said Forbes. "But these numbers would suggest otherwise. Unfortunately, there is no one individual marker or test or indicator of socioeconomic status that encompasses the entire problem," he added. "If only there was a single marker that could say, OK, this is a population that is at risk."

Screening rates for colorectal cancer lag behind those for breast and cervical cancer, and again, there's a significant difference across income levels. There's also a notable gender difference – women take advantage of colorectal cancer screening more than men. In one inner-city neighbourhood, just one in five eligible men were screened in 2009.

The good news is that colorectal screening rates through the use of a fecal occult blood test rose dramatically in the amalgamated city of Hamilton between 2005 and 2011. The bad news is that even with the increase, just 30 per cent of Hamilton's eligible population completed the test.

It's important, Forbes said, to remember the fundamental reasons for cancer screening programs such as FOBTs and colonoscopies. "We screen because a disease is common," he said. In the case of colorectal cancer, it's the third most common type of cancer in men and women in Hamilton. But we also screen for colon cancer and a number of other cancers because we can modify the outcome and that's the big deal," he said. "If screening didn't affect the outcome, then we wouldn't screen. But we know that if we catch colon cancer early, we can modify the outcome and improve survival rates."

When colorectal cancer is diagnosed at stage I, the five-year survival rate is 93 per cent, according to the American Cancer Society. But stage IV colorectal cancer? The five-year survival rate is less than 10 per cent. "We know that stage is the biggest predictor of mortality," said Forbes. One of the questions he's been helping research recently is whether or not there are differences in tumour stages based on a patient's socioeconomic status. "If there are more advanced-stage tumours coming out of the core or those with lower socioeconomic status, then it has something to do with diagnosis," said Forbes. "Are these people not getting screened as aggressively as people of greater wealth?"

One of the barriers to colorectal screening is the stigma that comes attached with the disease. For some people, it's a squeamish and uncomfortable topic they'd rather avoid. "Even when they come to me – and this is all I do, this all I talk about – you can see they're embarrassed," said Forbes. "There's nothing embarrassing about it. This is your life, this is your health we're talking about.

"We're here to help," he added. "There's a reason we're doing this."

Nelly Sinclair is a community outreach worker with the CASTLE project. Funded by the Public Health Agency of Canada, the goal of CASTLE – Creating Access to Screening and Training in the Living Environment – is to increase the woefully low cancer screening rates in three inner-city neighbourhoods.

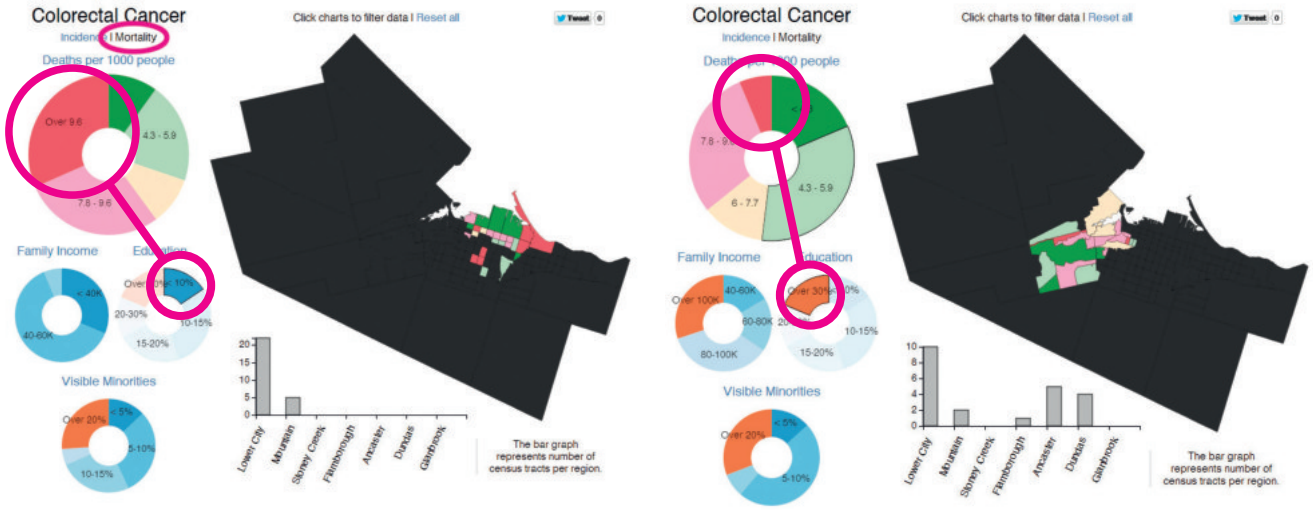
Since the start of the year, Sinclair has been to more church basement dinners, retirement homes, afternoon teas, group homes, seniors' aquatic programs and community meetings than she can count in the McQuesten, South Sherman and Crown Point neighbourhoods. "It's got to be the best job in the world because building relationships is a lot more fun than working," said Sinclair.

Gently, patiently, persistently, she's trying to persuade people to get screened for breast, cervical and colorectal cancer. At times, it seems like a person-by-person campaign. "They've got the majority of the people who are easy to do," said Sinclair, who is 46 years old. "I'm there to try to find the ones that aren't easy and to make change with them."

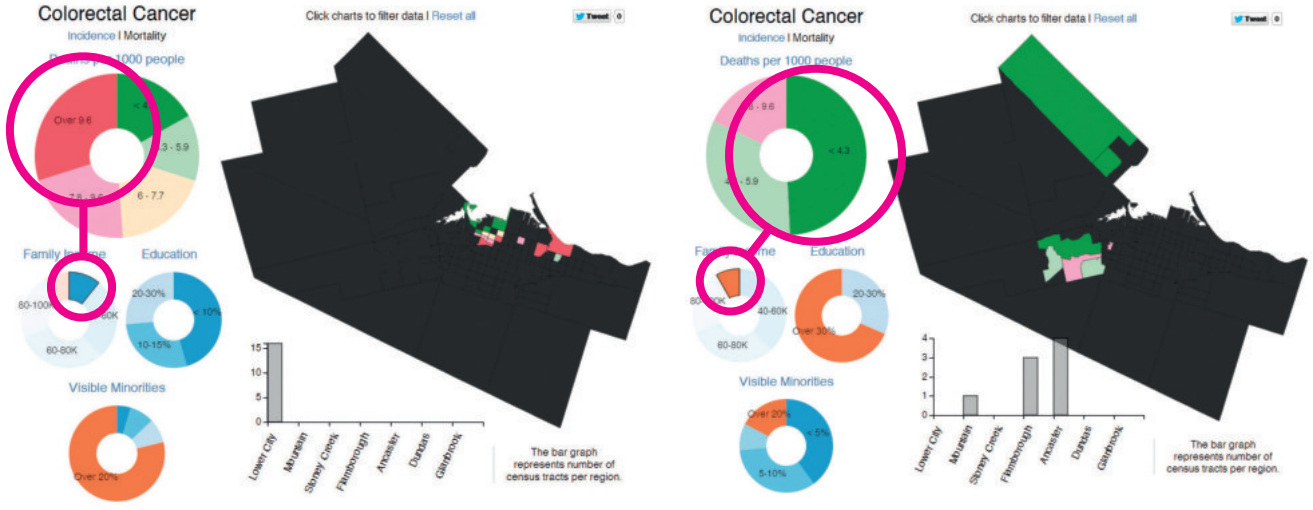
In some of the neighbourhoods she's responsible for, less than 30 per cent of eligible men had been screened for colorectal cancer and fewer than 40 per cent of eligible women had been screened for breast cancer prior to the start of the CASTLE project. "People don't

INFOGRAPHICS HIGHLIGHT THE LINKS WITH EDUCATION AND INCOME

Neighbourhoods can be selected according to their average education, income or visible minorities level by clicking on a segment of the relevant infographic. The cancer rate for those areas can then be seen in the colour coded map and the mortality/incidence charts.



Almost one-third of the neighbourhoods with the lowest educational level have the highest level of deaths from colorectal cancer (shown in red); while the same is true for only a small fraction of areas with the highest levels of education



Almost one-third of neighbourhoods with the lowest income level have the highest rates of deaths from colorectal cancer; while for areas with the highest income level, almost half show the lowest rates of death (shown in green) and not one has the highest rates of deaths

The stories behind the statistics

JOHN RENNISON & GARY YOKOYAMA, THE HAMILTON SPECTATOR

Steve Buist brought the statistics to life through many voices from the Hamilton community, from people living with cancer to those being failed by prevention, screening and care services, and the professionals and volunteers trying to address these access problems. They included (main picture) Janice McFadyen, mother of two, who has since died from her breast cancer, and (clockwise from top left): Bill Evans, retired head of Hamilton's Juravinski Cancer Centre; Steve Rudaniecki, living with advanced chronic lymphocytic leukaemia; Shawn Forbes, a local colorectal cancer surgeon. David Price, chair of the department of family medicine at Hamilton's McMaster's medical school; Kevin McDonald, manager of Hamilton's anti-tobacco programme; Nelly Sinclair, community outreach worker promoting attendance at screening; Theos Tsakiridis, prostate cancer specialist at the Juravinski Cancer Centre; Bill McArthur, living with advanced lung cancer

change just because you tell them they should," she added. "There are many good reasons why people are not doing cancer screening so my job is to find out what those reasons are and to get these people to the point where they're actually going to do the screening."

A pastor's wife, Sinclair, her husband and their four children moved to Hamilton two years ago from Alberta. She's not a health care professional by training – in fact, she was hired precisely because she wasn't one. For the people she's trying to reach, health care professionals can sometimes seem scary.

"When I talk with somebody, I start with where they're at and what their story is and where do we go from there," Sinclair explained. "The conversation's not finished if we're not talking about cancer. If they don't want to talk about cancer screening today, I'll be back next week," she said. "Whereas a health professional is providing a service, they let you know what the service is and then you come when you're ready. I go to where they are when they're not ready and try to work at that."

She tells the story of one man at a group residence who she convinced to take the fecal occult blood test after many weeks of effort. Along the way, she also had to help him navigate his way to finding a new doctor located closer to where he lives. "When I first talked to him, there was no way under the sun he was ever going to put his poop in the mail and he told me so in no uncertain terms," she said with a laugh. "So it's a process."

His case highlights some of the barriers she's found along the way – attitudes to screening, access to a health care professional, transportation. She's also seen the barriers placed by mental health issues when it comes to screening. Sinclair recalled the time she was in a convenience store and ran into a man she'd been trying to convince to go for colorectal cancer screening. "I asked him how he was doing and he said 'I had a really bad weekend,'" Sinclair said. "'I was in the hospital, I tried to commit suicide.'

"You learn that sometimes you have to back off with some people because their mental health issues flare up," she added. "It's real life, it takes priority." ■

This extract was taken from Praying for a Cure, part 7 of the Cancer: Code Red project (http://thespec-codered.com/day-7-enemy-within-conclusion/), which was first published by *The Hamilton Spectator* on 2 November 2013, and is reprinted with permission.

A seat at the table: patient advocates

Little by little, patient advocates are winning their battle to be involved in decisions that affect them. They are now focusing on how to use their new-found voice to deliver real change for the people they represent.

The days when patient groups were all about tea and sympathy are long gone. Over the past 20 years or so, cancer patients who choose to become active have focused increasingly on advocacy: campaigning for greater public awareness, lobbying for improvements in patient care, and educating patients about their disease and treatment options so they can play an informed role in decisions about their own care. They have also been knocking on the doors of researchers, regulators and policy makers, demanding the right to have a say, as equal partners, in decisions that affect them.

