Cancerworld

Education & knowledge through people & facts

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The challenge for St Gallen

Hans-Jörg Senn ■ GUEST EDITOR

In mid-March 2007, the breast cancer world will again converge on the beautiful Swiss town of St Gallen, for what will be the 10th Anniversary Conference on the Primary Therapy of Early Breast Cancer.

Over the past three decades, this gathering has grown to become one of Europe's largest cancer conferences, with 4000 delegates expected this year. It has achieved international status as the global forum for promoting the optimal curative treatment of early breast cancer, and the St Gallen consensus statement, voted on at the close of each conference, influences clinical practice across the world.

None of this was either intended or foreseen by the 79 delegates who first gathered in St Gallen in 1978. Pioneers of the first modern randomised trials on adjuvant chemotherapy in the US, Italy and Switzerland, they were simply looking to compare notes and draw conclusions that could be used to improve treatment protocols.

Yet this very practical and clinician-driven focus may be one reason why the St Gallen conference has grown to its present size and influence, while dozens of other breast cancer conferences have come and gone in the intervening years.

The most important reason, however, lies in the continuing authority and credibility of the consensus statement. It represents the considered views of a truly international and independent multiprofessional panel, composed of experienced experts in the field, selected by virtue of their respective scientific contributions in clinical breast cancer research in various important international and national trial groups. People trust it, and can be confident that it is not driven and supported by industry, politics or vested professional or social interests.

So what can we expect from this year's consensus statement? It will have to revisit, and hopefully confirm, the bold changes adopted in 2005, which stated that the hormone responsiveness of the patient's tumour should be the primary basis for selection of adjuvant treatment, rather than conventional risk factors such as tumour size, grading and nodal status.

This emphasis on tumour cell biology will certainly increase, as large quantities of data have accumulated since 2005 on adjuvant use of the monoclonal antibody trastuzumab and other targeted therapies.

Many questions remain about how to get the maximum clinical benefit from the drugs, and also how to use them most economically, as modern biological therapies are putting health budgets under serious stress. More critical and meaningful studies by independent breast cancer study groups are needed to analyse their true clinical usefulness in curative breast cancer treatment, without compromising their unquestionable potential and success. Topics and challenge enough even for St Gallen 2009!

Hans-Jörg Senn is the founder and chairman of the St Gallen International Oncology Conferences (www.oncoconferences.ch) and Scientific Director of the St Gallen Centre for Tumour Detection, Treatment and Prevention (ZeTuP)

Aron Goldhirsch: dogmatically anti-dogma

Marc Beishon

To find out what makes cancers tick and work out how best to treat them, oncology must continually reinvent itself, applying rigorous methodology to interpret the results of well-designed and accurately reported studies. So says Aron Goldhirsch, who has revelled in a career doing just that in breast cancer – possibly the most biologically complex cancer of all.

Controversy is one of the most devalued words in the oncologist's lexicon – or at least it can appear that way to outsiders looking at what seem like tiny differences in treatment variations. But for an insight into just how deep these controversies can actually lie, look no further than the St Gallen international expert consensus conferences and their influential breast cancer recommendations, and one of their equally influential organisers, Aron Goldhirsch.

The St Gallen conferences are now held every two years, with this year marking the 10th meeting at the main town in eastern Switzerland. Their focus is on the treatment of primary breast cancer and especially on adjuvant treatment, reporting and discussing some of the most pivotal topics in oncology, such as the trials of Herceptin (trastuzumab). The 4,500 delegates to the 2007 meeting not only have the chance to hear probably one of the best assemblies of top breast oncologists worldwide, but also to put them on the spot about a field which has moved very fast in the last few years and which generates enormous hype in the media.

In Goldhirsch, breast oncology has a professional with, according to close colleagues, a fierce ability to cut through such hype. In a career stretching back over 30 years in medical oncology, and breast in particular, he has gained a reputation for a constant search for new biological knowledge to apply to clinical practice and research – but balanced by a forensic ability and an encyclopaedic knowledge of the literature to rapidly knock down any results that are not reported with due rigour – as is all too frequently the case, in his view.

He is concerned about issues such as rushing into practice without adequate follow-up data, misleading presentation of results of the trade-off between benefit and harm in new treatments, and especially the pharmaceutical industry's involvement in controlling trials. "Tailoring therapies to prevent metastases in a million women a year around the world is big business – the way that results of trials are reported can change the entire interpretation," he says.

Such is the degree of tension between academia and industry that Goldhirsch and colleagues are this year aiming to elevate the issue to wider debate

ELIGIO PAONI / CONTRASTO

beyond oncology circles by submitting a paper to *Nature* on the importance of maintaining academic independence in conducting clinical trails. "We want to start a political discussion. By taking a major field such as adjuvant therapy in breast cancer we want to help people understand the methodology behind our research, and we hope then researchers in other diseases will follow our lead."

The research Goldhirsch refers to includes the large-scale adjuvant breast cancer work organised by groups such as the International Breast Cancer Study Group and the overarching organisation, the Breast International Group (BIG), both of which he has played a major role in since their inception.

International work occupies a large amount of his time outside of his two primary employed positions – he has the unusual arrangement of a two-day-week post at the Oncology Institute of Southern Switzerland, as head of medical oncology, and three days a week across the border in Italy at the European Institute of Oncology in Milan, where he is director responsible for the medical area, including care and research in medical oncology, haemato-oncology, new drugs, supportive care and palliation.

"The principle of academic freedom is especially important to our adjuvant research, as it is all about giving treatment to women who are free of disease so you cannot check for efficacy and benefit," says Goldhirsch. "But it is like insurance. Someone will always sell you insurance for any calamity in the world. But what is reasonable in breast cancer concerns the characteristics and risk of the disease and targeting only what is important – and leaving aside what is not important."

It is a point that goes to heart of his concern for the development of oncology as whole – it is often easier to give more treatment than is necessary based on what works on average rather than thinking more deeply about the characteristics of the individual patient – and this is precisely where Goldhirsch intends the St Gallen conferences to make an impact.

Goldhirsch's parents were among the few from his family to escape the Holocaust – he was born in a Jewish refugee hospital in Germany in 1946. Two years later, his family moved to Israel, where he lived until the age of 21. He wanted to become a veterinary surgeon,

"Tailoring therapies to prevent metastases in a million women a year around the world is big business"

inspired by an uncle who was in this field, but he ended up turning to human medicine, finishing his initial training at medical school in Milan. His interests at this stage lay in infectious diseases, and indeed he planned to become a gastroenterologist.

"I applied for a Green Card to go and work in America, and while waiting I went to Switzerland – and never left after all." He had met oncologist Franco Cavalli, who had designs on establishing a centre of excellence in southern Switzerland, and persuaded Goldhirsch to make the switch to cancer. "At first I wasn't interested at all," says Goldhirsch. Nevertheless, he first joined Cavalli as the only other cancer physician in Bellinzona, but did his main formative years in internal medicine and medical oncology in a 10-year spell in Berne from 1978 to 1988, before returning to help build what was to become the Oncology Institute of Southern Switzerland, one of Europe's pioneering multidisciplinary centres.

"The features of medical oncology that attracted me were the methodology and the lack of dogma – the fact that whatever we have developed for the patient today will almost certainly be obsolete in the future. It is true that there was a lot of dogma around in the 1980s – and there still is in some places – in that the ideas of how to kill cancer cells were far away from the reality of their biology. It has taken many years and a lot of effort by those not immersed in dogma to convince others that new methods must be found."

His interest in breast oncology arose once he saw that cancer was a wide set of diseases and it was clear that breast offered the highest volume and widest spectrum of disease in itself. "There is such a large spectrum of biological features – why do a 20-year-old and an 80-year-old die within a year, and a 25-year-old live for 35 years with the disease? And there is a huge human dimension in terms of women's personal lives. All the features of the disease, the treatments and the patients, and their interaction, means that each factor needs a lot of attention – and for an oncologist there must be a synthesis somewhere that you can summarise for the patient. I was fascinated by the complexity."

In Berne, Goldhirsch soon found himself involved as a young clinician with what was to become the International Breast Cancer Study Group (IBCSG – it was a breakaway group set up by Jan Stjernsward of the Lausanne branch of the Ludwig Institute for Cancer Research), where he met his closest long-term collaborators and good friends, biostatistician Richard Gelber and medical oncologist Alan Coates, who have worked with Goldhirsch on many clinical trials and papers, and on the St Gallen consensus meetings.

FIGHTING FOR ACADEMIC INDEPENDENCE

Goldhirsch and colleagues hope to make an impact this year with a short paper in *Nature* on 'the essential role of academic independence' in early breast cancer clinical trials. They note that falling mortality rates in many countries are the direct result of such trials, and highlight the implicit ethical contract between researchers and patients. The nature of adjuvant trials is crucial – studies need to be large scale to explore often small differences in outcomes, and should increasingly be tailored to certain groups and followed up properly.

This all requires a lot of resources, but they are concerned about conflicts of interest, particularly between investigators and pharmaceutical companies. While recognising that commercial success for industry is necessary, they feel that the interests of patients may not be served best if a number of issues are not addressed. These include the need to secure funding for translational work and follow-up beyond commercial implementation, data being controlled or suppressed by industry, and trial questions and design being skewed to commercial interests.

For these reasons, the authors ideally would like large-scale trials to remain in open research networks such as the IBCSG and, for global collaboration, the BIG.

Another big issue driving Goldhirsch and colleagues to print is, of course, the overall regulatory constraints on clinical research, of which industry involvement is just one part. Increased bureaucracy, the cost of drugs, lack of healthcare cover for trial participants and disparate insurance requirements in some countries are all factors that "have made it almost impossible to conduct academically independent clinical research," according to another paper written by Goldhirsch and colleague Alan Coates.

BIG prize winners. Martine Piccart and Aron Goldhirsch co-chair the Breast International Group. They are pictured here at last year's ESMO conference, Istanbul, where BIG was presented with the Lifetime Achievement Award in Targeted Therapies in Cancer Research and Treatment

The forerunner to the IBCSG, the Ludwig Breast Cancer Study Group, was specifically established to run large-scale, international trials of the then very new field of adjuvant chemotherapy and endocrine therapy (and it's said that the designs for the first trials were written on a napkin in a hotel in Lausanne). "The trials were the first of their type in the world," says Goldhirsch. "They were also among the largest trials for any cancer at the time for the type of questions we were asking. We could not involve all the countries we wanted to in the early years, but now the IBCSG is working in countries such as China, India and Nigeria – our aim is to give as many women as possible at least the chance to be offered the opportunity to enrol in clinical research."