Slowly but surely, doors have started to open. Some national health technology assessment (HTA) bodies invite patient advocacy groups to submit evidence on the impact of new drugs and other 'medical technologies' on their quality of life. Some trial sponsors consult them over priorities and acceptable trial designs. Europe's regulatory body, the European Medicines Agency, is beginning to involve patient advocates in the approvals process. Some funders even include patient group involvement as a criterion, or at least a plus point, when awarding research grants.

While progress is patchy, this seems to amount to a welcome trend towards

prepare for life on the inside

ANNA WAGSTAFF

the ideal of "nothing about us without us", adopted as a motto by the European Cancer Patient Coalition (ECPC). But contributing at this level poses a huge challenge for patient advocacy groups, whose members work largely on a voluntary basis, with little or no background in medicine or in running an organisation at a national – let alone international – level. They have to tackle this role on top of the effects of living with cancer or the legacy of having gone through cancer, or having lost someone to the disease.

In May, advocates representing a wide range of cancer patient groups gathered in Baveno, Italy, for a Masterclass to help them fulfil the 'expert partner' role they have been demanding.

Valued as partners?

Sitting at a table alongside scientists, regulators, health economists or health technology assessors can be a scary business, and even the more experienced advocates admitted they sometimes feel intimidated. They shouldn't, was the message from Ken Paterson, former chair of the Scottish Medicines Consortium, the body that evaluates new drugs for funding.

Patients bring to the table expertise that is both valuable and unique, Paterson said. While clinical trial data for a new drug focus on its 'anti-cancer' properties, what HTA bodies care about is its 'pro-patient' properties – and there is often no direct correlation. Only patients can say how their disease impacts on them and on their families. "They know the problems with existing treatments, and they know what they want most from new treatments, not just in terms of longer survival, but quality of life and greater convenience."

This was music to the ears of the advocates, but did not chime with many of their experiences. HTA bodies don't really care about quality of life, they look only at survival figures, was one comment. Another said that HTA bodies took little account of their input. "If we ever talk to pharmaceutical companies or accept their funding for our activities, they see our evidence as tainted." The time taken by HTA reviews was said to be "absurd", delaying patient access to a new drug they

ILLUSTRATION: FRED VAN DEELEN, WWW.ORGANISART.CO.UK

"There will be a need for more patient involvement in both licensing and HTA"

may desperately need. Many felt that HTA bodies put demands on patient groups they are in no position to fulfil. Deb Maskens of the International Kidney Cancer Coalition said that, in Canada, HTA bodies expected them to provide impossible standards of evidence they were not resourced to achieve. "We use the internet and are told it is a biased survey that will not reach, for instance, older patients. We are told to organise focus groups and one-to-one interviews. But if no one is paying for us to do this, is it really valued?" she asked.

"We do value it, and we certainly take account of impact on quality of life," Paterson responded, though he conceded that attitudes vary from country to country – many European countries give patients no say at all in evaluating new therapies. Patient input, he said, won't override all the other evidence, but it can certainly sway a decision that is finely balanced. "It could tip the balance in favour of the therapy, or allow sub-groups to be identified – for instance patients whose comorbidities put them at particular risk from side-effects of existing therapies – or it may show extra benefits to the health system – for instance through fewer emergency hospital admissions."

The Scottish Medicines Consortium does not expect patient groups to produce 'gold standard evidence', said Paterson, and it also provides them with some expert assistance. While questionnaires, surveys and focus groups are all valuable sources of information, anecdotal evidence and individual patient stories and opinions also have a role to play.

Suspicion about pharma influence is a problem, he agreed, and it needs gradually to be broken down. "The problem is that there have been examples of bad practice, and then people extrapolate from the bad to the general, and we do need to move beyond that." The advice given by the Scottish Medicines Consortium is simply to be upfront about any interrelations or sponsorship. As for the time taken to evaluate new therapies, in Scotland they take no more than 16 weeks, he said. "If we can do it, why can't everyone else?"

In Paterson's view, the answer to many problems lies in proposals to identify what patients really want from a new drug before it enters phase II or III trials, so that relevant data can be collected and made available to HTA bodies as soon as trials are complete. Patient groups need to be involved at the trial design stage to help identify what data should be collected and how best to go about it. "There will be a need for more patient involvement in both licensing and HTA," he said. "Patient advocacy groups need to grasp this change."

Expert partners. Advocates are no longer always bystanders at research conferences – here Musa Mayer from the advocacy group AdvancedBC.org (front row, left) and Elizabeth Bergsten-Nordström from Europa Donna (back row, second from left) sit on the consensus panel at the closing session of the ABC2 conference on advanced breast cancer, Lisbon, November 2013

JORGE NOGUEIRA

Partners in care

As an example of how to go about gathering robust evidence from a large and disparate constituency of patients, Giora Sharf of the CML Advocates Network described a survey they conducted on how well patients stuck to their Glivec prescriptions and the reasons for non-adherence.

This produced a highly influential report, documenting the surprising extent to which patients on long-term medication miss doses, either through

forgetfulness or by design, even when their illness is potentially life-threatening. It took a patient group to do this, because patients are often reluctant to admit to their doctors that they have mixed feelings about their medication – especially when the medication in question is a 'wonder drug'.

Sharf described how they worked with medical and psychology experts to draw up a pilot survey which was translated into eight languages, and distributed online, attracting 150 responses from patients across 10 countries. The results were presented at a major haematology conference, where they won support for a larger scale study. They validated a scale for measuring adherence, translated the survey into four additional languages, set a budget, and employed a logistics organisation company to help with distribution. To control for the bias towards younger and more educated patients associated with administering the survey online, paper versions of the survey were distributed by doctors in three countries and their results compared against online survey results from the same countries.

The final CML advocates network survey received more than 2,150 responses online and almost 400 on paper. It revealed the surprising finding that only one in three patients who responded were "highly" adherent, while more than one in five had "low" adherence – a serious problem given that patients who take less than 90% of the prescribed dose have only a one in five chance of achieving the desired outcome of a "major molecular response".

The survey flagged the importance of looking beyond serious medical side-effects to learn from patients about what they find most burdensome, whether it be bloating or the endless tyranny of "take 1 with a meal, 4 times a day". Feedback from independent patient groups is therefore vital not just at the point of evaluating new therapies, but also helping ensure they are used to greatest effect.

Partners in research

So long as patients continue to die, establishing an effective relationship with the research community remains a priority. Bettina Ryll, a medical doctor and molecular biologist, talked about how her perspective on clinical research changed dramatically after her husband was diagnosed with advanced melanoma and he participated in several clinical trials. "There is good research and not so good research. When you are dying you need research that gives you the answers you need to make informed decisions on the best treatment options," she said.

Researchers need to interact directly with patients to better understand their needs, to ensure that efforts and resources are focused on the most clinically relevant issues, said Ryll.

This in turn means patients should be involved right from the inception of a clinical trial, rather than having their role confined to being consulted over the wording of consent forms. Referring to the Helsinki agreement on research ethics, Ryll argued that patients' interests must take precedence in clinical trials, "And before patients want nice patient information leaflets, they want the chance to survive and see their children grow up," she said.

POWER POINTS

Estelle Lecointe, from Sarcoma Patients EuroNet, said advocates must build relationships with experts and the pharmaceutical industry to open their eyes.
"They have no idea why patients should be involved. We need to establish our credibility and credentials."

Ulla Ohlms, representing the PATH Foundation, the biggest tumour bank in Germany (7,000+ donors) run by and for breast cancer patients, talked of the value of having control over resources researchers need.
"Having tumour tissue in the freezer means having power."

Kathy Oliver, from the International Brain Tumour Alliance, advised advocates to go and talk to researchers face to face.
"If you haven't visited a laboratory, do. You learn about what makes researchers tick, how they work and what their priorities are. Many of them never meet patients or caregivers to hear about what's important to us. So don't be scared to engage."

Feedback from patient groups is vital in ensuring therapies are used to greatest effect

"Scientists value your input. They would love to see their work having a positive impact"

Ryll also argued for patient groups to take a more active role in the drugs licensing process – something that is beginning to happen at the level of the European Medicines Agency (see Editorial, page 3). Patients can bring a sense of reality to deliberations over the degree of certainty required about the risk, she says. They have an insight into the benefit of a new drug that represents the only glimmer of hope – however uncertain – to a group of patients with no other options. "We need timely and innovative drugs with a risk–benefit profile that is appropriate for our conditions." She pointed out that patients with advanced melanoma, where the historic survival rate has been between six and nine months, are likely to accept far higher risk levels than, for instance, people living with CML, who have many well-proven and effective options.

Participants in this Masterclass had clearly been struggling with some of these issues, where they felt they were not technically equipped.

"We're afraid we don't have the capacity to be involved on an equal basis with the scientists," was one comment, to which Ryll responded, "Most scientists value your input. They are highly specialised technical experts who would love to see their work having a positive impact. Go and tell your story – it's about pointing out the questions, you don't have to come up with answers."

Derek Stewart, a survivor of throat cancer who provides expert patient input within the UK National Institute for Health Research, questioned how much knowledge and experience people really need. "All I needed to know was that they weren't working together and focusing on relevant stuff. Don't accept slick answers. Simple powerful questions are what is needed."

Europa Donna, the European Breast Cancer Coalition founded in 1994, has the longest involvement with research of all the groups. They were cofounders of the European Breast Cancer Conference in 2000, alongside EUSOMA (the Society of European Breast Cancer Specialists) and EORTC (the cancer research and trials organisation). Head of Policy Karen Benn related how they had been invited to sit on the scientific committee of the Breast International Group research network, which led to their involvement in MINDACT – "a pro-patient trial" aimed at reducing overtreatment of women with low-risk early breast cancers – where they are now on the steering committee, the legal and ethics committee and the "spreading of excellence" committee.

Europa Donna is currently involved in a broad spectrum of major international collaborative trials and research projects, from treatment of early breast cancer to advanced breast cancer and issues of survivorship. It has also been approached by a number of groups applying to the EU's Horizon 2020 programme for funding for breast cancer research. "It's important to evaluate potential research projects carefully," said Benn, "to ensure that the trial/study answers an important question of interest and of use, and that advocates are involved from the outset and have adequate resources for their involvement." Getting that seat at the table, she added, is not enough in itself. "Advocates are not there to rubber stamp the materials. You need to ensure the patient's role is respected, and you need to be attentive and assertive. Advocates need time to study materials in advance, ask questions and participate actively in order to ensure credibility and independence, and provide a real consumer perspective." Out of its experience, Europa Donna is developing a training module for advocates who serve on trial committees.

Better together

The success stories were inspiring, but Markus Wartenburg, from Sarcoma Patients EuroNet, suggested that cancer patient groups might be more effective if they pooled their efforts. "The international cancer patient community lacks a voice," he said. "We need coordinated action. We need to talk to the EMA [regulators] and EORTC [Europe's main cancer trials organisation], to ESOP [the pathologists] and to ESMO [the medical oncologists] and also to the pharmaceutical industry. We need to speak with one voice."

Jan Geissler, representing the CML Advocates Network, agreed, pointing out that issues such as early involvement in shaping research are relevant to all types of cancer, and it is a mistake to insist that patient experts should stick to just one cancer type. "We can work across diseases," he said. One suggestion was a forum for patient experts in research that works across cancers. This could

UNITY AND DIVERSITY

Representatives from European and international patient advocacy groups covering 12 types of cancer gathered together for the first time at the ESO Masterclass to talk about how to strengthen the credibility, vibrancy, focus, reach and sustainability of their own organisations, and discuss how far they can work together to streamline their interactions with regulatory, research and HTA bodies, to maximise the impact of the patient voice

not only have the advantage of pooling resources and knowledge, but also make it easier for the patient advocacy community to choose who represents them, rather than leaving it up to regulatory or research bodies to decide who to approach.

All but a handful of participants at the Masterclass were patient advocates, but there were also some representatives from supporting pharmaceutical companies present, and they agreed that fragmentation could be a problem. One industry delegate said, "In Germany alone, there are 20 breast cancer groups, and if we work with one, the others say it is not representative." They stressed that they find it easier to convince their companies to engage with patient groups on research if they can work with umbrella groups that are widely supported. Sarcoma Patients EuroNet was given as an example of a group with "visible value". Industry delegates also suggested that patient groups could do more to urge specialists to make the case for companies to involve patients groups more closely.

Some participants, however, felt it was unreasonable to expect groups advocating on more common types of cancer to achieve the level of unity Europe's sarcoma patient advocates have achieved. They also questioned why patients had to have a single voice, when the industry did not demand the same from clinicians, commenting: "You don't ask the same of doctors – you ask all of them."

The skills for the job

Many participants at the Masterclass had played a key role founding the organisations they were representing. None had gone into advocacy for the love of a well-written strategic plan, fund raising, or organisational planning. But patient groups hoping to build strategic partnerships and gain the skills credibility to participate in decision making processes need to attend to these things, and the Masterclass offered an opportunity to address this.

The expertise concentrated in the Europa Uomo delegation – comprised mainly of older men – came in handy here, and they helped organise the sessions on strategic planning and managing risk.

Europa Donna also shared the benefits of their experience. Susan Knox, Executive Director, explained how they sought help from the Boston Consulting Group in 2007 to help them reassess where they were going and how to get there. They needed a strategic review to build on a decade that had seen a rapid rise in the number of member groups across Europe, spiralling activity, and a transformation of the environment in which they were working.

Sustainability is a big issue for many. Advocates from lung and melanoma

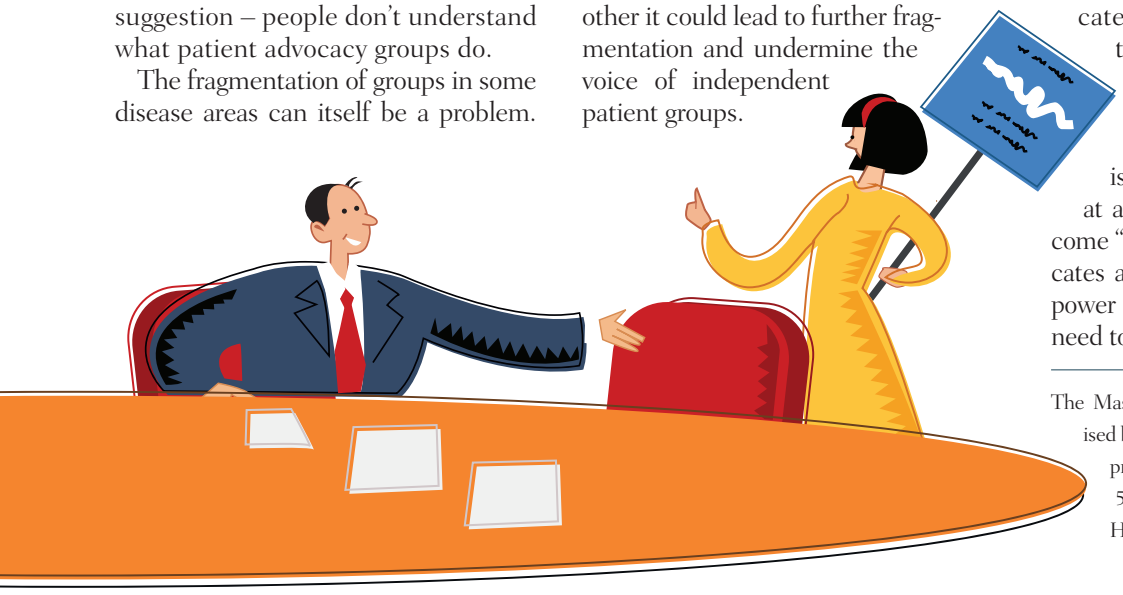
"The most powerful change agents will be patient advocates who can communicate with clarity and passion"

groups pointed out that in cancers that progress fast and have few effective therapies, a high turnover of patients is inevitable. After a death, family members may be traumatised by the experience and not want to continue their involvement. Patients whose cancers are under long-term control, or apparently cured, may also be reluctant to stay involved, as they want to minimise the impact of cancer on their lives.

This means that patient groups always need to attract new active members. And the question of why patients make contact – or do not – was a key area for discussion. Stigma can be an issue – patients often prefer to make anonymous contact online. Doctors are not good at passing on information about advocacy groups to their own patients – they need to be convinced of the value. There may be an image problem, was another suggestion – people don't understand what patient advocacy groups do.

The fragmentation of groups in some disease areas can itself be a problem. "In patient circles it seems typical for patients to start new organisations all the time, because they don't like what is there," was one view. Others saw this as a strength. "There are different types of organisation that are all close to patients and useful to them. This is to be expected, as patients have so many different problems to deal with, including for instance rehabilitation and return to work. Some problems can be addressed by small organisations that offer support and advice, while others need the strength and efficiency of unified umbrella organisations," said Francesco de Lorenzo, of the European Cancer Patient Coalition.

There were mixed feelings on whether hospitals should be encouraged to set up their own patient groups; on the one hand it could lead to more patients getting the benefit of support from people who understood what they were going through, but on the other it could lead to further fragmentation and undermine the voice of independent patient groups.



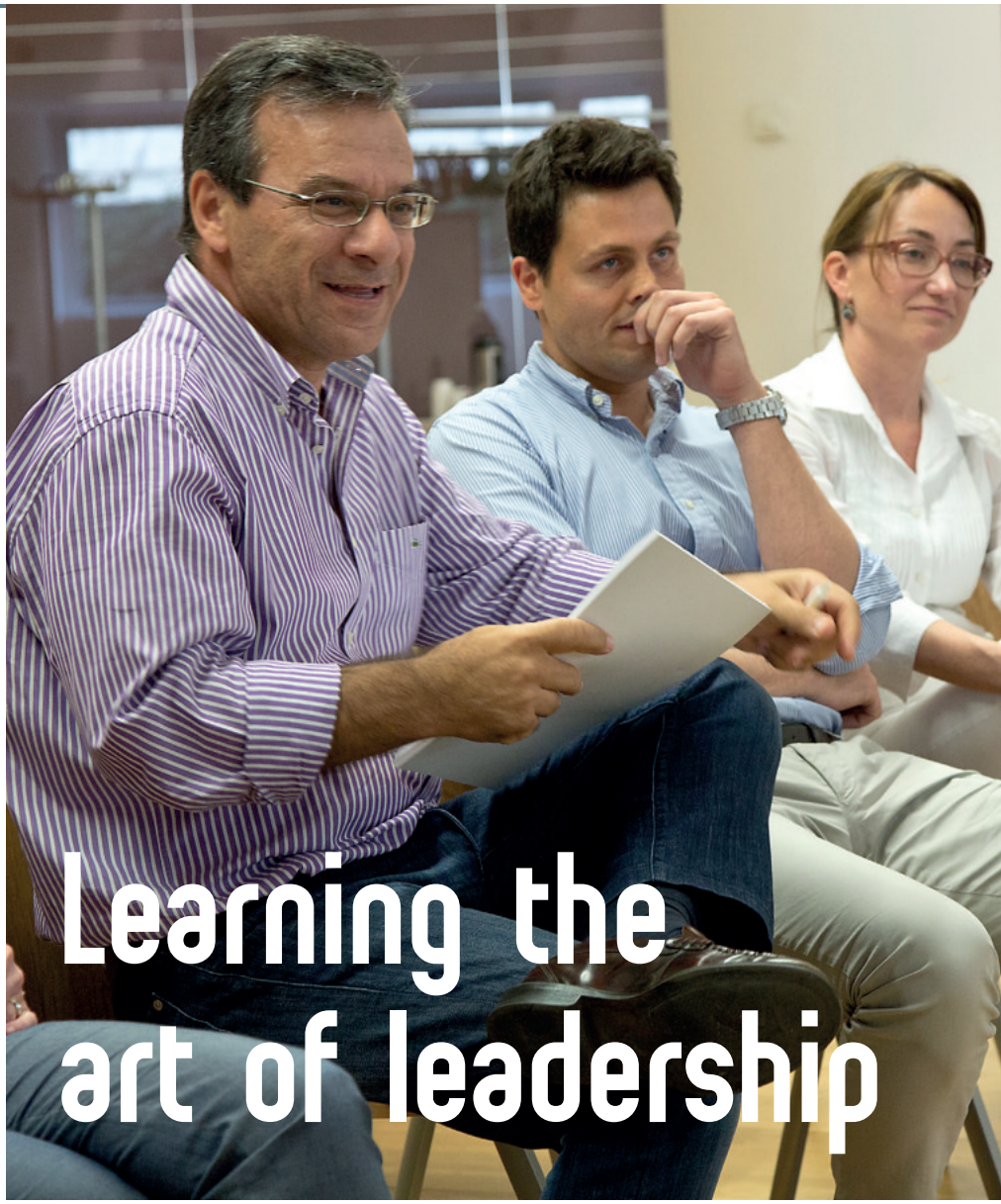
Insiders or outsiders

Everyone agreed on the need to foster a spirit of collaboration. But there was a big question about how to work in a coordinated and streamlined manner without stifling the initiative of individual groups.

This may be one of the big dilemmas for patient groups seeking to maximise their impact. Influencing decisions that shape research agendas, reimbursement and service delivery takes more than 'input' and 'involvement'; it also takes the raw human emotions that only patients and carers can express. Is it possible to work 'from the inside' and not be assimilated?

Clifton Leaf, a survivor of Hodgkin lymphoma and an award-winning journalist, concluded the Masterclass by making an impressive case for changing the research culture. "The most powerful change agents, I believe, will be patient advocates who can communicate with clarity and passion what the research process looks like now, what the opportunities for change are – and, perhaps most important, what the human cost is likely to be should we do nothing at all." The change, said Leaf, must come "from within". But if patient advocates are to retain the passion and the power to effect that change, they may need to keep one foot on the outside. ■

The Masterclass in Patient Advocacy was organised by the European School of Oncology. ESO provided 50% of the funding. The remaining 50% was provided in equal parts by GSK, Helsinn, Novartis, Lilly PACE, and Roche



Learning the art of leadership

A course teaching leadership skills to cancer clinicians is proving a hit among the growing number of oncologists now finding themselves being asked to take on management roles.

PETER MCINTYRE

According to a 2012 report from Leeds University Business School – 'Clinicians in Management: Does it Make a Difference?' – increasing the number of doctors on NHS hospital boards significantly increases quality in terms of Health Commission ratings, lower morbidity and increased patient satisfaction. A McKinsey Quarterly report – 'When Clinicians Lead' – also supported the need to harness the energies of clinicians as leaders, but pointed out that in many healthcare systems becoming "management" leads to a loss of income.

Medical education hardly addresses what makes a good leader or how to become one. Doctors who take over departments – perhaps the most talented or simply longest serving – have no pre-existing training in management. They have learned to fight for their own patients; now they have to learn how to get the best out of colleagues, and to make a case for resources and use them effectively.

In 2012, the Milan-based business school, SDA Bocconi, launched the Programme for Oncology Leaders in Europe (POLE), for mid-career clinicians who are preparing for leadership roles. Rosanna Tarricone, director of the Bocconi Centre for Research on Health and Social Care Management, says that all European governments are struggling with how to offer comprehensive healthcare while containing costs, and cancer treatments are amongst the most expensive. "Clinicians need to know how to manage scarce healthcare resources, including human resources. There is little preparation for this role. POLE came about to fill this gap, at least in part."