Goldhirsch says there are three main areas that have been brought forward from this work on early-stage breast cancer. "The first is that women may need a combination of chemotherapy and endocrine therapy to try and reduce the risk of relapse. Then by studying the biology of the disease you might understand why one treatment, both or none might be the priority. And third, we introduced quality of life measurement into the adjuvant setting. We wanted to quantify this, as we must not forget that adjuvant treatment is given to well women, free of disease after surgery and being treated to prevent relapse. Not all will relapse and to find out who benefits most from treatment is the big challenge and is where the study of endocrine response and non-response comes in. It was the early days of targeted therapies, which we were pioneering in."

Quality of life issues concern Goldhirsch greatly. He helped Richard Gelber, of the Dana-Farber Cancer Institute in the US, develop Q-TWiST – Quality-adjusted Time Without Symptoms or Toxicity – which aims to produce a single measure that integrates both quality and quantity of life. It is still in evolution in evaluating trials, he says, but adds that he is concerned that what he calls 'market forces' – the powers behind many trials – do not routinely report the quality side of the trade-off.

"The features of medical oncology that attracted me were the methodology and the lack of dogma"

"The language of two- or five-year survival is a notion you need to know, but it's often given the importance it does not have and greatly irritates me," he says.

It is an issue that has very much crossed over to clinical practice during his career. As he explains, with Franco Cavalli he helped develop what he calls an interdisciplinary model for cancer care in southern Switzerland, the distinction being with multidisciplinary working in a more narrow setting of, for example, tumour boards. Interdisciplinary working is, he says, about a much wider understanding of the patient's journey and experience as well as new drugs and treatments.

This can mean networking with colleagues in remote referral centres, working with disciplines outside of oncology, developing expertise in palliative care, especially when working with new drugs, and in general being able to understand how all the issues surrounding the patient shape their personal experience.

"Most medical oncologists don't have this ethos and their weaknesses relate mainly to knowledge of other problems," says Goldhirsch. "We must understand that a person who by chance has a disease may have several other problems that must be approached systematically. There is a tendency to put the malignant diseases ahead of all the other medical and social problems, not least where payment is linked to medical oncology treatment. You can't see a tumour as unrelated to a person."

As a simple example, he says he remembers well a woman with metastatic disease with no other symptoms other than suffering greatly from an ingrowing toenail, which he treated himself. "The oncology surgeon didn't know what to do," he says.

Goldhirsch chairs a weekly meeting every Thursday at the European Institute of Oncology where upwards of 70 patients are discussed in three hours, attended by as many as 50 people from both the institute and other hospitals in the region. He says his style is to pose a lot of questions about the context of the patient – where they live, for example – and he imparts often offbeat related knowledge, to keep minds as focused on patient 70 as patient one.

"I forbid discussion on patients in the café or hallway, because that's unprepared and unstructured. At the meetings, all disciplines involved discuss the patients, and senior oncologists are responsible for recording the discussion." It's a meeting not to be missed by local oncologists.

"My work at the European Institute of Oncology is a highlight of my professional life," Goldhirsch says. He gives a special mention to Umberto Veronesi, director of the Institute, who in 1996 gave him the opportunity to lead medicine at the newly created institution, which emphasises innovation in patient care. "Umberto Veronesi's research over decades changed much of the surgical and radiotherapy approach in caring for women with breast cancer, allowing minimal damage to normal tissue while still efficiently treating the disease. This is a challenge for medical therapies too."

Interaction with several colleagues at the Institute has become extremely intensive on these specific lines. "Giuseppe Viale and his team of pathologists are at the forefront of our translational research and provide continuous clinical guidance on how to better define and report on features that help prediction of prognosis and responsiveness to therapies."

It is the latter issue – defining which tumours respond to which therapies – that has been assuming centre stage in the St Gallen conferences, and looks set to do so again this year. The conference is the brainchild of Hans-Jörg Senn of the St Gallen Tumour Detection and Prevention Centre, and Goldhirsch has been one of the main contributors to the scientific part of the programme.

The need to discuss controversial issues at St Gallen was mooted with Richard Gelber and other famous cancer specialists such as oncologist John Glick and surgeon Bill Wood, says Goldhirsch, evolving from its initial purpose of a gathering of clinical trialists. Since the third meeting, the expert consensus has been in operation, and its recom-

mendations – not guidelines – have become increasingly cited in the literature.

"Guidelines are important as they confer regulatory and payment responsibility, and put order on what can and cannot be done in oncology, as the spectrum of abuse in diagnostics and therapeutics can be huge," says Goldhirsch, adding wryly that changing a payment regime can be the fastest way to change the behaviour of medical oncologists. "The St Gallen consensus is a set of recommendations on areas of grey – commonsense judgements from experts of what to do in controversial areas. We are trying to help people improve their understanding of the features of disease and not restrict themselves to dogma."

The main trend at the last few St Gallen meetings, says Goldhirsch, is a move "away from risk of relapse as the main treatment criterion to treating features of disease. We are now recommending treating first according to endocrine response and non-endocrine response, and we also define a group where endocrine response is uncertain." Categories of risk of relapse are at a secondary level – just a few years ago risk, based on the nodal status of the tumour, was the first category for consideration.

Such has been the accumulation of new evidence on adjuvant therapy since the St Gallen meeting of 2005 that Goldhirsch and colleagues issued an update last year under the title 'First – select the target…' (*Annals of Oncology* 2006).

One of the main reasons why St Gallen is an expert consensus, says Goldhirsch, is that they are making recommendations based on indirect evidence from population groups in trials, ideally after sufficient follow-up time. "When several subgroup analyses show the same direction it starts to be good evidence, such as avoiding chemotherapy in women in a high-risk group whose disease shows a huge endocrine responsiveness."

Goldhirsch is quick to dispel the notion that St Gallen is a club of like-minded oncologists, mentioning that among the experts there are several oncologists with whom he is in disagreement about several controversial areas.

The consensus can no doubt be hard to reach and the term 'robust debate' may well be an understatement. Goldhirsch is said to step up to such debate – as a colleague says, "Others may not suffer fools gladly: Aron is apt to destroy them comprehensively. It must irritate his opponents that he is so often proved right."

Goldhirsch is also among the strong critics of the presentation and interpretation of trials that are considered for evidence, mentioning the recent push to use aromatase inhibitors instead of tamoxifen as adjuvant medication. He says that their side-effects and cost are major factors, and while they are proven to better prevent relapse and death in women at high risk, long-term efficacy, a strong feature of tamoxifen effects, is still to be demonstrated. The ATAC (Arimidex, Tamoxifen Alone or in Combination) study, one of the largest ever studies on postmenopausal women with early breast cancer, certainly led to a division of opinion in the oncology

ST GALLEN: AN INTERNATIONAL CONSENSUS

Although the word 'adjuvant' no longer appears in the title of the St Gallen conference – the term 'primary therapy' is used – the expert consensus panel that convenes after three days of presentations has focused on adjuvant therapies. The 2005 recommendations emphasised endocrine responsiveness and a modified risk classification, a major development from 2001 when the focus was on multiple categories of risk based on the nodal status of a tumour. "Prognosis per se was considered less relevant to treatment selection," a 2006 update reports.

Goldhirsch says that the key topics for this year's consensus discussion are as before – endocrine therapies for pre-and post-menopausal women, chemotherapy regimens, and trastuzumab – and in addition radiotherapy will have a higher profile. The core recommendations from 2005 boil down to a simple table of three endocrine categories versus three risk categories, and recommended therapies.

The St Gallen consensus is not of course the only such classification. One other, the US National Institutes of Health Consensus Development Conference on Adjuvant Therapy, has been compared with St Gallen by researchers who noted in 2002 that, despite looking at evidence from the same trials, the resulting recommendations from the two meetings (held three months apart then) were slightly different (Breast cancer consensus meetings: vive la difference? *Journal of Clinical Oncology* 2002).

The details are now history, but the writers considered that the make up of the panels was, not surprisingly, the key to the difference, with St Gallen being a group of international breast experts and the NIH panel being only American citizens from diverse medical fields and also the public.

Members of this year's St Gallen panel include John Glick, Martine Piccart, Alan Coates and Richard Gelber – 37 in total – with Goldhirsch and Bill Wood in the chair.

Frontiers men. Aron Goldhirsch and Richard Gelber, president and vice president of the clinical/translational research support organisation Frontier Southern Europe, taking advantage of a photo opportunity

community, and it is notable that despite pressure to report otherwise, the latest St Gallen advice simply concludes: "Much less information is available on the long-term safety of aromatase inhibitors than for tamoxifen."

He expresses disappointment at the presentation of the pivotal Herceptin trials in 2005 in the *New England Journal of Medicine*. His group's results – the BIG Herceptin Adjuvant (HERA) trial, led by another of his close collaborators, Martine Piccart of the Jules Bordet Institute in Brussels – has graphs with disease-free survival plotted from 0 to 100%, whereas the joint American trials evaluation results were presented with plots truncated at the 50th percentile (50% to 100%) giving an entirely different graphical impression. "And that's the same journal, the same editors," he notes.

Goldhirsch says he's always pleased when the St Gallen recommendations are picked up by other researchers – an important recent example being their use as a benchmark for the new work on gene profiling in breast cancer, although he notes that "the majority of genes are related to endocrine and non-endocrine response," and that the information could probably be obtained at less cost with other means. However, he is a participant in the TRANSBIG MINDACT (Microarray In Node-negative Disease may Avoid ChemoTherapy) gene profiling trial, but only after he insisted that it was extended to cover node-positive as well as node-negative women to widen its value.

He feels St Gallen also offers better guidance for professionals than tools such as Adjuvant! Online (www.adjuvantonline.com). If nothing else, the meeting is for Goldhirsch a crucial educational exercise, and the opening state-of-the-art progress reports are well worth the trip.

But for breast cancer professionals in Europe, he considers there is still a missing piece of the conference jigsaw. St Gallen is providing state-of-

He would welcome more problem-based learning, particularly where it involves talking with patients

the-art recommendations; there is the Milan Breast Cancer Conference on Innovation in Patient Care; and the big European Breast Cancer Conference (next in Berlin in 2008) is a meeting of all professionals and, increasingly, advocate groups. "What's missing is a meeting on translational research just for breast cancer," he notes, adding that plans are already afoot to plug this gap. "I think our profession lacks a methodology to continually reinvent itself – we need all these four conferences to give us the right tools."

Goldhirsch has avoided most senior committee positions offered to him outside of breast cancer, but one post he did occupy for 10 years was president of the prestigious Swiss Group for Clinical Cancer Research (known as SAKK). His involvement came to an abrupt end in 2004 when he resigned after conservative rules were introduced in Switzerland that he says curtailed opportunities to carry out clinical research. He is now president of the recently established Frontier Southern Europe (www.frontier-se.org), based on the model and principles of the Frontier Science and Technology Research Foundation, its famous parent organisation, which was set up in Boston in 1975 to support trials of early cooperative groups such as the American Eastern Cooperative Oncology Group (ECOG).