The course started in 2012 with 14 doctors from across Europe selected through a competitive process with the support of their cancer units. POLE is now in its third iteration; 15 days training over five weekends covering nine months. It has already become one of the highest rated courses in this highly rated business school, with

PETER MCINTYRE

strong feedback from participants.

The course covers five major topics: European healthcare systems and policies; leading 'self'; leading others; leading organisations; and health economics and health technology assessment. The emphasis is on practical hands-on knowledge, delivered by international experts alongside Bocconi staff: Nadia Harbeck from Munich on bringing research into practice, Denis Lacombe from EORTC on regulatory challenges in pan-European trials and how best to participate in large cooperative groups, Alberto Costa from Milan on certification of breast cancer units and David Cameron from Edinburgh on hospital management issues. Participants swap workplace experiences over dinner with peers and form friendships that may even turn into professional collaboration.

Leading role. Participants practise their communication and presentation skills with the help of a professional actor

PETER MCINTYRE

New skills, new confidence

Five doctors taking part in the current POLE course spoke to *Cancer World* about the challenges they faced in becoming leaders.

Simon Malas felt the transition from medical oncologist at Limassol General Hospital in Cyprus to head of oncology was a jump into the unknown. "We complete our speciality without knowing anything about health economics, about communication, about how to manage other people or yourself. You have to learn on the job, which is very difficult. How do you know if you have got it totally wrong?

"From one day to another you become the boss. One day you were with your colleagues at the same level and the next you are head of the department. I also have my clinical work and if they do not accept you as a clinician then you have failed."

His biggest problem is getting new drugs into the system after the Cyprus health budget was cut by 10–15%. If I have a cancer patient who has to have this treatment and I cannot give it, that makes me feel very bad and frustrated." What he is learning gives him the confidence to tackle resource issues. "I feel more secure. It gives me the strength to talk a bit more about health economics."

Since her boss retired last year, Noemia Afonso has been running the medical oncology area of the breast cancer unit at the Portuguese Institute of Oncology in Porto, where 1,000 patients are admitted every year.

"It was very challenging. It was something I had never done before. I think we are not very used to working like a team: nurses, medical oncologists, surgeons. My efforts, together with my colleague responsible for the surgery area, are to make sure they all follow the same way of treating patients, and when there are

"Because of the limited resources today, we need to streamline our potential to do something more fair"

doubts, they come to a discussion and we have a unanimous decision."

Today, more cases are discussed at multidisciplinary meetings and nurses have a greater sense of involvement. "I find that if I give people more responsibilities, they cooperate more."

Being young means she has to win the support of colleagues, not rely on a hierarchy. "It's difficult to deal with people – to see if they are happy, they like to work here, they want to do something for this unit. Every group needs a leader. I'm not sure if I can be that leader yet, but I am trying to get all the information I can to make that decision."

Etienne Brain chairs the committee that evaluates clinical research at the Hôpital René Huguenin, part of the Institut Curie at Saint-Cloud, France. In October he takes over as president of the International Society of Geriatric Oncology (SIOG).

He believes it is no longer enough to be an excellent clinician. "Because of the limited resources today and the price of new drug development, we need to streamline our potential to do something more fair and right for the general population."

POLE is giving him the confidence to lead. "It is opening my eyes to a better way. If you don't incorporate health economic issues with the different sources of power which impact on how you deal with resources, I think you miss a point. The challenge is to bring input from different colleagues to work together to contribute to improvements in the care delivered to patients. I want to be an actor in this process."

He also values the chance to meet colleagues from across Europe. "I am half French and my mother was Ecuadorian. My wife is half Dutch and half English. I believe in sharing and cross-border collaboration!"

Surgeon Radoslaw Tarkowski from Wroclaw Medical University has a vision to build breast units in Poland. Having trained with the best in Italy and Germany, he is determined to improve the standard of surgery practised on women in his country.

"There are general surgeons who perform mutilating surgery. There are surgical oncologists performing mutilating surgery or breast conserving treatment, but it doesn't look good. I'm ashamed I did it, but there came a time when I learnt new possibilities, so I do it another way now.

"My vision is to create a breast unit. I think I can learn a lot here, because I work in a multidisciplinary team where we treat patients with colorectal cancer or breast cancer."

Tarkowski threw himself into role play, as actor Amedeo Romeo demonstrated the art of persuasion. "What I saw showed me ways to communicate with people. I'm a doctor so I always want to learn. When I go back, I will understand better my colleagues and my boss. They are more experienced doctors than me, so I need the knowledge of how to talk to them."

Medical oncologist Margaret Hutka trained at the Maria Skłodowska-Curie Memorial Cancer Centre in Gliwice, Poland, and worked at the Royal Marsden, London, before becoming lead medical oncologist in gynaecology at the Champalimaud Cancer Centre in Lisbon. Hutka aims to develop a team and research environment that will allow this relatively new unit to become a centre of excellence for gynaecological cancers.

She wants to share the experience she gained at her previous centres and implement it in this new setting. "The need to become the leader is from wanting to create a solid clinical and research structure so that at the end of the day it becomes a part of a successful professional journey.

"What attracted me to POLE was the idea of really understanding how to develop one's skills and personality to become a leader; to be someone creative, inspiring and motivational at the same time, to effectively design a competitive unit."

Course director, Rosanna Tarricone, says that the POLE course is going brilliantly. "Oncologists are excited about learning concepts and paradigms that seem so far from their background but that – at the same time – are so close to what they are expected to do in their own hospitals. They also enjoy networking with each other and exchanging experiences from so many different countries."

Feedback places POLE amongst the highest ranked programmes at SDA Bocconi, which itself is one of the leading management schools in Europe. Tarricone puts this down in part to the partnership with joint organisers the European School of Oncology, with its knowledge of what oncologists want, and the fact that it receives an unrestricted grant from Novartis. Tarricone calls them "true partners". ■

Accreditation of breast centres: why and how

The European Commission is developing a Europe-wide accreditation scheme for breast centres to push up standards of diagnosis and care. Here experts from both sides of the Atlantic take a look at existing schemes, the criteria they use and the challenges in applying them across diverse populations.

Cary Kaufman: In the US we were prompted to change our approach to breast cancer care in response to a number of factors, including two reports from the Institute of Medicine (1999, 2013) demonstrating that many patients did not receive the care they should. We wanted to reduce the wide gap between the care that many breast cancer patients experienced and the ideal treatment they should be receiving. We also wanted to improve the value of healthcare by increasing the quality while possibly decreasing the cost, with these two factors going hand in hand.

A map of the US (see overleaf) shows the wide range in use of mastectomy in 2007, with some regions having a 50% higher than average use of mastectomy (shown in dark brown) while others had a 50% lower use than average (shown in light tan). Why was that? Some areas may have had appropriate rates, but we wanted to know whether mastectomy was being used too much or too little for individual patients. We wanted to be sure that it is being used

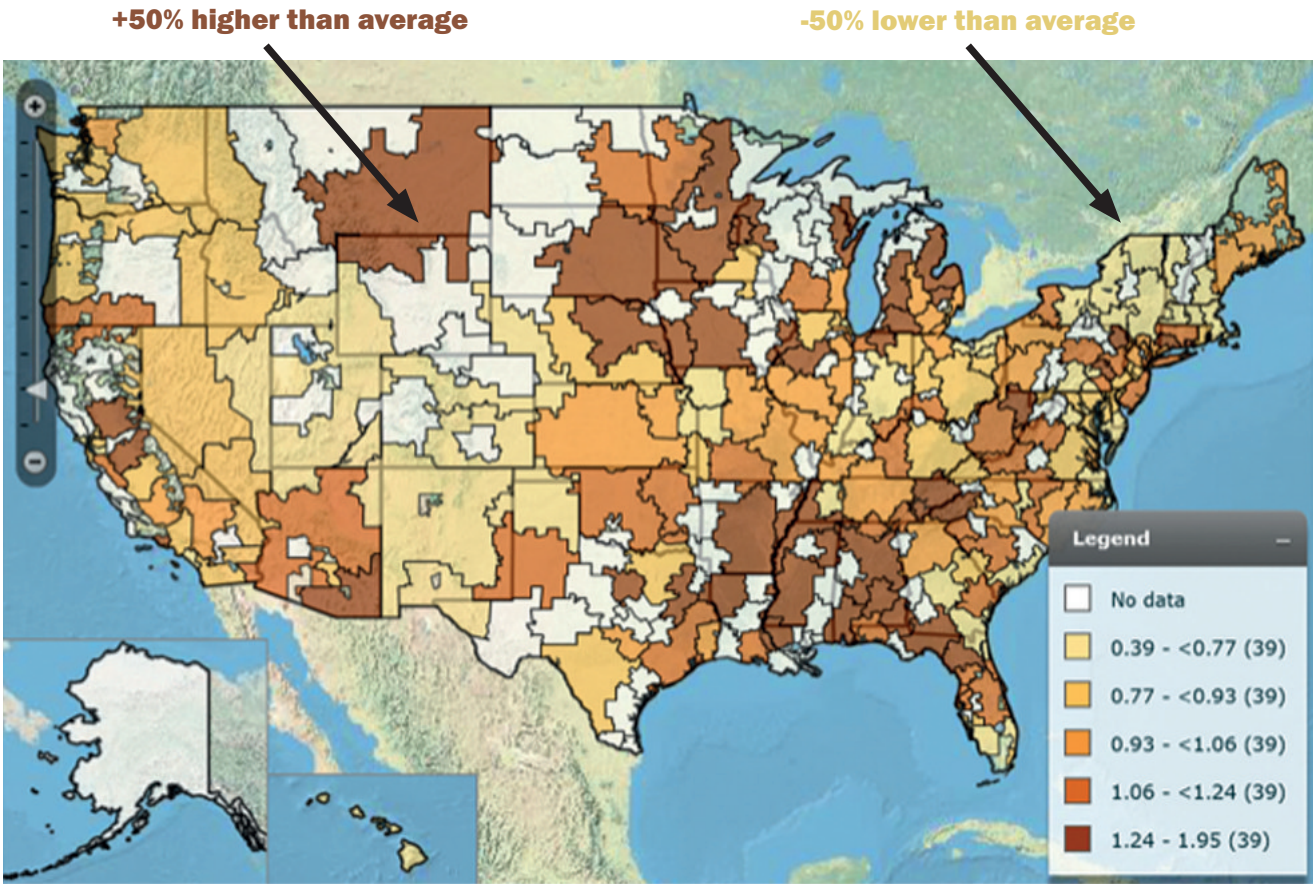
European School of Oncology e-grandround

ESO presents fortnightly 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, Cary Kaufman, chair of the US National Accreditation Program for Breast Centers, explains why an accreditation system for breast centers was introduced in the United States, and how it was done. Fatima Cardoso, EORTC secretary general and director of the breast unit at the Champalimaud Cancer Centre in Lisbon, Portugal, outlines the systems for breast centre accreditation in Europe and plans for the future. Edited by Susan Mayor.

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

RATES OF MASTECTOMY FOR BREAST CANCER (2007)



Major geographical variations in the rates of mastectomy for breast cancer across the USA prompted questions about how far these variations were appropriate and how far they reflected differences in the quality of care

Source: The Dartmouth Institute for Health Policy & Clinical Practice, www.dartmouthatlas.org/data/map.aspx?ind=95

appropriately. Maps for use of radiation therapy, systemic chemotherapy or breast reconstruction would show the same type of mosaic, and we need to be sure that the kind of care that people should get is what they actually do get.

The National Accreditation Program for Breast Centers (NAPBC) was set up in 2005 to address three main issues:

- gaps between the desired care and the actual care that women were receiving
- the need for adequate written guidelines to impose consistency of breast care
- the recognition that standards should be written by the clinicians and not by the payers or government.

We invited 21 organisations encompassing the range of professionals involved in breast cancer care, including the American College of Surgeons, the American Society of Clinical Oncology and the American Society for Radiation Oncology, to join with us to figure out what standards should be provided by a specialised breast unit or breast centre.

We divided into five committees, organised to identify key concepts that were passed on to other committees to develop further:

- Quality – to identify key quality breast cancer care concepts, such as recommending needle biopsy rather than surgical biopsy
- Standards – to develop and write

standards for quality concepts that are universally applicable across different breast cancer centres
- Education – to disseminate standards to providers
- Advocacy – to disseminate standards to patients and the public
- International – to disseminate and collaborate outside the US, to be sure that we are all asking the same questions and can learn from one another.

Accreditation process

It generally takes six to nine months for the accreditation process, from the time a centre first looks at this until they receive a survey. This is not because we're slow in sending out surveys, but because centres realise that they may not be providing the standards we are asking for. They may be providing high-quality care, but elements may be missing even at academic centres, for example the integration of care, communication between specialists, consideration of neoadjuvant chemotherapy for surgery, or holding a conference to discuss patients.

We start with an application process, where the centre applies, reads the requirements and then reviews the standards. They can upload documents to the survey application record (SAR), which is a computerised site where applicants can upload information. Once they have completed the data, the surveyor reviews the SAR. At that point we identify issues that need to be addressed and completed, so communication goes back and forth. Before any survey is carried out there is a lot of communication and upgrading of care to ensure that facilities comply with our standards.

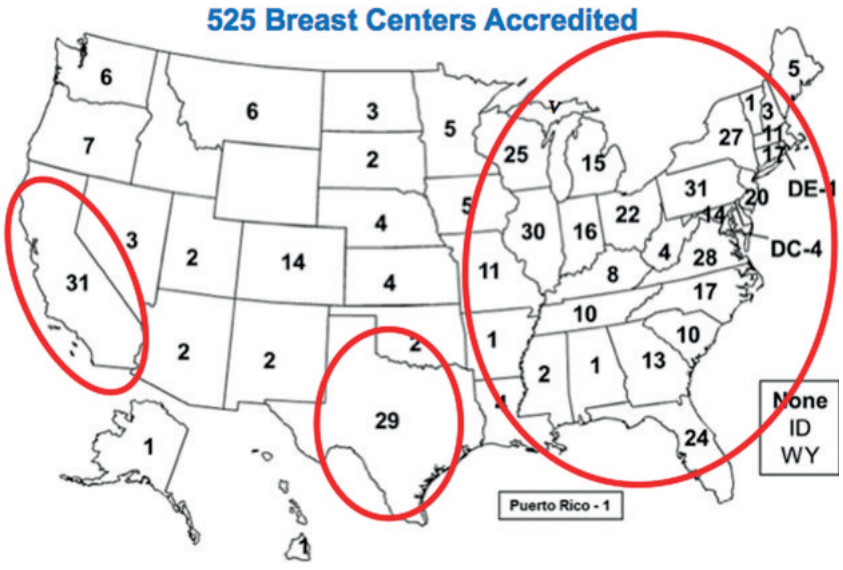
Finally, a single surveyor goes out to the centre, already aware of the kind of care they are providing. The surveyor spends a day meeting with clinicians, attending meetings and multidisciplinary conferences, and looking at information including reviewing charts and discussing findings for both cancer and benign disease, recognising that breast centres take care of both.

The surveyor then makes their report and presents it to the site, and reports back to the centre on their findings, including advice on where they can improve – this may include things that are not on our standards if they find areas where the centre can improve. If the centre passes at least 90% of our 27 standards (24 out of 27) they are deemed accredited or certified. However, they must comply with 100% of the standards within one year.

Our Breast Cancer Center Standards Manual provides information on our standards, which are updated every year (http://napbc-breast.org/standards/2013standardsmanual.pdf). The manual has six chapters:
- Breast centre leadership
- Clinical management, which addresses physicians and allied healthcare disciplines
- Research, which we consider important and we require a certain number of patients participating in research at each centre
- Community outreach, including ensuring provision of screening and diagnosis
- Professional education, to maintain skills
- Quality improvement, to ensure centres comply with our quality improvement items. They also need to have at least two quality improvement projects each year that are focused on their own needs.

The figure below shows the geographic distribution of accredited breast centres across the US, with 525 breast centres currently accredited. Our state, Washington, has six

GEOGRAPHIC DISTRIBUTION OF ACCREDITED BREAST CENTRES (2014)



Circles identify areas with greatest concentration of accredited centres © Cary Kaufman 2014

centres that are accredited, which could be higher. The circles show the population concentration, which is where most centres are found.

What are the standards?

The standards can be divided into two main areas: administrative leadership and comprehensive clinical breast care. The administrative leadership is responsible, and should be independent and really focused on the breast centre. It should ensure that treatment guidelines are available for clinicians and are being followed, and confirm that providers are being educated and that quality programmes are being performed. The leadership should make sure that data for each patient is collected in a database so that the quality of care can be reviewed, and that the centre is participating in research and maintaining outreach to the community.

A comprehensive approach to clinical breast care should ensure that the ideal care is the actual care provided. There are three main areas:

- Interdisciplinary breast conference (or multidisciplinary meeting), where all clinicians meet to discuss a patient, including presentation of their case, data, mammograms and pathology. The team discusses what is the best approach for that individual patient, including any potentially appropriate research studies, optimising their integration and collaboration across all disciplines, with input from the most junior nurse to the most senior doctor.
- Clinical breast care, providing multidisciplinary care by specialised breast physicians across the entire range of disciplines.
- Allied breast care, which is the allied healthcare by multiprofessional providers that really makes a breast centre. Even the very best surgeon or radiation oncologist needs the glue that puts things together, with oncology nursing, patient navigation, genetics, research co-ordination, social workers, psychotherapy, physical therapy and survivorship.

Accreditation schemes give recognition to breast centres that reach the required standards and signpost patients to services they can trust

Why do centres seek accreditation?

We asked 525 centres about their reasons for applying for voluntary accreditation and got 219 responses, with the main reason being to validate their high-quality breast cancer care (89%). Other reasons were executive leadership decisions, marketing and access to a national database, but the main reason is because centres want to improve their quality by complying with standards that are recognised by specialists.

Early on, medical university centres and National Cancer Institute (NCI) centres did not sign up, but it just took them longer. Today university centres account for 13% of all breast centres, and 28% of NCI-designated cancer centres are now NAPBC accredited.

Lastly, it is worth commenting on

the difficulty in setting these standards and how we go about it. We have a standard that says the breast conservation rate should be at least 50%. On average in our centres the breast conservation rate is 66%, but some centres are below 50%, because women want a mastectomy and they have access to high-quality reconstructive procedures. On the other hand, some areas, such as Massachusetts, have a very low mastectomy rate, so I think when we set quality targets we have to adjust to the realities of location.

The European perspective

Fatima Cardoso: One of the challenges in Europe is that we have many different countries with different healthcare systems, regulatory systems and reimbursement systems. This leads to different access to care and access to different types of care, which impacts on the quality of care. This non-uniform situation is an extra hurdle for establishing a European accreditation or certification system. Some countries are more advanced than others, and have already developed their own national accreditation systems – Germany and Switzerland for example. However, they have different criteria, so when we try to do something at a European level we need to take existing national systems into account.

The European Society of Breast Cancer Specialists (EUSOMA) is leading their programme in Europe, and has developed a voluntary, uniform accreditation system that can be applied in any European country. However, it does not take into account the different realities in different countries. Mastectomy with immediate reconstruction is sometimes a

EUSOMA MANDATORY QUALITY INDICATORS FOR BREAST UNIT CERTIFICATION

	INDICATOR	MANDATORY	MINIMUM STANDARD	TARGET
1	Preoperative diagnosis (proportion of B5/C5 in cancers)	M	80%	90%
2	Proportion of invasive cancer cases with primary surgery, for which the following prognostic/predictive parameters have been recorded: histological type; grading; ER & PR; pathological stage (T and N); size in mm for the invasive component	M	90%	98%
3	Proportion of non-invasive cancer cases for which the following prognostic/predictive parameters have been recorded: dominant histologic pattern; grading	M	80%	98%
4	Proportion of patients with invasive cancer and axillary clearance performed with at least 10 lymph nodes examined	M	85%	98%
5	Proportion of patients (invasive cancer M0) who received postoperative radiotherapy after surgical resection of the primary tumour and appropriate axillary staging/surgery in the framework of BCT	M	90%	95%
6	Proportion of patients with invasive breast cancer not greater than 3 cm (total size, including DCIS component) who underwent BCT	M	70%	80%
7	Proportion of patients with non-invasive breast cancer not greater than 2 cm who underwent BCT	M	70%	80%
8	Proportion of patients with DCIS who did not undergo axillary clearance	M	93%	98%
9	Proportion of patients with endocrine-sensitive invasive carcinoma who received hormonotherapy, out of the total number of patients with this diagnosis	M	80%	90%
10	Proportion of patients with ER/PR-negative invasive tumours ≥2cm and/or node+ disease, who received adjuvant chemotherapy	M	80%	90%

B5/C5 – preoperative definitive diagnosis; BCT – breast conserving therapy; DCIS – ductal carcinoma in situ *Source*: www.eusoma.org

Realities differ across countries, but there are quality criteria that are essential wherever the centre is located

better option than breast conserving surgery, where oncoplastic surgery is available. However, high rates of mastectomy without oncoplastic surgery usually indicates inappropriate treatment. The availability of radiotherapy equipment is also important. However, there are quality criteria that are essential no matter where a breast centre is located. The system is voluntary, as in the USA, and there are pros and cons for making it mandatory. The European Commission is starting to develop a guidelines and accreditation project to be carried out at the European level, which could be a good way to go.

The EUSOMA accreditation system was launched in 2002 and updated in 2007 (*EJC* 2007; 43:660–675). Certification is provided by an independent body, through the European Cancer Care Certification, and not by EUSOMA.

The most important criteria for a breast unit or centre are:

- A single integrated unit – as mentioned by Cary Kaufman, it is very important to have the different specialties available, working in a multidisciplinary and integrated way
- A sufficient number of cases, to provide experience and continuing expertise
- Care by breast specialists in all of the required disciplines
- Provision of all the necessary services, from genetics to prevention to treatment of primary breast cancer and advanced breast cancer, and also links to palliative care
- Patient support
- Data collection and audit.

The latest update of the EUSOMA requirements for a specialist breast centre (*EJC* 2013, 49: 3579–87) still emphasises being an integrated breast centre or unit, with multidisciplinary and specialised care provided in an integrated way. In terms of numbers, the consensus is that a centre should see at least 150 newly diagnosed cases of primary breast cancer (all ages and stages) each year, covering a population of about 250,000 inhabitants. A breast surgeon must perform at least 50 breast surgeries, so a larger centre with more than three surgeons will need to see a higher volume than 150 newly diagnosed patients each year to provide each specialist with an adequate number. Centres must provide services throughout the patient pathway and also ensure data collection and audit.

There is growing discussion about providing continuity of care for patients with advanced or metastatic breast cancer, and also what competences are needed to provide a multidisciplinary approach for these patients. European accreditation systems are focused on primary breast cancer, but we also need to develop good quality indicators for advanced and metastatic breast cancer.

The services provided do not necessarily all have to be centralised in one breast centre. For example, if you have two breast centres in the same area, you might decide that you need only one radiation oncology department, and some centres may decide to outsource some other service(s). However, all decisions must be made by the multidisciplinary team of the centre where the patient is being treated.