If he could make one change now it would be in the training of medical students, and he would certainly welcome the widespread implementation of problem-based learning, particularly where it involves talking with patients. "Who teaches skills such as negotiation with patients?" he asks. Well, he and his colleagues go some way towards this aim at Milan – "We have developed a methodology for communication with various patient groups. Approaching, say, an older woman who may have a high chance of relapse is more efficient when issues specifically related to her needs are taken into account." Teaching professionals what they need for actually carrying out adjuvant treatment (or not) is not really being taught anywhere, he reckons.

Goldhirsch's own research interests, not surprisingly, home in on the cutting edge – the endocrine responsiveness of breast cancer in selecting the appropriate adjuvant therapy. He has, though, a particular interest in younger and older women – typically the 20–30- and 70–80-year-olds, who he feels are still neglected populations, despite breast cancer being such a large field. He mentions two important IBCSG studies that are addressing premenopausal women – Suppression of Ovarian Function Trial (SOFT) and Tamoxifen and Exemestane Trial (TEXT), but if there is one wish he has for a major trial he'd like to see through in his career, it would be a more specific study aimed at younger women.

That would naturally be another major international collaboration, and it is fitting that of all the awards he has received in his career, it is an honorary doctorate from the University of Gothenburg for his international work that he is most proud of.

Goldhirsch, who is now a Swiss national, lives in Switzerland with his wife, Francesca, an ophthalmologist, and three children who keep him on his toes with the latest pop music (although the 'Hot Red Chili Peppers' isn't quite what they're called). A big hobby is photography, and his main reading interest is science fiction, which is apt given his philosophy of doing away with dogma wherever necessary in medicine.

Given that the field of breast cancer has undergone a huge knowledge explosion, even Goldhirsch recognises that it is not possible to know everything, and indeed he foresees a time when it may need to be divided into sub-specialties – but without losing vital cross-fertilisation among professionals.

And there lies an increasing challenge for oncologists, who Goldhirsch would like to see abandoning dogma and participating in cultural – and political – changes to improve attitudes to care and research he feels are needed to apply new knowledge to best effect.

Don't sideline the guidelines

How to ensure clinical guidelines translate into better treatment

➜ Emma Mason

Many patients are still being let down by a failure to follow clinical guidelines. It's all very well to blame know-it-all doctors, but if the guidelines are hard to access and tricky to use, and if treatment centres don't take steps to ensure new guidelines are implemented and continue to be observed, then what should we expect?

AS international experts meet in St Gallen to consider the best treatments for breast cancer and to disseminate their accumulated knowledge to the world with the 2007 St Gallen consensus statement, the focus is again on clinical guidelines.

The argument these days tends to be less about whether they improve patient outcome – there's now plenty of evidence in literature that they do – and more about how widely they are implemented, which ones are best for which cancers in which countries, their purpose (standardisation of care or treatment rationing), and how to help and encourage clinicians to implement guidelines and to do it effectively.

Guidelines for the treatment of cancer in clinical practice are intended to give physicians around the world up-to-date information and recommendations on the best prevention, diagnosis and treatments for every cancer, in order to improve patient care. In other words, to provide the *right care*, at the *right time*, for the *right person*, in the *right way*.

However, clinicians and guideline writers face a number of barriers to successful implementation of clinical practice guidelines, and these vary in different countries, with some easier to surmount (e.g. lack of knowledge) than others (e.g. lack of resources or systems).

The picture is further complicated by the array of guidelines available to clinicians. These range from guidelines produced by several different organisations for the treatment of individual cancers from diagnosis through to palliative care, to guidelines (again, from several organisations) on one particular aspect of care, such as radiation, chemotherapy, or control of anaemia, neutropenia or vomiting, for instance.

So how is the busy oncologist expected to choose from amongst this plethora of guidelines, and find and use those that work best for them? Is it any surprise that, faced with such a choice, many fall back on their personal experience, perhaps supplemented by information they have picked up at conferences and their hospital's standard practice?

Bruce Barraclough, medical director of the Australian Cancer Network (ACN), has a wide experience of developing and implementing guidelines. He and his colleagues have written "evidence-based guidelines on how to implement guidelines", and he warns that producing and implementing them is not a simple or easy process.

"To make it simplistic is to underrate how difficult it is to change practice in humans," he says. "It's the same in any human organisation, from hospitals right through to families.

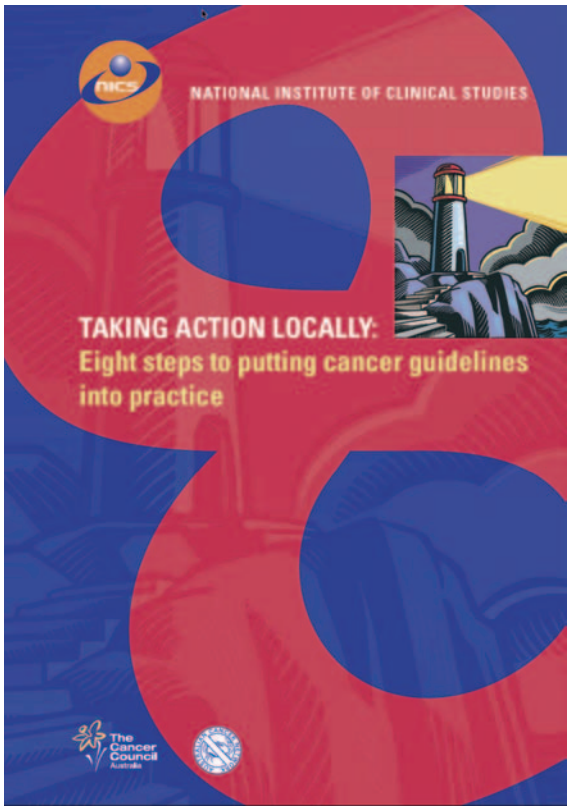
"Change is not simple, change is not

PUTTING GUIDELINES INTO PRACTICE

The Australian Cancer Network's eight-step guide has been disseminated widely throughout the Australia, and its general principles are applicable everywhere.

1. Appoint the team – clinical champions and executive sponsor
2. Decide which recommendation to tackle first – size and importance of evidence/practice gap
3. Is current practice in line with guideline recommendation? – audit
4. Understand why we are not achieving best practice – individual and system
5. Prepare for change – engage stakeholders
6. Choose the right approach
7. Put your theories to the test – plan, do, study, act
8. Keep things on track – communication – change takes time

The guide can be downloaded at www.cancer.org.au/content.cfm?randid=352233.



"A simplistic approach to guidelines underrates how difficult it is to change practice in humans"

quick, change is not the same in every place, because systems might be different, leadership lacking in some places and good in others. In some smaller, more remote places where people don't get enough interaction with their peers, there may be lack of knowledge."

The ACN and the Australian National Institute of Clinical Studies (NICS) have produced a short booklet called *Taking action locally: eight steps to putting cancer guidelines into practice* (see box). "When we first put the booklet out, we were inundated with requests for it. It is aimed at leaders and managers looking to encourage their people to put guidelines into practice and arming them with the information to do so," says Barraclough.

Overcoming obstacles

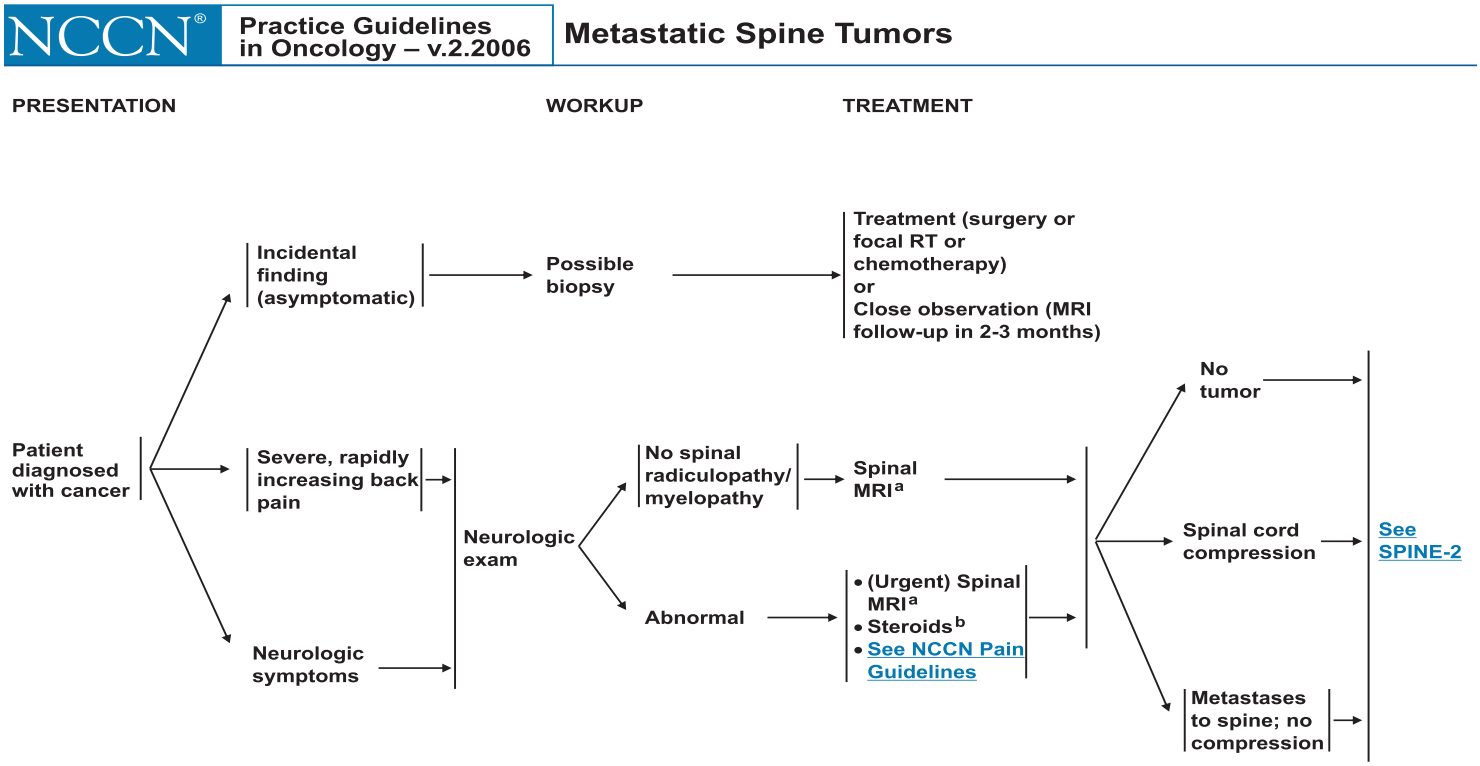
In the sixth step of the booklet, "choose the right approach", some of the key barriers to successful implementation are identified, together with strategies to overcome them.

Barraclough says, "There are number of issues here. If we are going to improve cancer care through guidelines, we need to review and understand the literature, and then write guidelines that people who are very busy at work can use." The guidelines need to be easy to read so that clinicians can absorb the essential information in "a quick flick through while at the coal face", he explains.

"Work has to be done on understanding change, and when you are changing long-established practices, this requires a change management process."

He identifies barriers and suggests interventions to deal with them:

- Lack of knowledge – supply educational courses and provide aids to decision-making
- Mismatch between perception and reality – audit and feed back the results. "If they think differently, you need to explain the evidence and audit the work so that people are confronted with what they are doing, rather than what they think they are doing"
- Lack of motivation – provide leadership and have a system of incentives and sanctions



[a] If the patient is unable to have an MRI, then a CT myelogram is recommended.

[b] The recommended minimum dose of steroids is 4 mg of dexamethasone every 6 hours, although dose of steroids may vary (10-100 mg). Methylprednisolone can be used instead of dexamethasone. For rapid neurologic deterioration or significant myelopathy, a stat MRI is recommended. A randomized trial supported the use of high-dose steroids (Sorensen PS, Helweg-Larsen S, Mouridsen H, Hansen HH. Effect of high-dose dexamethasone in carcinomatous metastatic spinal cord compression treated with radiotherapy: A randomized trial. Eur J Cancer 1994;30A:22-27). Steroid use should be tapered within 3 days.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Easy to use. The US National Comprehensive Cancer Network presents its guidelines in the form of decision trees, making it easy for doctors to track their patient's specific problem and work out the recommended treatment*

Source: Reproduced with permission from the NCCN 2.2006 Central Nervous System Cancers Clinical Practice Guideline in Oncology, The Complete Library of NCCN Clinical Practice Guidelines in Oncology *[CD-ROM]. Jenkintown, Pennsylvania:© National Comprehensive Cancer Network, June 2006. To view the most recent and complete version of the guideline go online to www.nccn.org*

- Attitudes and lack of belief in benefits – use peer influence and opinion leaders
- Systems of care – "If the system of care makes implementation of guidelines difficult, there needs to be a process redesign (involving managers etc)"

Other oncologists identify additional barriers, including the availability and accessibility of guidelines, whether they have been translated into other languages, lack of resources (including lack of funding, drugs, training, people and equipment, and problems associated with geographically remote locations), as well as the very practical issue of how easy the guidelines are to read and use.

Shortly before he died in a plane crash in December, Christopher Desch, National Medical Director of the US National Comprehensive Cancer Network (NCCN), spoke to *CancerWorld*. The NCCN is an alliance of some of the leading US cancer centres, dedicated to improving the quality and effectiveness of care provided to patients with cancer. The organisation creates clinical practice guidelines appropriate for use by clinicians, patients and others involved in cancer care. All the NCCN guidelines are on its website and available to anyone to download.

Desch identified the format and the availability of guidelines as two of the barriers. "There are plenty of reasons why doctors may or may not use guide-

"Some guidelines are long documents of text and it's difficult to work out what the solution is"

lines. The format is very important. The NCCN guidelines use an algorithm, or decision tree, that enables the physician to track the specific problem your patient has and work out what the treatment should be. Some guidelines from other organisations are long documents of text and it's more difficult to work out what the solution is.

"Some guidelines are available only in paper copies and not on the web. This is a problem for doctors, because if you cannot get them exactly when you want them, it doesn't help. Also, the amount of time available during the clinical interaction [between the doctor and the patient] can be a problem," he said.

Often, cancer patients can find themselves being treated by clinicians who are not necessarily cancer specialists. Desch said, "The less training the clinician has had in cancer care, the less likely they are to use guidelines, sometimes because they do not even know of their existence."

However, like every other oncologist interviewed for this article, Desch was in no doubt about the usefulness of guidelines. "I still practice oncology. I use the guidelines to help me manage patients with unusual cancers, such as thyroid cancer. They help me to find the right treatment and also the experts, as the members of each guidelines panel are listed at the front of the NCCN guidelines. As a user I use them almost every day in practice."

He continued, "Ten years ago people were not sure what they should do with guidelines. Today, there are a number of factors that make people appreciate them more:

- They are associated with quality care
- Guidelines are now used in training programmes; so in every programme, guidelines are put up [on slides] to show where the patient fits along the pathway
- Young physicians have incorporated them within the training process, so they see them as a tool that helps, rather than as 'cook book' medicine. Fewer and fewer doctors look on guidelines as a constraint."

The cook book charge

The charge that guidelines can be dictatorial, inflexible and a way of delivering cancer care through 'cook book' medicine is one that most of those involved in formulating or implementing guidelines have frequently had to counter. Barraclough argues that, "Even if the guidelines are not perfect, the evidence shows that they still improve patient outcome. We do better by making care standardised, than by changing care to take account of the latest and most incremental advances."

They are a tool to be used, said Desch. "They don't define what *has* to be done, because many patients don't fit exactly into them because of age, comorbidity, patient preference and so on." He also believed that guidelines could be used to re-assure patients that they were being treated in accordance with the best advice, even if their particular circumstances required some variations.

Barraclough agrees. "Guidelines are not some holy writ. They need to be interpreted for the patient in front of you, with patient preference taken into account."

He refers to the theory of evidence-based medicine as propounded by David Sackett: that clinicians need evidence of what treatment works best, but then there needs to be clinical expertise to apply it to the patient and patient preference is also important and needs to be taken into account.

In Australia, the huge distances can also have an impact and influence on patients' preferences, as some may not wish to travel hundreds of miles to receive a treatment that might have only a marginal benefit.

"As the leader of a cancer team, you say 'this is the evidence, these are the results we have and this is how we can interpret it for our environment,'" says Barraclough.

Nicholas Pavlidis, chairman of the European Society for Medical Oncology (ESMO) guidelines group and professor of medical oncology at the University of Ioannina, Greece, says, "There will always be people who are against guidelines and say they are oversimplifying things and that they lead to 'cook book' medicine. In a recent systematic survey of clinicians' attitudes to clinical practice guidelines, 70%–75% of clinicians agreed that guidelines are helpful sources of advice, good educational tools and intended to improve quality. However, 30%–52.8% of them also considered that guidelines are impractical and too rigid to apply to individual patients; they reduce physician autonomy, they oversimplify medicine, they would increase litigation and are intended to cut healthcare costs."

He says that physicians from countries in Europe that are less organised

ESMO decided to do something very short, so the practitioner can read them and make a decision fast

and have fewer resources are more likely to say guidelines are not good for them to use. "But if you're talking about organised societies and health systems, then I think the majority of doctors are in favour of them."

Pavlidis has been a member of the ESMO guidelines group since 1997 and chair since 2006. The society publishes the 'ESMO clinical recommendations' which, until recently, were called the 'minimum clinical recommendations.'

The idea for the ESMO clinical recommendations originated with Heine Hansen (Copenhagen, Denmark) to meet the needs of Eastern Europe. The recommendations are no more than three pages long and all are available on the ESMO and *Annals of Oncology* websites.

Pavlidis says, "ESMO decided to do something very, very short, so that it would be convenient for the practitioner to go through them and make a decision fast. That's why they were originally called the 'minimum clinical recommendations'. Other guidelines have a huge amount of information in many, many pages, which are less easy to use."

He continues, "The principle of the guidelines are:

- to create a statement of the basic standards of care
- to be disease- or topic-orientated
- to be evidence-based
- to have an emphasis on medical oncology
- to be regularly updated every year

"They have informed thousands of people. Between January and August 2006 there were 57,887 downloads from the *Annals of Oncology* website. The most frequently downloaded were the common cancers: lung, breast, colorectal, gastric, ovarian and prostate cancers."

Updating all the guidelines annually ensures that they keep abreast of medical advances. While Pavlidis makes no claims that doctors should choose to use the ESMO guidelines instead of, or in preference to, other guidelines, he says, "We do hope that the ESMO guidelines could become the most practical, easy-to-use, annually updated guidelines, not only in Europe, but worldwide."

But clinicians can choose from guidelines produced not only by ESMO, but the European Organisation for Research and Treatment of Cancer (EORTC), the Multinational Association of Supportive Care in Cancer (MASCC), the UK's National Institute for Health and Clinical Excellence, the American Society of Clinical Oncology (ASCO) and the NCCN, to name but a few.

Of the NCCN guidelines, Desch said that although he couldn't put a precise figure on it, he was sure they were widely used. "Doctors all over the country say how useful they are, and when we count the number of times they are accessed on the Internet, it's over a million times a year. We also know that insurance companies in the States use them to ensure that the care that doctors are giving is within reason."

Matti Aapro, director of medical oncology at the Clinique de Genolier, Switzerland, and co-author of several EORTC and MASCC guidelines, believes that there is a problem with too many over-lapping guidelines, and that the different guidelines need to be harmonised. The way to do this is through collaboration.

"If you look at the MASCC guidelines, for example, we called on all organisations to send a representative to join the guidelines committee, in order to harmonise the guidelines. I think that's been very successful for the anti-emetic guidelines. ASCO [who had a representative on the MASCC guidelines committee], acknowledged the MASCC guidelines and the work that had been done by the MASCC when they started to formulate their own guidelines.

"If you look at members of the EORTC group that wrote the guidelines on the use of G-CSF [to reduce neutropenia in patients with lymphomas and solid tumours], you will realise that there are members of the ASCO G-CSF group on this committee. We try to have members from Europe and the USA so that we don't have conflicting messages."

One guideline fits all?

But can guidelines formulated in one country be useful in another country that may have a different system of health services and funding? Is it possible to have guidelines that are universally applicable? What about the differences between developed and developing nations, both in terms of resources and structures?

These are questions that appear to have complicated answers, but the simple message is that, although it's possible for doctors to follow guidelines written in

"Guidelines are not some holy writ. They need to be interpreted for the patient in front of you"

another part of the world, they have to adapt and supplement them to suit their local situation. Aapro, for instance, points out that one of the main differences between the US and Europe is the availability and the use of drugs – the US Food and Drug Administration (FDA) has not approved certain drugs that are available for use in Europe, while other drugs are not available for certain uses in some European countries that are available in the US. In some European countries, government policy dictates that there should be national guidelines, which physicians have to, or are expected to, follow. The use of Herceptin to treat early breast cancer is a good example of differences between countries.