What's the definition of the multidisciplinary team? The new EUSOMA recommendations describe a 'core team' that includes a radiologist, radiographer, surgeon, reconstructive surgeon, pathologist, medical oncologist, radiation oncologist, breast care nurse and data manager, with specific requirements about the percentage of time each dedicates to breast care. The 'non-core' team are other specialists who are also important, but not necessarily part of the 'core' team, including: nuclear medicine specialists, gynaecologists, psycho-oncologists and clinical geneticists. In my breast unit, both the psycho-oncologist and nuclear medicine specialist are part of the 'core team', but this differs from centre to centre.

Quality indicators

There are 10 mandatory quality indicators for breast unit certification, each with a minimum standard and also an ideal standard (see table, page 47). So taking as an example: 'What is the optimal percentage of breast conserving therapy?', EUSOMA recommends a minimum of 70%, although the target is 80%. Of course, this depends on the location, the country, and the availability of reconstructive surgery and radiation oncologists. But in breast centres that have all of these specialties, the target is 70–80% for breast conserving surgery.

Breast Centres Network

We go to all the effort of being accredited and ensuring quality care is established and appropriately implemented in centres, but how can we give this information to the public and the patients?

I was recently discussing this with European advocacy groups and they made the point that this information needs to reach people before they develop cancer, because when patients first receive a diagnosis they feel lost and it is not the best time to select a breast centre to go for treatment.

The European School of Oncology has developed the Breast Centres Network, which is the first international network of clinical centres for breast cancer. Every breast centre in Europe can enter their information in a standardised way, and indicate whether they are EUSOMA accredited or have other accreditation. The voluntary network website is user friendly and can be accessed by anyone, so a patient or member of the public can search for information on breast centres and their level of accreditation in their own country.

The European Commission and the European Parliament have also been working on this issue.

Focused on progress. The Breast Centres Network aims to encourage breast centres to work together to standardise care in line with international guidelines, and to promote continuous improvement through fostering training and developing and validating new guidelines. Patients can use the directory to locate breast units, and find out which have been accredited and exactly what services they offer

In 2003 the European Parliament noted that all breast cancer patients should be treated in a specialised breast unit, and recognised the need for a multidisciplinary approach. More recently, it has approved a resolution that by 2016 member states should have enshrined in law that all breast cancer patients are treated in a specialised breast centre or unit. Unfortunately, this is not yet in place in the majority of European countries, so this provision must be fought for at the level of individual countries.

Alongside this resolution, the European Commission has started a guidelines and accreditation project, aiming to incorporate the best breast cancer guidelines available in Europe, develop quality indicators and then establish an accreditation system that will be common to all European countries. This will still be a voluntary accreditation system, which has pros and cons, but it will cover all cancer services from prevention, screening and early detection to palliative care, so will be a very important effort. I hope that in two years' time we will have another e-grand-round discussion about how the project has been implemented in all European countries. ■

The EU is establishing an accreditation system that will cover all cancer services, from prevention to palliative care

impactfactor

nature REVIEWS CLINICAL ONCOLOGY

Dropping bars or rising hoops – phase III outcomes of NSCLC

HERBERT H LOONG AND TONY S K MOK

Over the past three decades, the interpretation of clinical trial outcomes in studies of advanced-stage non-small-cell lung cancer has changed. The robustness of findings from these trials has been called into question. We believe this change is a reflection of the improved understanding of molecular-based therapeutics and continued advances in this field.

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Advanced-stage non-small-cell lung cancer (NSCLC) is the leading cause of cancer-related death in the world.[1,2] As such, effective systemic treatment for patients with NSCLC has been a subject of intense investigation over the past decades with the hope to improve survival. Sacher and colleagues recently published a retrospective analysis of the changes in study design and interpretation of randomised phase III trials in patients with advanced-stage NSCLC over time, particularly noting the changes in the primary endpoint of such trials, study outcomes, statistical significance and conclusions.[3] For the purpose of comparison and analysis, trials were arbitrarily divided into three categories, based on the decade of publication: 1980–1990, 1991–2000, and 2001–2010. In their analysis of over 200 trials, the authors commented that overall survival remained the most common primary endpoint in all trials, although more trials from the past decade have used progression-free survival (PFS) instead of overall survival as the primary endpoint (0% in 1980–1990; 13% in 2001–2010, P=0.002).[3] The interpretation of trials has also changed. The percentage of trials reporting a positive outcome that did not meet their primary endpoints has increased from 30% in 1980–1990 to 53% in 2001–2010 (P<0.001). Trials were reported as "positive" based on improvements seen in secondary endpoints, such as PFS and adverse effects. More importantly, the trials from the past decade have also been seen to assert non-inferiority despite a lack of a statistically appropriate non-inferiority design or had recommended further study on the basis of a nonsignificant trend in primary outcome. A trend toward decreasing magnitude of survival gain in trials reporting a statistically significant survival improvement was seen over time (3.9 months in 1980–1990, 2.5 months in 2001–2010, P=0.11). There has also been an increase in sample size of clinical trials over time, indicating that 'statistical significance' was only achieved owing to the accrual of a larger number of patients, but leading to a lower magnitude of survival gain per patient. Specifically, when all trials deemed positive were considered, the decreasing magnitude of improvement in survival was even more apparent, with median net survival of 3.9 months in 1980–1990 compared with only 0.9 months from trials from the period 2001–2010.

The authors of this study conclude by warning that "the bar is dropping" with a significant shift in the past three decades in the design and interpretation of randomised phase III trials in patients with

advanced-stage NSCLC. This shift is evidenced by the declining use of overall survival as the primary measure of benefit, and the magnitude of benefit itself.

While we appreciate their efforts and agree that the trend of randomised phase III trials in patients with advanced-stage NSCLC have changed considerably over the past three decades, we are hesitant to concur with the belief that this has a negative impact on drug development for NSCLC as a whole, and we disagree with the authors' conclusion that the bar is dropping. There is an overriding concern about the design of the analysis of Sacher and colleagues.[3] Specifically, there is no mention of the rationale of why clinical trials were arbitrarily 'pigeon-holed' into the three categories based on their decades of publication. To the best of our knowledge, there is no justification to use these specific time points as cut-offs, apart from 'rounding off' these numbers for analysis purely for convenience. There is no reason to believe that the nature of a trial and the attitude of the authors may switch according to the decade. Categorising trials on the basis of their publication dates inherently introduces bias into the subsequent data analysis and conclusions.

"We disagree with the authors' conclusion that the bar is dropping"

Notably, specific landmark advances in science would change clinical trial design. There have been significant changes in the systemic management of patients with advanced-stage NSCLC over the past three decades. The key milestones of these changes are the discovery in 2004 of driver oncogenes such as EGFR and in 2007 the identification of the translocation mutation of anaplastic lymphoma kinase (ALK).[4,5] With a better understanding of molecular subtypes of NSCLC, specific tyrosine kinase inhibitors, such as gefitinib, were shown to be superior to standard platinum-based cytotoxic chemotherapy, whereas treatment outcomes were the opposite in patients without EGFR mutation.[6] Since then, patient selection according to the tumour molecular profile has become a crucial component of many monumental phase III trials in patients with advanced-stage NSCLC. We believe that if an analysis of patterns and interpretation of NSCLC trials is to be done fairly, these particular milestones should be taken into account and grouping of trials should be based on the disease biology.

As we move towards a new era of molecular targeted therapy trials according to the genetic profile of each patient, it is only natural to adopt PFS as the primary study endpoint. Improvement in overall survival might not be reflected in these clinical trials given that it would be unethical not to offer the experimental drug to patients (with the driver oncogene) in the control arm upon a clear PFS advantage. For example, Kwak and colleagues have established in a phase I study that patients with an ALK mutation attained high tumour response rates (overall response rate 57%, stable disease 33%) and prolonged PFS (probability of 6-month PFS is 72%) with crizotinib.[7] Thus, in the randomised phase III study comparing crizotinib with single-agent chemotherapy, Shaw et al.[8] intentionally (and ethically) allowed all patients to receive crizotinib upon disease progression following chemotherapy. This study has successfully demonstrated prolongation of PFS, which proves the true efficacy of crizotinib, whereas the lack of overall survival benefit is merely a reflection of the crossover-effect.

The proposal that the "bar is dropping" could be correct if lung cancer remained a homogenous disease. Clinical trials that used overall survival as the primary endpoint might have made a small impact on survival in the past. However, the one-size-fits-all approach of large phase III trials comprising of a 'basket' of NSCLC patients with diverse molecular subtypes is unlikely to provide further improvement in clinical outcomes. As we understand more about the heterogeneity of NSCLC and its reliance on different driver oncogenes for propagation, we believe the pendulum will swing towards smaller and molecular-based trials.

We, therefore, believe that the bar is not dropping; rather, the opposite effect is true. The design and interpretation of clinical trials for NSCLC will likely become more stringent and complex given the smaller numbers of patients available as we break NSCLC down into numerous molecular subtypes. Further advances in the science of this disease will likely produce more bars and possibly even hoops, which we will need to overcome. ■

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References for this article can be found at www.cancerworld.org

The letter to which I couldn't reply

SEAMUS O'REILLY

With all the investigations, imaging and testing involved in personalising treatments, it can be hard to remember to listen to what the patient is saying. One doctor keeps a letter with him as a permanent reminder.

The letter arrived on Tuesday. Although it had been written by the patient four months earlier, it arrived simultaneously with a letter from the hospice outlining the sender's death the week before. The hospice letter summarised an illness with cancer that had started four years earlier. Initially starting with the crisis of diagnosis, it tracked the subsequent optimistic hope of cure, the hardships of adjuvant chemotherapy, the adjustment of survivorship, followed by the onset of chest discomfort two years later, and with it the devastation of relapse and the shattering realisation of impending mortality that would leave a grieving widower and children without a mother.

On that Tuesday, the two letters lay coincidentally on top of one another. Written months before, the patient's letter was designed to be posted after the writer's death. Although shorter than the hospice letter, it was equally comprehensive, charting a four-year therapeutic relationship, expressing gratitude for care received, apologising for searching but appropriate questioning, acknowledging the behind-the-scenes work that orchestrates treatment, emphasising