There are other differences too. Aapro says, "There are differences in priorities and the way the results of studies are looked at in Europe and the States. In the States, they concentrate a lot on North American studies and ignore the European studies, and this can make a difference to the content of the resulting guidelines, while in Europe we tend to look at data that comes from phase three studies from all over the world. The St Gallen consensus statement is a good example of the differences that exist in the treatment of breast cancer between the two continents. It places a lot of weight on the evaluation of the tumour, and whether it is endocrine responsive or not, and that drives thinking about the use of adjuvant treatment. The Americans use too much chemotherapy without consideration of data that show that the advantage of chemotherapy can be minimal in certain situations."

Knowing these political, financial and structural constraints that have influenced the formulation of guidelines is crucial. Barraclough says, "Provided that you know how the guidelines were produced, you can share them with other countries. A number of guidelines in different countries are evidence-based to an extent, but then there appear to be variations depending on the resources of the country. If a certain medication is not going to be available for a particular treatment, then it's not included in the guidelines. Some countries seem to use guidelines in this way to help allocate resources because there's not endless supplies of money to do everything for every patient, every time."

Benjamin Anderson is director and

chair of the Breast Health Global Initiative (BHGI) at Fred Hutchinson Cancer Research Center (Washington, Seattle, USA) and professor of surgery at the University of Washington School of Medicine. The BHGI international alliance, co-sponsored by the Hutchinson Center and the Susan G. Komen Breast Cancer Foundation, develops evidence-based, economically feasible guidelines that can be used in developing countries with low resources to improve outcomes for women with breast cancer (*Breast Journal*, vol 12 suppl.1, 2006). He believes that guidelines written for well-resourced countries are likely to be unworkable in countries with limited resources and inadequate systems for delivering healthcare. But guidelines written for developing nations could be useful to developed nations.

"Many of the obstacles observed in developing countries are also present in under-served regions or populations in developed countries. In particular, the social and cultural boundaries among ethnic groups that may limit women's access to care appear to have a commonality," he says.

Developing countries struggle with a number of barriers to providing adequate healthcare, let alone following guidelines. "Availability of resources is one limitation," says Anderson. "But I would suggest that information and organisation are more commonly the obstacles to early detection and adequate treatment. Many of the basic therapies that we provide, such as surgery, radiation therapy and basic drug therapy, are reasonably affordable, if provided in a system where patients can be reached in a timely and adequate fashion. Social and cultural barriers can be major, unanticipated obstacles for improving healthcare, especially when the care is being imported from outside communities that may not appreciate the cultural beliefs that shape a woman's willingness to undergo diagnosis and/or treatment."

Therefore, structures rather than individual clinicians and their ability or willingness to follow guidelines, can be a major barrier. "It is overly simplistic to view healthcare delivery as being defined by physician knowledge and communication. Clearly, proper education of physicians and the public is mandatory. However, the delivery system needs to be organised in such a way that this knowledge can be acted upon.

"In many circumstances, the obstacle is not the clinicians at all, who may be well aware of the ideal tools and therapies. Rather, the problem has to do with the healthcare system's capacity to provide the sustainable resources for healthcare delivery, despite the fact that resources are inevitably being spent on patients with the disease. More often, the obstacles are system-wide and beyond the clinicians' scope of control. These issues are prevalent in developed and developing countries alike, because in all settings, there are populations where healthcare fails to penetrate," says Anderson.

The BHGI approach is described in the US Institute of Medicine publication, *Cancer control opportunities in low- and middle-income countries*, in a chapter on resource-level-appropriate interventions (*National Academy Press*, 2007). Anderson says that one of the issues that the BHGI considers is whether a country's resources could be re-allocated in a way that makes better use of them, and involves the people in the country, rather than solutions being handed down from outside, which is an approach that will fail.

"The BHGI international guidelines provide a framework for an integrated, cohesive system for breast healthcare and cancer treatment by which these solutions could be brought about in a sequential manner, taking into account real resources." Different countries have different levels of resources, and so the BHGI suggests a tiered, step-wise system of resource allotment, defined using four levels: basic, limited, enhanced and maximal. These levels are based on the contribution of each resource to improving clinical outcomes. So, for instance, in the poorest countries, surgery might be the only available treatment, while better resourced countries might be able to afford chemotherapy, and so on.

"This is an economically stratified approach for the real world to frame how limited-resource countries can 'step up the ladder'," says Anderson. By approaching the formulation of guidelines from this different direction, and biennially revisiting and refining them, he hopes that the BHGI will be simultaneously learning where the problems lie and implementing solutions in order to fill in the missing rungs of the 'ladder'.

Allocation of resources

The issue of resources is a recurring theme in relation to guidelines. In the US, private health insurance finances most medical treatments, and here, as Desch pointed out, insurance companies find guidelines useful for establishing standards of care, but also for ensuring that

Guidelines written in another part of the world must be adapted to suit the local situation

Guidelines can be used to ration treatments, but they can also ensure all patients are treated equally

they don't have to pay out for treatments that have little evidence of efficacy. In other countries, where the state provides healthcare, funded either through taxation, or a combination of taxation and insurance, guidelines can also be about the allocation of resources, or rationing.

Ingvar Karlberg, professor of health services research at Gothenburg University, Sweden, has been interviewing politicians, health service managers and clinicians for his research into guidelines. He believes that guidelines need to be formulated by all the parties or 'stakeholders' involved with them; this includes not only managers, clinicians and patients, but also what he calls the 'third party payer' – the organisation that pays for the healthcare.

"In all economic systems, whether it's a tax-based system or whether it's an insurance-based system, there's always a third party payer. The problem is that doctors and patients meet, discuss, decide on treatment and then send the bill to the third party payer, who has not been involved in the discussions. One way to involve the third party payer in these discussions is through clinical practice guidelines. If they are based on scientific evidence and take account of priorities, finances and incentives, they will probably work well and make the third party payer part of the process," says Karlberg.

He believes that a consensus needs to be reached between all parties on issues such as cost, treatments and priorities, otherwise guidelines are in danger of appearing to be 'wish lists' of what clinicians think are the best treatments, without any regard for how they are to be financed – at which point arguments break out between the different stakeholders.

Media coverage of the latest 'breakthrough' or 'wonder drug' helps to create patient pressure for treatments, and "politicians want everyone to have everything available, and that's a political pressure," says Karlberg. "Guidelines need to be used to support political management in order to restrict care in some cases, but you can also turn that argument around and say guidelines enable political management to ensure equity and accountability in the delivering of healthcare."

In other words, guidelines can cut both ways: they can be used by funders to ration treatments, but also to ensure that all patients are receiving an equal standard of care.

This may be a message that some people will be reluctant to hear, particularly clinicians and patients. But in this day and age when more and more treatments are being developed for more and more diseases, the fact that there is not a bottomless pit of money to pay for all patients to receive the very latest treatment relevant to them is an important one, especially for nations with fewer resources. Guidelines could be a way of building consensus on these thorny issues, but only if all the different parties are involved in their formulation.

TIPS FOR WRITING AND IMPLEMENTING GUIDELINES

FORMULATING GUIDELINES:

- Involve multi-disciplinary teams (clinicians, radiotherapists, nurses etc) and a wide range of stakeholders, such as funders, managers, advocates, patients
- Develop an evidence-based, consensus approach
- Be aware of existing guidelines – try to harmonise with them to create an integrated, cohesive approach
- Keep guidelines concise, in an easy-to-use format so that a busy clinician can see at a glance recommended strategies (use of algorithms/decision trees)
- Non-profit/NGO retains total control of guidelines publication to avoid conflict of interest with for-profit organisations
- Update guidelines annually or biennially

IMPLEMENTING GUIDELINES:

- Provide vision, leadership, organisation, internal support and appropriate structures to ensure the guidelines are introduced and continue to be used in day-to-day practice
- Educate health professionals about the value of guidelines (via training, peer pressure etc)
- Make the guidelines easily and freely accessible via the Internet
- Publicise the availability and down-loadability of guidelines
- Provide translations of guidelines if possible
- Regularly remind health professionals that guidelines exist and should be used (via training, conferences, use of incentives, debates, discussions etc)

No-name heroes can save Europe billions

Anna Wagstaff

European countries struggle to fund new cancer drugs which bring benefits at a high price. Meanwhile billions of euros are wasted, say researchers, because doctors prescribe branded drugs when a generic equivalent is just as good, and because the cost of generics is far too high.

IN late January 2007, two more cancer drugs fell victim to health rationing, when England's National Institute for Health and Clinical Excellence (NICE) decided against making either Avastin (bevacizumab) or Erbitux (cetuximab) available on the National Health Service for metastatic colorectal cancer. The decision followed the rejection last October of the case for public funding of Velcade (bortezomib) in the treatment of multiple myeloma, and a preliminary decision in November against Tarceva (erlotinib) for lung cancer.

At issue was not whether the drugs offered clinical benefit, but whether the cost–benefits represented the best use of limited National Health Service resources. NICE decided they did not.

The decisions sparked protests from patients and doctors alike, but public anger is tempered by a recognition that healthcare expenditure is escalating faster than the country can afford and that some form of rationing is the only answer. NICE – an independent body, taking expert advice from all stakeholders and following transparent procedures – seems the fairest way to achieve this. But is it looking in the wrong direction?

Panos Kanavos is a health economist based at the London School of Economics. He and his colleagues have spent the last few years researching pharmaceutical policies in Europe and the US, and he believes that if the public and politicians were aware of how much money is wasted in the overall drugs bill, they might think again about denying cancer patients drugs that could help them.

Much of his recent work has focused on the market for generics. A generic drug is the chemical and bioequivalent of a drug that has an expired patent (usually after 25 years), and which can therefore be copied by other companies and sold under the generic drug name. Because generic medicines replicate an existing drug, there are no research and development costs and no 'innovation' or 'risk' premium to be reflected in the price. In a free market, the price of generics should therefore be the cost of production plus a reasonable profit margin.

The problem is, says Kanavos, the market is distorted. Price levels are maintained significantly above what the companies would accept. Wholesalers and pharmacies negotiate major discounts from the manufacturers, which are not passed on to the end-payers. A failure to encourage doctors and pharmacists to opt for equally effective lower priced drugs results in inefficient prescribing practices, particularly where there are heavily marketed branded products, which often command a price close to the original patented medicine.

These 'branded generics' may be a continuation of the original product supplied by the same manufacturer at a slightly lower price, or a new brand name produced by a generic company when the original is newly out of patent. The research by Kanavos and colleagues showed that these 'branded generics' tend not to go down significantly in price as new suppliers enter the market, and that prescribers often

That implies savings of 1 to 1.5 billion euros, up to 10% of the entire drug budget

stick with the brand name, despite the price difference.

Taken together, this represents a massive area of potential saving, according to Kanavos. "The situation varies widely from country to country, but speaking very generally, we have shown that in a country that spends about 15 billion euros on medicines, and about 5 or 6 billion of that on generics, we could save about a quarter of that, simply because we are paying too much." That implies savings of 1 to 1.5 billion euros, up to 10% of the entire drug budget.

Evidence for this comes principally from comparing the prices at which a selection of generics retail to health services or health insurance schemes in a number of European countries, the USA and Canada.

A12-FOLD PRICE DIFFERENCE

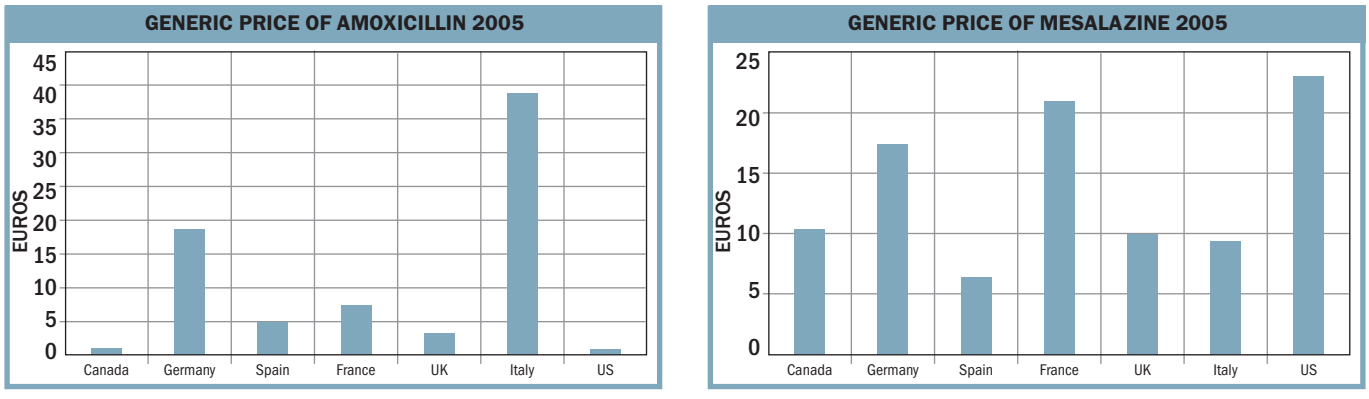
Take mesalazine, used for inflammatory bowel disease, and mooted as a preventive for IBD-related colorectal cancer. In the UK it retails at an average price of 10 euros, in Germany at 17 and in France at around 21 euros. Metformin, a drug widely used to control diabetes, retails for around 0.7 euros in Spain and the UK. In Germany the price is closer to 1.8 euros, in France 3.5 euros and in Italy 4.2. In other words, Italy is paying six times the price paid by their Iberian cousins, for the same product. The story is similar for the antibiotic drug amoxicillin, for which you pay 3 euros in the UK, 5 in Spain, 7 in France, 18 in Germany and 38 in Italy – more than 12 times the UK price.

These findings are set out in an LSE discussion paper (Kanavos and Costa-Font 2007) which looked at 13 generic molecules. Though none are used primarily in cancer patients, they are all paid for out of the same, overstretched drugs budget. A saving on this would allow for greater flexibility when considering how to pay for new and expensive anti-cancer drugs.

But while the study shows that, overall, prices tend to be significantly lower in the UK and Spain than, for instance, Germany, France or Italy, it would be wrong to conclude that the UK price must therefore be somewhere close to the lowest price companies would agree to sell at. A further piece of research into the UK distribution chain (*Curr Med Res Opin* vol 23, pp105–116) has revealed that pharmacies are able to negotiate substantial discounts from wholesalers or the manufacturer, without passing on the savings. This means that while the National Health Service is paying the prices quoted above, the manufacturer is content to supply the product for far less.

The maximum discounts offered by the manufacturer exceeded 60% of the price paid by the NHS in 20 of the 31 generic products included in the study, while in a further seven the maximum discount ranged between 50% and 60%. It is hard to avoid the conclusion that if European health systems got their act together, they could purchase the same generic drugs for a fraction of the current price.

This situation would not be sustainable in a free market, where in theory



Why pay more? Significant price differences for identical molecules across countries indicate the potential for very substantial savings in Europe's drugs budgets

Source: Generic Competition in Drug Markets and the Impact of Regulation, Kanavos and Costa-Font, LSE discussion paper, 2007

excess profits attract new entrants and competition pushes the price down. But that's not how pricing in most European countries tends to work.

Drug prices in Europe are heavily regulated, and every country has its own system. Prices, including those of generics, tend to be agreed in negotiation between the government and the drugs companies, often with the involvement of health insurance agencies. Kanavos and colleagues have identified a number of practices that tend to result in high generic prices.

Often the price of a generic drug is closely related to the price of the original patented drug. When the drug's patent ends, negotiators look to lop around 20%–30% off the patented price. Very often, this is taken as a 'reference' price, which means that additional generics of the same molecule cannot come onto the market as a higher price. However, unless there is pressure within the system to purchase at the lowest price possible, or incentives for pharmacists to give priority to lower priced products, new manufacturers coming into the market have every reason to keep their prices close to the original reference price, preventing prices from falling.

It seems hard to believe that, while patients are denied drugs that could help them, and health professionals are obliged to tailor decisions to budgets, this inefficiency in the price of generics is allowed to continue. Kanavos puts it down to a combination of inertia and caution. "We are humans, and we are creatures of habit. Some policy makers are convinced that it is much better for them to stick with a particular system that delivers them 30% say, as opposed to a system which, if they dare implement it, could deliver them twice as much. But it takes knowledge, guts and pressure to do all that."

Else Borst Eilers, Minister for Health in the Netherlands between 1994 and 2002, is an interesting case in point. She joined a government under intense pressure to cut back public spending, and she is widely respected for having had the guts to look for savings not where they were easiest but where they would hurt patients least – in her own words: "I always argued that before we set priorities in the sense of withholding treatment from those who need it, we should try to make healthcare much more effective and efficient". One of the areas she targeted was the price of generic medicines. It commenced with an average pricing scheme through legislation introduced in 1996. This was followed up eight years later by an agreement brokered between health insurance funds, pharmacists, generic medicines companies, and the government to reduce prices of generic medicines by a further 40% (including 'claw-back' of discounts).

Price, however, is not the only obstacle to bringing down drugs bills. The other major factor, which has received more attention in recent years, is the extent to which prescribers switch from branded drugs to take advantage of cheaper generics.

Making the switch

Here too the picture varies widely across Europe. Figures from the European Generics Association indicate that generics account for a very high proportion of all drugs prescribed in most central and eastern European countries – more than 85% in Poland. These countries have traditionally relied heavily on generics, many of which they produce themselves. They represent some of the poorer countries in the EU, where cancer patients are fighting to get access to cancer drugs such as Glivec [imatinib] or Herceptin [trastuzumab].

At the other end of the scale eight countries, including Italy, Spain and France, prescribe only between 3% and 13% of drugs as generics. In the middle come those western European countries that are actively pursuing policies to encourage the use of generic medicines. Denmark leads the way, with almost 65% of all prescriptions made out as generics, followed by the UK and the Netherlands, at close to 50%, and Germany and Sweden at around 40%.

A hypothetical exercise conducted by the Research Centre for Pharmaceutical Care and Pharmaco-economics at Leuven's Katholieke Universiteit in the Netherlands (Simoens and De Coster, 2006) tried to quantify the savings different countries could make by increased use of generics. For each country, they selected the ten branded originator medicines that accounted for the highest expenditure, and looked at what would happen if 95% of prescriptions for those active substances were made out to generics.

They estimated that, even at the current price of generics, there are savings to be made ranging from 21% in Poland to 48% in Denmark (47% in

"We are creatures of habit. It takes knowledge, pressure and guts to change the system"

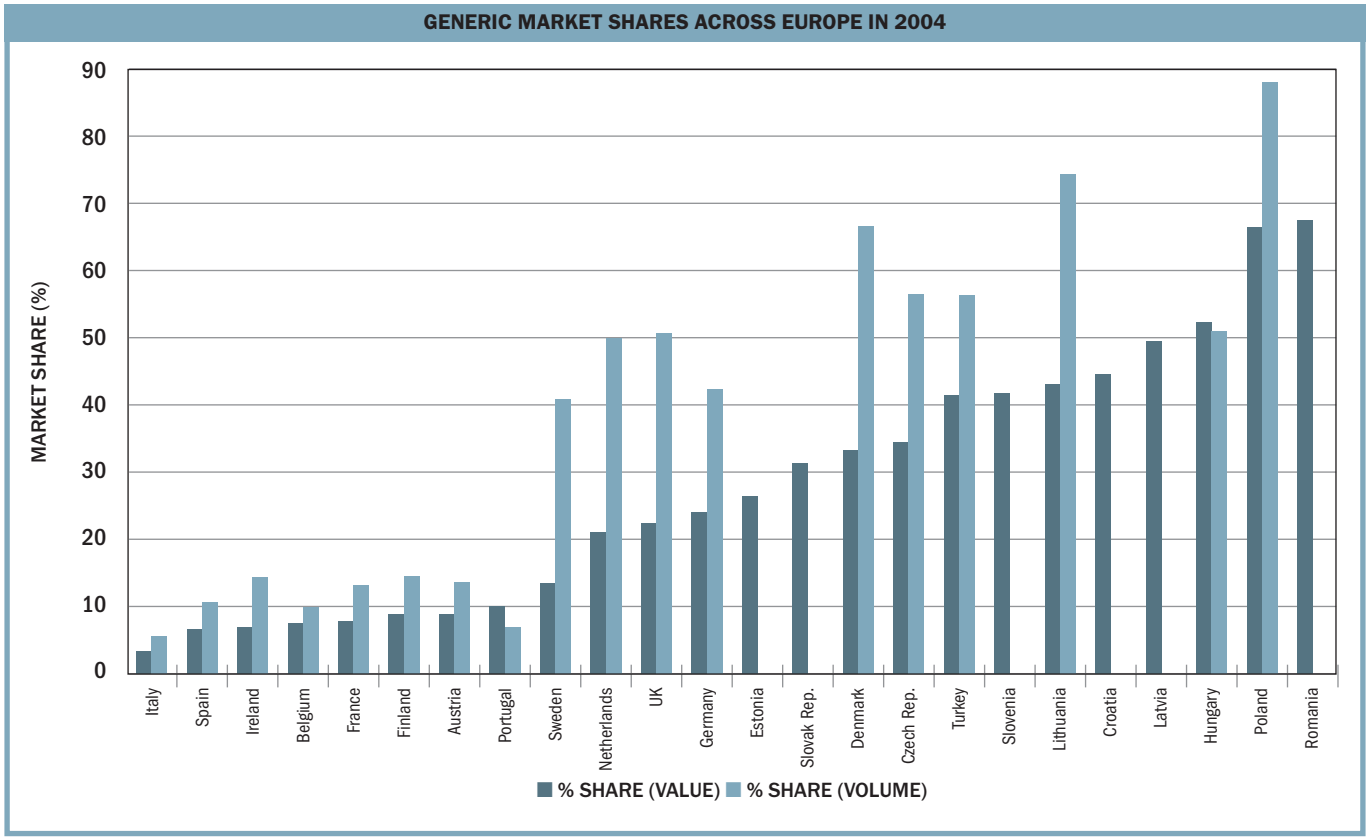
Eight countries, including Italy, Spain and France, prescribe only 3%–13% of drugs as generics

Germany, 42% in Portugal and Belgium, 41% in the Netherlands, 35% in France, 33% in Spain and the UK, 31% in Italy, 27% in Austria). Though the authors stress that the exercise was done for illustrative purposes only and failed to take into account many relevant factors including possible differences in form, strength or package size, it nonetheless indicates that substantial sums could be saved from national drugs bills by encouraging greater use of generics.