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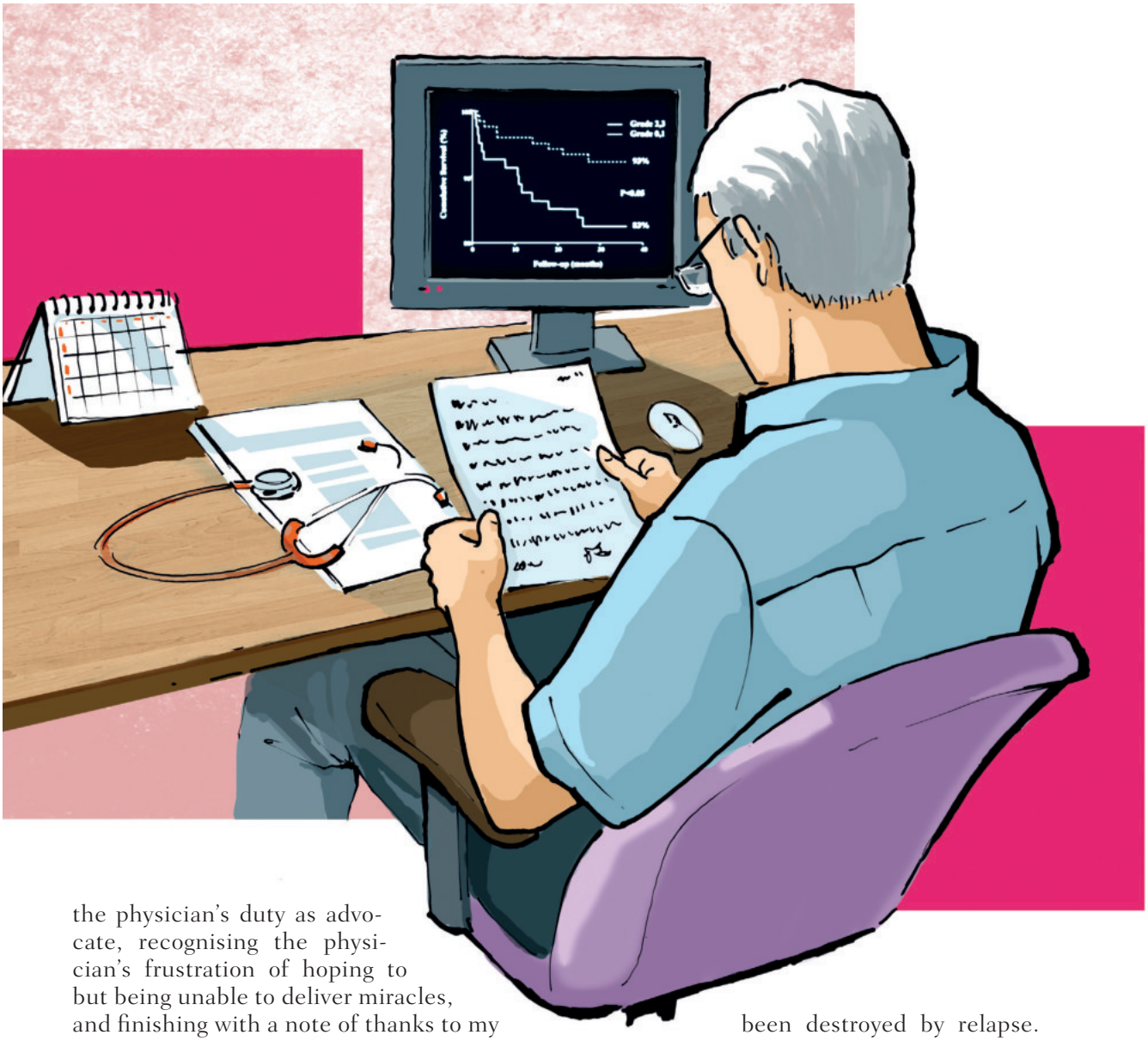

ILLUSTRATION: FRED VAN DEELEN, WWW.ORGANISART.CO.UK

the physician's duty as advocate, recognising the physician's frustration of hoping to but being unable to deliver miracles, and finishing with a note of thanks to my family for time spent with her that could have been spent with them. Other letters had been written for her children.

The letter haunted my thoughts for days. In more than two decades as a medical oncologist, I had never received a letter from a patient following his/her death. The preceding months had seen the deaths of several patients who had become friends and friends who had become patients. For all of them, the initial promise of cure had been destroyed by relapse.

All had led their lives with cancer to the full. As their doctor, I found them to be inspiring, remarkable people, but their deaths were marked for me by both bitter disappointment that their lives were cut short and soul searching regarding their care. Could different therapy after initial, potentially curative cancer surgery have prevented relapse? Could better treatment selection have increased their chance of living with cancer?

Had I used what she and others had said to me to advocate for them? Was I more focused on her diagnostic imaging?

Gandhi said, "You must become the change you wish to see in the world." As a medical student fascinated by the biology of cancer and recognising that the needs of patients with cancer were unaddressed, I decided to become a medical oncologist. Now, three decades later, I find myself struggling mentally in a career that I love. The science that fascinated me has led to transformative treatment advances, and, whereas my predecessors had therapeutic relationships of what were often only several months, these are now thankfully measured in years for my contemporaries and me. These welcome advances in treatments and technology have produced their own challenges, paradoxically increasing workload, dehumanising medicine, and diminishing time for listening by prioritising tests, investigations, images, and documentation, drowning the patient's voice as a consequence.

Two days after I received the letter, I met a patient who was living with metastatic breast cancer. She asked me what she would say to God when she dies. I couldn't answer, so she did, saying that she would tell him to "f*** off," because she was living in hell here so she might as well live in hell in the afterlife also. Her thoughts reflected trauma that I was poorly equipped to deal with other than to make time to listen, to explore symptoms I could treat, and to identify symptoms for which I could solicit the help of others.

What she hadn't asked, but perhaps should have, was what I would say to God when I die. Had I cared well for her? Had I worked to my satisfaction rather than hers? Was I kind? Had I used what she and others had said to me to advocate for them? Was I more focused on her diagnostic imaging than on her? Had I been the doctor she needed rather than the doctor she ended up with? Had I taught future doctors the science of medicine, rather than how to provide the care that she needed?

My mentors taught me that, for patients with advanced cancer, the quality of their journey is more important than its length. These patients have taught me that scientific advances will only achieve their full potential if they are used to facilitate rather than replace benevolent care. The physician William Osler said, "Listen to the patient and they will tell you the diagnosis." My interactions with patients have led me to believe that the greatest source of education in medicine is the patients we treat. We would do well to add to Osler's words, "And they will be your greatest teachers."

The patient's letter remains unanswered. Any inadequate reply that I could compose will never be read. It can't be.

I have placed the letter in a compartment in my briefcase in which I keep treasured letters from my children. It will remain there until I retire as a daily reminder of my professional responsibility and of a privileged therapeutic relationship. ■

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newsround

Selected reports edited by Janet Fricker

New treatment option for premenopausal women with hormone-sensitive breast cancer

New England Journal of Medicine

In premenopausal women with hormone-receptor-positive early breast cancer the aromatase inhibitor exemestane plus ovarian suppression is more effective at preventing recurrence than tamoxifen plus ovarian suppression, a combined analysis of the TEXT and SOFT trials has found. The studies, which were led by the International Breast Cancer Study Group (IBCSG), in partnership with the Breast International Group (BIG) and the North American Breast Cancer Group (NABCG), were presented at the 2014 ASCO annual meeting.

Treatment with an aromatase inhibitor, such as exemestane, has previously been demonstrated to benefit postmenopausal breast cancer patients more than treatment with tamoxifen.

The phase III TEXT (Tamoxifen and Exemestane Trial) and SOFT (Suppression of Ovarian Function Trial) were both conducted to determine whether such benefit could be extended to premenopausal women by combining exemestane with ovarian function suppression. Between November 2003 and April 2011 the TEXT trial enrolled 2,672 premenopausal women and the SOFT trial enrolled 3,066 premenopausal women, from a combined total of more than 500 medical institutions in 27 countries. The women were randomly assigned to five years of adjuvant treatment with exemestane plus ovarian suppression or tamoxifen plus ovarian suppression. SOFT also included a third arm assigned to tamoxifen alone, which will be analysed in late 2014. Suppression of ovarian oestrogen production was achieved with use of triptorelin – a gonadotropin-releasing-hormone agonist – oophorectomy, or ovarian irradiation. The women could also receive chemotherapy as part of their adjuvant treatment.

Results show that after a median follow-up of 68 months, disease-free survival at five years was 91.1% in the exemestane–ovarian suppression group versus 87.3% in the tamoxifen–ovarian suppression group (HR for disease recurrence, second invasive cancer, or death =0.72, 95%CI 0.60–0.85; $P<0.001$).

Furthermore, the rate of freedom from breast cancer at five years was 92.8% in the exemestane–ovarian suppression group, versus 88.8% in the tamoxifen–ovarian suppression group (HR for recurrence =0.66; 95%CI 0.55–0.80, $P<0.001$). Overall survival did not differ significantly between the two groups (HR=1.14, 95%CI 0.86–1.51; $P=0.37$).

Grade 3 or 4 adverse events were reported for 30.6% of patients in the exemestane–ovarian suppression group versus 29.4% in the tamoxifen–ovarian suppression group, with hot flushes, musculoskeletal symptoms and hypertension being the most frequently reported symptoms.

"We conclude that for premenopausal women with hormone-receptor-positive breast cancer, adjuvant treatment with ovarian suppression plus the aromatase inhibitor exemestane, as compared with ovarian suppression plus tamoxifen, provides a new treatment option that reduces the risk of recurrence. Premenopausal women who receive ovarian suppression may now benefit from an aromatase inhibitor, a class of drugs that until now has been recommended only for postmenopausal women," write the authors.

■ O Pagani, M Regan, B Walley et al. Adjuvant exemestane with ovarian suppression in premenopausal breast cancer. *NEJM*, published online 1 June 2014 doi:10.1056/NEJMoa1404037

Exercise could enhance drug delivery

JNCI

Exercise enhances tumour perfusion and diminishes tumour hypoxia, a rat model of prostate cancer has found. The US investigators believe their study suggests that encouraging patients to exercise could enhance the delivery of tumour-targeting drugs.

Despite recommendation of exercise for cancer patients, the effects of exercise on tumour blood flow and oxygenation have been unknown. Previous studies have hypothesised that tumour blood flow may be elevated or reduced during exercise, which could exert an impact on tumour microenvironments.

In the current study, Bradley Behnke and colleagues, from the University of Florida, Gainesville, randomised 66 male rats aged four to six months to have rat prostate carcinoma cell lines (Dunning R3327-MatLyLu) injected into their ventral prostate (n=42) or saline (n=14). Both injections took place during a surgical procedure. The saline control arm was intended to explore whether results were due to the cancer state or the surgical procedure.

After surgical recovery (>4 hours), the rats were placed on treadmills, and blood flow in the conscious condition was measured at rest and five minutes after the onset of exercise. The vasoconstrictor responsiveness of resistance arterioles was also investigated *in vitro* after the animals had been sacrificed, using the isolated microvessel technique.

Results show that exercise resulted in an approximately 200% increase in prostate tumour blood flow, which led to an increase in O_2 delivery from a resting value of 3.0 ml O_2/min/100 g to 9.3 ml O_2/min/100 g during exercise.

During exercise, the average number of patent (i.e. open) vessels per field in the tumour was 14.3±0.6, which represents an increase from the resting number of 12.7±1.3 (Student t-test two-sided P=0.02).

Vascular resistance within the prostate tumour was statistically significantly greater at rest when compared with the prostate tissue of control rats. During the rest–exercise transition, prostate tumour vascular resistance decreased approximately 65%; whereas resistance increased slightly in the prostate of the control group.

In arterioles taken from rats that had been injected with tumour cells, the maximal constriction elicited by norepinephrine was blunted by approximately 95% versus rats with healthy prostate arterioles (the control group injected with saline) (P<0.001).

"Overall, these data demonstrate that exercise augments tumor oxygenation, which, considering hypoxia is associated with a more aggressive phenotype, provides a potential mechanism for the reduced rate of metastasis and tumor growth observed in most studies with chronic exercise and the beneficial effects of exercise after diagnosis of prostate cancer," conclude the authors, adding that it is unknown whether the same response is observed in other solid tumours or at different intensities of exercise.

In an accompanying commentary, Lee Jones, from Memorial Sloan-Kettering Cancer Center, and Mark Dewhirst, from Duke Cancer Institute, write, "Mechanistically driven preclinical investigations in conjunction with biomarker-driven clinical studies will be required to unravel the complex and dynamic relationship between exercise, the host–tumor interaction, and response to therapy."

■ D McCullough, J Stabley, D Siemann et al. Modulation of blood flow, hypoxia, and vascular function in orthotopic prostate tumors during exercise. *JNCI* 4 April 2014, 106:dju036

■ L Jones, M Dewhirst et al. Therapeutic properties of aerobic training after a cancer diagnosis: more than a one-trick pony? *ibid* dju042

Robotic-assisted lobectomy results in more complications and higher costs

Chest

Robotic-assisted lobectomy is associated with higher rates of intraoperative injury and bleeding than thoracoscopic lobectomy and is significantly more expensive, finds a population-based US analysis.