However, doctors are likely to stick with the drugs they know, and the ones that are most effectively marketed, unless they have sufficient information and incentives to persuade them to switch.

A variety of approaches are used to promote the use of generics. The first step is to make doctors aware of the cost implications of their decisions and of the generic alternatives. Some countries use prescribing software that substitutes the generic (international non-proprietary name – INN) of the drug for the branded name, with various rules on whether and when the doctor can insist on a particular brand.

Some countries set prescribing budgets at the level of the individual general practitioner (as in Ireland) or at the level of a family doctor practice or at local or regional levels (as in Germany, the UK and some counties in Sweden). These provide an incentive for GPs to bear costs in mind when making out a prescription, but only work if they are enforced. They can be unresponsive to changing circumstances and result in sudden alter-



Missed opportunities. Increasing the proportion of prescriptions made out to generic medicines could relieve the pressure on many of Europe's overstretched drugs budgets

Source: Internal survey, European Generic Medicines Association, 2004

"If a doctor prescribes a drug, he is spending public money, and must get the most health gain available"

ations in prescribing as the financial year ends and the budget runs low.

In reimbursement systems that include some element of patient co-payment, variations in charges are sometimes used to encourage patients to opt for a cheaper generic version.

Another option is to allow pharmacies to substitute generic versions when presented with a prescription for a branded product. In Denmark and Germany, for instance, this is mandatory and widely practised, although in Germany doctors have the power of veto. In the UK, the pharmacist only has discretion when a prescription has been made out for an INN. In Greece and Ireland, generic substitution is not permitted at all. Policy makers have to bear in mind how the dispensing fee to the pharmacist is calculated. If the fee is a percentage of the cost of the drug supplied, the pharmacist has an incentive to use a higher priced drug.

One approach being introduced increasingly in Europe is the promotion of prescribing guidelines, which encourage doctors to prescribe rationally and consistently according to a medicine's indications and the therapeutic needs of their patients. This should increase value for money, by cutting expenditure on drugs for which there is scant evidence of effectiveness. It also offers an opportunity to promote cheaper drugs among those that are medically interchangeable.

These measures do not always go down well with doctors. In Hungary, a recent law obliges all physicians to use a free downloadable software package when prescribing, showing the various options for each type of drug. Mihály Kökény, chair of the health committee of the Hungarian Parliament, says that this is part of a major overhaul of the Hungarian health system, which also includes a novel system for conducting negotiations about the price of generics over a publicly accessible Internet system.

"The minimum requirement is that the patient should always be informed that there are various options, 'I would like to offer you this and this, but there are other versions of that molecule'. The doctor must also put in writing in the patient notes that this information was given to the patient. If the doctors do not use the available generics they need to give a reason for this in the documentation, and this can be checked by the insurance.

Sanctions

"If the insurance can see that a doctor in most cases prescribes more expensive drugs, without giving an appropriate reason, the insurance has the right to introduce certain types of sanction, such as a fine for the doctor.

"The doctors are not happy. But everybody should understand, if a doctor makes a prescription, he is spending public money, and it is a must to obtain the maximum health gain available."

Kökény blames heavy drug marketing for some of the resistance, but he believes that raising awareness about the reasons for these changes and reassuring doctors about the strict quality control measures now applied to generics will help overcome it. The sanctions, he says, will not come into force for many months, which should give time for doctors to get used to the system.

There are, however, good reasons for doctors – and patients – to be suspicious of prescribing guidelines, which are sometimes used not to ensure the best value for money, but to ration healthcare. When a doctor is asked to prescribe a non-branded version of mesalazine or amoxycillin, they are being asked to choose a cheaper version of an identical molecule. However, guidelines increasingly consider classes of drugs as a whole, (e.g. anticoagulants or cholesterol-lowering drugs) and pressure doctors to use a cheaper drug, which may be similar but not identical.

In this case there may be a number of reasons why a doctor will argue that a more expensive drug is required – maybe the side-effect profile is different, or the mode of administration means the patient is more likely to comply with one drug rather than another. If doctors are prevented from prescribing a drug that they have good reason to believe is the most appropriate for their patient, this constitutes rationing. It is important to be transparent about the distinction between this and promoting generic prescribing.

Kanavos and his colleagues argue that significant savings can be made by changes to pricing, distribution and use of generics, without affecting patient care. Some form of rationing is also likely prove necessary. But if governments seek to deny clinically effective innovative drugs to patients in need, without taking every step they can to save money in ways that don't affect patient care, they should expect resistance from doctors, patients and the public.

You need to divorce to become good friends

Peter McIntyre

Hernán Cortés-Funes scored a victory for medical oncology when he helped convince Spain to become the first European country to grant the discipline specialist status. A bitter split with radiotherapy dating from that time has now given way to mutual respect, and the big challenge today is how to get specialists and hospitals working together in an effective cancer network.

As gap years go, 1967 was not typical for the young Argentine medical graduate who found his way to Europe. This was the 'summer of love' when thousands of students postponed their careers for hedonism and the first stirrings of revolt. Hernán Cortés-Funes did not fit the mould. He graduated from medical school in Buenos Aires at the tender age of 21, with ambitions. "I was totally convinced that I wanted to be a surgeon," he says, with a shake of the head at the follies of youth.

"I decided to travel to Europe, not as a tourist but to do some complementary medical training."

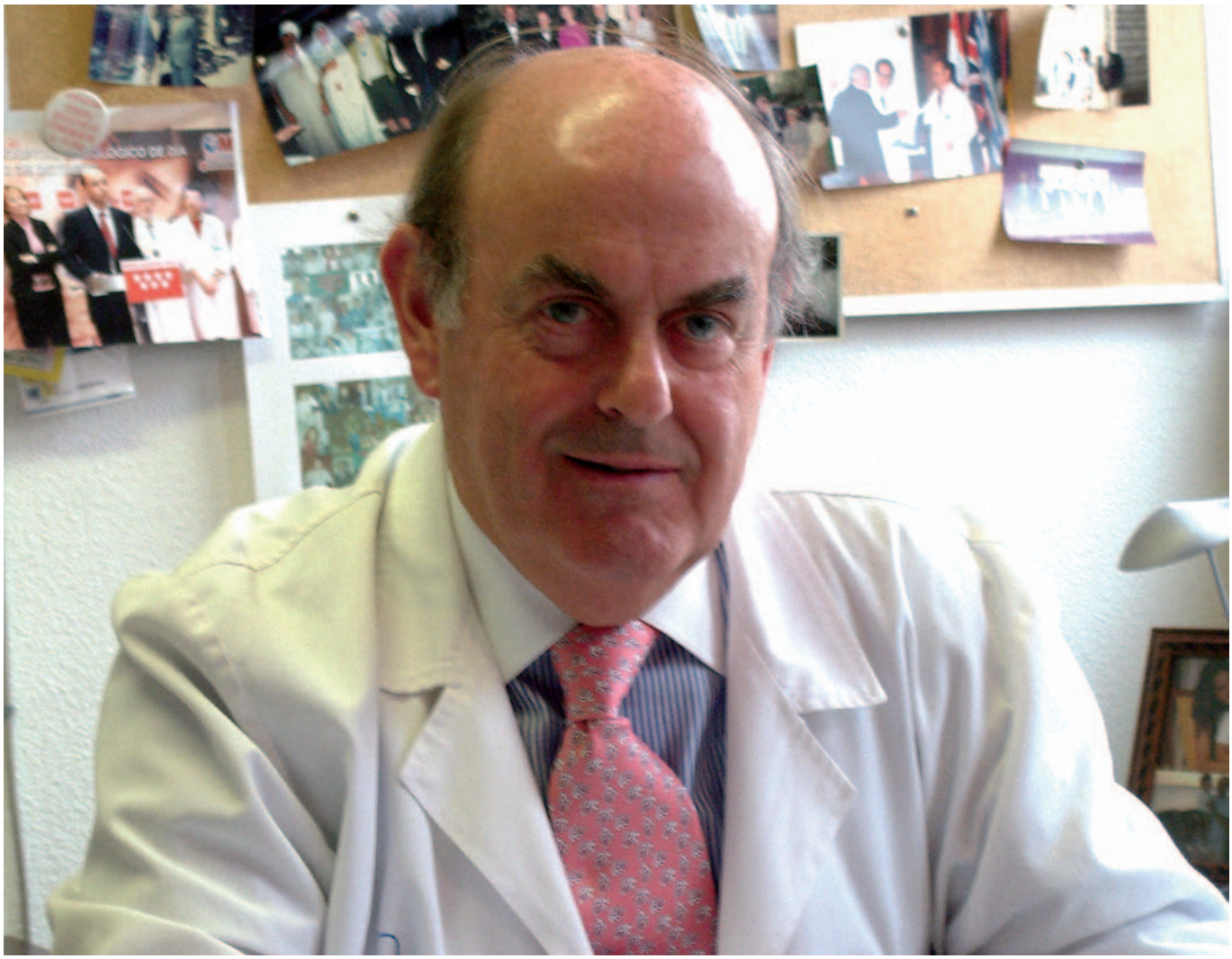
He chose Spain, for its affinity with Latin America, and obtained a scholarship at the Fundación Jimenéz Diaz in Madrid, a well-known but traditional hospital with good departments. He found himself working alongside one of the first oncologists in Spain, at the beginning of a drive to improve training in internal medicine.

Today, 40 years on, he is still in Madrid, from where he has played a significant role in the development of medical oncology across Europe. For more than half that time he has directed clinical oncology at the Hospital Universitario 12 de Octubre. Over the next few years he will – he hopes – complete the process of establishing this highly regarded teaching specialty in a new building, while helping to develop Madrid's cancer networks.