The perceived benefits associated with robotic-assisted surgery include less postoperative pain, fewer complications and quicker recovery times. Furthermore, in contrast to current minimally invasive methods, it is considered easier to train surgeons using robotic techniques. However, studies in hysterectomy patients have shown that robotic-assisted procedures (for both benign and malignant conditions) are no better than their laparoscopic counterparts.

For the current study, Subroto Paul and colleagues, from New York Presbyterian Hospital–Weill Cornell Medical College, identified 2,498 robotic-assisted procedures and 37,595 thoracoscopic lobectomies, performed between 2008 and 2011. The procedures were identified from the Nationwide Inpatient Sample (NIS), which contains information on 20% of all hospital discharges from non-government institutions in the US. Codes identified which patients underwent which procedures.

Results showed that the number of lobectomies performed by thoracotomy during the period declined from 74.6% of all lobectomies in 2008 to 59.4% of all lobectomies in 2011.

The unadjusted rate of any complication was 50.1% for robotic-assisted lobectomy compared to 45.2% for thoracoscopic lobectomy (P<0.05). Cardiovascular complications occurred in 23.3% of robotic-assisted lobectomy patients versus 20% of thoracoscopic lobectomy patients (P<0.05) and iatrogenic (due to activities of surgeons) bleeding complications occurred in 5% of robotic-assisted patients versus 2% of other patients (P<0.05). After risk adjustment, only the rate of iatrogenic bleeding complications was found to be higher among those who underwent robotic-assisted lobectomy (adjusted OR=2.64, 95%CI 1.58–4.43).

Robotic-assisted lobectomies cost $22,582 compared to $17,874 for thoracoscopic procedures (P<0.05).

The study also showed that a greater proportion of robotic-assisted operations were performed in smaller- to medium-size hospitals, non-teaching hospitals and hospitals with moderate lobectomy volumes.

"Our population based analysis of a national database demonstrates that robotic-assisted lobectomy does not offer any substantial benefit over thoracoscopic lobectomy; and may increase operative risk," write the authors.

Robotic platforms, they add, provide no tactile feedback, and use of the high-

definition three-dimensional operative cameras comes at the cost of a lack of surgical perspective. "Both of these factors can also lead to increased chance of injury by robotic arms by inadvertent excess use of force or their movement out of the field of view. This off-screen damage is neither seen nor felt with the greatest risk from surgeons who are not completely familiar with the technology."

Recent introductions of robotic energy and stapling devices and dual consoles for two surgeons, they add, could in future decrease both the costs of robotic surgery and the potential for harm.

■ S Paul, J Jalbert, A Isaacs et al. Nationwide Inpatient Sample (NIS) analysis of robotic-assisted lobectomy. *Chest*, published online 8 May 2014, doi:10.1378/chest.13-3032

Changes in health-related quality of life predict outcome in lung cancer

British Journal of Cancer

Changes in health-related quality of life (HRQoL) scores from baseline during treatment provide significant prognostic factors for survival in patients with advanced non-small-cell lung cancer, a secondary analysis of an EORTC study has found.

Many studies and meta-analyses have demonstrated that a patient's baseline HRQoL can predict overall survival across different cancer types, independent of socio-demographic and other clinical prognostic factors. Few studies, however, have investigated whether change in HRQoL from baseline over time offers added predictive value.

In the current study Divine Ediebah, from the EORTC in Brussels, Belgium, investigated whether changes in HRQoL scores from baseline over time were associated with survival, independent of baseline HRQoL scores, in patients with advanced non-small-cell lung cancer. For the study, 391 patients with stage IIIB or stage IV disease enrolled in the EORTC 08975 study (comparing palliative chemotherapy regimens) had HRQoL assessed at baseline and after each chemotherapy cycle, using the Core 30 and lung cancer modules of the EORTC Quality of Life Questionnaire (EORTC QLQ-C30 and QLQ-LC13). The EORTC QLQ-C30 contains: five functioning scales (physical, role, emotional, cognitive and social), nine symptom scales (fatigue, pain, dyspnoea, appetite loss, sleep disturbance, constipation, diarrhoea, nausea and financial difficulties) and the global health status/QoL scale. The LC13 module contains eight scales assessing lung-cancer-associated symptoms: dyspnoea, pain, coughing, sore mouth, dysphagia, peripheral neuropathy, alopecia and haemoptysis.

The prognostic significance of HRQoL scores at baseline and their changes over time were assessed with Cox regression, after adjusting for clinical and socio-demographic variables. Three different change scores were calculated by subtracting the baseline score from the scores at the end of the first, second and third cycle of treatment.

Results showed that after controlling for covariates, every 10-point increase in baseline pain and dysphagia (difficulty in swallowing) was associated with 11% and 12% increased risk of death. Additionally, every 10-point improvement of physical function at baseline was associated with a 7% lower risk of death, and every 10-point increase in pain was associated with an 8% increased risk of death at cycle 1. Every 10-point increase in social function at cycle 2 was associated with a 9% lower risk of death.

"Our work suggests that the regular HRQoL assessments during the course of treatment could be an early signal of patient deterioration, and raises the hypothesis that interventions to improve pain, physical functioning, dysphagia and social function could have potential to improve survival outcomes," write the authors, adding that appropriate care procedures should be taken when there is an indication that the patient's HRQoL has deteriorated. The utility of this approach to patient management, they add, should be investigated in prospective studies in patients with non-small-cell lung cancer.

■ D Ediebah, C Coens, E Zikos et al. Does change in health-related quality of life score predict survival? Analysis of EORTC 08975 lung cancer trial. *Br J Cancer* 13 May 2014, 110:2427–33

Melatonin improves sleep in breast cancer survivors

Breast Cancer Research and Treatment

Among breast cancer survivors melatonin use was associated with improvements in subjective sleep quality without any significant adverse effects, a US study has reported.

Sleep disturbances are common among breast cancer survivors and can have a significant impact on quality of life. Melatonin has been widely evaluated as treatment for jet lag and insomnia, with more limited evidence suggesting a potential role for melatonin supplements in the treatment of depression. It has also been observed that melatonin levels decrease with age, particularly around menopause and may affect hot flushes.

In the current study, Wendy Chen and colleagues, from Brigham and Women's Hospital, set out to examine the effects of melatonin supplementation on sleep, mood and hot flushes in postmenopausal breast cancer survivors. Between March 2007 and March 2009, 95 postmenopausal women with a prior history of stage 0–III breast cancer, who had completed active cancer treatment (including hormonal therapy), were randomly assigned 1:1 to either 3 mg oral melatonin (n=48) or placebo (n=47) daily for four months. Women were instructed to take tablets nightly at 9 pm due to melatonin's possible sedating effects. Sleep, mood, and hot

flushes were assessed at baseline and four months using two self-administered questionnaires – the Pittsburgh Sleep Quality Index (PSQI) and the Center for Epidemiologic Studies-Depression (CES-D) questionnaire – as well as the North Central Cancer Treatment Group (NCCTG) hot flush diary, which records both the frequency and intensity of hot flushes over the past seven days.

Results showed that, at baseline, 52% of participants reported poor sleep in the month prior to enrolment. The mean change in PSQI score was –0.1 in the placebo group compared to –1.9 in the melatonin group ($P<0.001$) – with a higher PSQI score reflecting worse sleep quality. No statistically significant differences in change scores were noted, however, between the two treatment arms for any of the components of the assessed hot flush scores ($P=0.19$), or the average change in depression scores ($P=0.66$).

"In this double-blind randomized controlled trial, we have demonstrated the efficacy of melatonin in improving sleep among breast cancer survivors," conclude the authors, adding that it is possible that higher doses than 3 mg melatonin might prove even more effective.

That the investigators did not see any effects on depression or hot flushes might be explained by the fact that the study was not powered to detect these differences, and also that the subjects were not clinically depressed and only 44 subjects reported hot flushes at baseline.

Future studies, say the authors, should evaluate the efficacy of melatonin in helping sleep in patients undergoing active cancer treatment, and whether sleep improvements translate into improvements in fatigue, since this is the primary complaint of many breast cancer survivors.

■ W Chen, A Giobbie-Hurder, K Gantman et al. A randomized, placebo-controlled trial of melatonin on breast cancer survivors: impact on sleep, mood, and hot flashes. *Breast Cancer Res Treat* June 2014, 145:381–388

Adjuvant! Online inaccurate for older breast cancer patients

Lancet Oncology

Adjuvant! Online, a programme predicting 10-year outcomes for patients with breast cancer, does not accurately predict overall survival and recurrence in older people with early breast cancer, a study funded by the Dutch Cancer Foundation has concluded.

Optimum combinations of adjuvant endocrine therapy and chemotherapy in breast cancer now result in relative risk reductions of between 20% and 57% in 15-year mortality. In patients with a high absolute risk of recurrence, the potential benefit of adjuvant treatment is large. Such benefits, however, might be attenuated in the presence of increased comorbidities or old age, because of shorter life expectancy and competing causes of death. Adjuvant! Online is an online, open-access prediction program that predicts 10-year breast cancer recurrence, breast cancer mortality, mortality due to other causes, and expected benefits of specific adjuvant treatment options for individual patients. The model was developed using a large database derived from the Surveillance, Epidemiology, End-Results (SEER) registry, involving a population of 34,352 patients aged 35 to 69 years.

In the current study Gerrit-Jan Liefers, from Leiden University Medical Centre, and colleagues set out to investigate the discriminatory accuracy and calibration of Adjuvant! Online in a cohort of 2012 women aged 65 years or older diagnosed in the south west of the Netherlands between January 1997 and December 2004 with *in-situ* and invasive breast cancer. The women had a median age of 74.0 years.

For the study, investigators undertook two separate models, one in which comorbidity of all patients was defined as average for age (model 1), and another in which comorbidity was individualised and identified by an expert panel (model 2). The authors then entered this, together with patient and tumour characteristics, into the Adjuvant! Online program version 8.0 to calculate predicted 10-year overall survival and 10-year cumulative recurrence for every patient.

Results showed that 904 patients (45%) died during the follow-up and 326 (16%) had recurrence. Using model 1, Adjuvant! Online overestimated 10-year overall survival by 9.8% (95%CI 5.9%–13.7%, $P<0.0001$) and 10-year cumulative recurrence survival by 8.7% (95%CI 6.7%–10.7%, $P<0.0001$).

By contrast, using model 2, Adjuvant! Online underestimated 10-year overall survival by –17.1% (95%CI –21.0% to –13.2%, $P<0.0001$). However, when using model 2, Adjuvant! Online predicted cumulative recurrence accurately (–0.7%) in all patients (95%CI –2.7% to +1.3%, $P=0.48$).

"This study shows that Adjuvant! Online does not accurately predict survival and recurrence in older patients with breast cancer. We suggest that Adjuvant! Online's predictions for older patients should be interpreted with caution," write the authors. "Therefore, we propose that an improved prediction model specifically for older patients should be developed to individualise clinical decision making and improve outcomes in this heterogeneous and growing population."

In an accompanying commentary Etienne Brain, from the Institut Curie, Saint-Cloud, France, writes, "Aside from showing the inadequacy of Adjuvant! Online for the older population with breast cancer, this work also stresses the crucial need for better methods to assess individual risks and potential benefit brought by treatments in older people."

■ N de Glas, W van de Water, E Engelhardt et al. Validity of Adjuvant! Online program in older patients with breast cancer: a population-based study. *Lancet Oncol* June 2014, 15:722–729

■ E Brain. Breast cancer in older women: predicting adjuvant benefit. *ibid*, pp 672–674