What persuaded Cortés-Funes to stay at the Fundación Jimenéz Diaz to do his PhD was his growing interest in the large number of patients with malignant lymphomas.

"Hodgkin's disease was becoming the second curable cancer after leukaemia. In a little more than a year I had the opportunity to study more than 100 Hodgkin's disease patients. There were several new treatments for advanced stages, such as IV procarbazine developed by Roche, which probably today nobody knows about. We treated patients with that experimental drug, and that was the first trial I ever did in my life."

He completed his thesis in 1970, still only 25, in a hurry to return to Argentina and resume his career in surgery. However, he met and married his first wife, Fabiola, while the Jimenéz Diaz offered him a full-time post in its small cancer unit. The offer was too good to turn down.



"We thought for many years that our goal to was cure a cancer patient by killing the last cancer cells"

In the early 1970s he met Gianni Bonadonna on a visit to Madrid. "He wrote down for me on a small piece of paper a new regime that he called ABVD (adriamycin, bleomycin, vinblastine and darcarbazine) – four totally different drugs with a complementary effect. He told me something incredible and visionary, that this combination was much less toxic than MOPP (mechlorethamine, vincristine [Oncovin] prednisone and procarbazine – the standard regime used at that time), and could be equally effective. ABVD became, after comparative studies, the new standard combination for Hodgkin's disease."

Cortés-Funes had learned something about the ability of European centres to make significant contributions. "This has happened a lot in medical history. The [US] National Cancer Institute has the power of publication, but Europe has a lot of new ideas. Adjuvant breast cancer therapy CMF was also developed by Bonadonna. Americans found it incredible that one man could have such expertise in two different fields of oncology."

"We worried that the training in medical oncology was totally different from one country to another"

In 1976, Cortés-Funes presented results from Madrid on 20 patients treated with ABVD at the American Society for Clinical Oncology (ASCO) meeting. In the same year he went to the National Cancer Institute in the US, where he worked at the Cancer Therapy Evaluation Program.

"Medical oncology was handling a new weapon. Chemotherapy was very successful in leukaemia and we thought for many years that our goal to was cure a cancer patient by killing the last cancer cells. Today that would be seen as a very poor concept."

Under director Franco Muggia, he learned how to conduct clinical research in co-operative groups at more than one centre, and about the role of the pharmaceutical industry in developing new drugs.

At that moment, the most exciting was cisplatin, offering a cure for testicular cancer. Wherever he went next, Cortés-Funes wanted to offer these new treatments. There seemed few prospects in medical oncology in Argentina. In Spain, however, 30 new hospitals were being built, including La Paz in northern Madrid, the Vall d'Hebron in Barcelona, where José Baselga is now based, and Hospital Universitario 12 de Octubre. It was here he arrived as attending physician in oncology in 1978, and this was to become his home for the next 30 years.

A CHANCE FOR CHANGE

The Hospital Universitario 12 de Octubre is a teaching hospital within a social security system providing universal healthcare in Spain. As a new hospital, it provided an opportunity to change Spain's rather old-fashioned approach.

At that time, oncology meant radiotherapy. However, in the year it took the machines to arrive, Cortés-Funes took advantage of the 27 beds and matching staff to develop medical oncology. He got in touch with the European Organisation for Research and Treatment of Cancer (EORTC) and made contact with the few nascent medical oncology groups in Europe that were presenting research at ASCO, working within the EORTC to develop clinical research in Europe and making direct links with each other. These included the Istituto Nazionale Tumori in Milan, the Regina Elena in Rome, the Institut Gustave-Roussy and the Institut du Cancérologie in Villejuif, Paris, the Jules Bordet in Brussels, the Royal Marsden and Christie hospitals in London and Manchester, and centres in the Netherlands and Switzerland.

The specialty in Europe was rapidly finding its feet. Georges Mathé founded the Société de Médicine Interne Cancérologique at the Gustave-Roussy in 1975, which by 1980 had grown to become the European Society for Medical Oncology (ESMO). Cortés-Funes joined its board in 1978, as the first Spanish representative.

In 1980 Cortés-Funes with Marcel Rozencweig, who headed the investigational drug section of the Jules Bordet, organised one of the first European new drugs meetings, in Madrid, which attracted many of the leading European specialists. Fifteen years later, he would go on to launch the European Spring Oncology Conference, which is devoted to presenting and analysing the latest data from clinical research into new anticancer agents, and is held in alternate years in Marbella on the Costa del Sol.

Cortés-Funes became increasingly involved in the development of ESMO, and from 1989 to 1991 was its president. His key contribution, with Bob Pinedo from Amsterdam, was to develop the European certification of medical oncology. "We worried that the training in medical oncology was totally different from one country to another. We were lucky in Spain, because in the big political changes in democracy, we achieved official recognition of medical oncology as a different speciality from radiotherapy. We were the first country in Europe to do that.

"A lot of European institutions copied this. ESMO decided to apply this medical oncology certification for ESMO members. Pierre Alberto from Geneva developed the examination and a

With children Jaime, aged 2 and Alejandra, aged 5, boating in Marbella, summer 2006

"They would say, 'this looks promising' and everyone would try it. It was a small club"

Board. This was a totally voluntary academic certification, with academic power, but everybody wanted to have it. Today more than 500 medical oncologists have been certified by ESMO."

In those days, clinical research teams in Europe regularly shared findings about experimental drugs, particularly through the EORTC early clinical trials group.

"Each centre developed their own phase I trials, receiving drugs from many sources. Then they would say 'this looks promising', and everyone would try it. It was a small club. When the big laboratories and pharmaceutical industry started producing drugs and offering them to different people, then came competition between the units.

Today, tumour-orientated research has been globalised and the pharmaceutical industry has a much stronger hand. However, Cortés-Funes believes the relationship is mostly positive.

"Our objective in developing a drug is trying to find something active. The philosophy of the pharmaceutical industry is to develop a drug that will give profit. That is why they try to develop a drug with a niche indication, where no other treatment is available. Sometimes this is not the way that we would do it, but they produce a lot of new ideas.

"We cannot survive without them and they cannot survive without us. They have the power and the money and they have the drugs and you have to accept that. Both sides have an interest in the relationship."

Developing a separate identity for medical oncology inevitably led to tensions. "We felt that a pure medical oncologist is an internist who can

Developing a separate identity for medical oncology inevitably led to tensions

treat a cancer patient and develop chemotherapy and also treat leukaemia and lymphomas. In some places, oncology was run by radiotherapists, as it still is in Scandinavian countries. A good haematologist can become a medical oncologist, and in some countries like Germany and Austria the haematologists took on the role of oncologist and started treating solid tumours. But to become a medical oncologist it is very important to first be a good internal medicine specialist."

In Cortés-Funes' own hospital medical oncology split from radiotherapy. "I cut my relation with radiotherapy because after my growth years in the hospital, we were not compatible."

Cortés-Funes says that today, rivalry has been replaced by mutual respect. "Radiotherapy has developed very well. They have new machines and new techniques and new technology, and today radiotherapy could replace surgery in a lot of situations. Radiotherapy and chemotherapy is the future of cure for a lot of tumours.

"Somebody told me it is like a when two people are married. You need to have a divorce to become good friends. That has happened to us because we needed each other."

Something similar seems to be taking place between ESMO and the Federation of European Cancer Societies (FECS) – if not a divorce then at least separate bedrooms. Cortés-Funes was involved in building FECS alongside ESMO, and was its president from 1987 to 1989.

"We decided as Europeans to have a big cancer meeting in Europe in order for it not to be necessary to present our data at the ASCO meting in America. We created FECS and invited radiotherapists, surgical oncologists, pathologists, paediatricians and basic researchers. Together we created and organised the European Clinical Oncology Conference (ECCO). The first one was chaired by Umberto Veronesi, another outstanding Italian visionary for oncology. We felt that it was important to regroup and to create our European ASCO."

Cortés-Funes believes that the ECCO project was ultimately doomed. "It was totally impossible to compete with ASCO. It was hard to accept this, but I can do so after many years. The ECCO Project was a very good project, but the really important scientific oncology meeting in Europe was ESMO."

Until now, ECCO and ESMO meetings have been held on alternate years. The next ECCO meeting (ECCO 14) takes place in Barcelona in September 2007, while the next ESMO meeting is a year later in Stockholm. However, from 2009 both meetings are due to take place in the same year and will in effect be in competition.

Moving ahead

Medical oncology at Hospital Universitario 12 de Octubre is housed on the second floor of the maternity hospital – an interesting sociological marker, since it contrasts the way that oncology has grown with the falling birth rate in Spain, which made room available. The hospital is being largely rebuilt, and medical oncology will have a new home within two years. Cortés-Funes (now 61) plans to stay to see the new department bedded in.

"I am planning two or three years, probably, to reorganise this department with other people. It has happened in the past that people retire and do not leave anything behind, and that would be very sad. But I want to be useful. I don't want to be kept here because in the past I was important."

There are 20 hospitals in Madrid within the social security system, and during 2007 10 more will open. Madrid has recently made a priority of investing in the Metro and healthcare. (As an interesting note on health economics – the cost of building a new hospital is the same as building one kilometre of underground railway.)

Although the new hospital will not officially be a cancer centre, specialists at the hospital are working as a team, and hospitals in South Madrid are developing the OncoSur Madrid cooperative group network. "We are a reference hospital and we

are coordinating a group of six hospitals in South Madrid, with four more to open this year. The network will cover two million inhabitants and 10,000 new cancer patients a year.

"We are working to have common standard protocols, because how they are treated depends on which door a patient comes in. A breast cancer patient who comes from general surgery is treated one way, and from gynaecology another. We are creating guidelines so that a patient is not sent to medical oncology only in a metastatic situation or after an operation for adjuvant therapy. They should all know that a tumour larger than two centimetres must be treated with chemotherapy as the primary treatment from the beginning. It is very difficult to do that in a hospital or a group of hospitals. But we are working on that project and I am very involved."

Keeping up to date with new treatments is an increasing challenge. Chemotherapy drugs have been in use for many years – in some cases for decades. However, Cortés-Funes says the new and upcoming targeted biological therapies are changing the rules for treatment.

"It is amazing and it is extremely complex to be involved with everything. We have a medical meeting inside our unit, and I learn every day from my people. I attend the new drug meetings and pick up ideas from that."

So far in most regions of Spain the social security system has met the cost of new drugs, but this too will become an increasing challenge. He cites the new renal cancer drug sunitinib [Sutent], the first drug to be granted conditional (early) approval by the European Medicines Agency, which offers new hope for patients, but costs €3,500–4,000 a month. "We could treat patients from the very beginning in this hospital, through compassionate use. Renal cancer is not very common and the social security is paying it, but I don't know for how long. There is the same problem with Herceptin [trastuzumab] and with Avastin [bevacizumab]. There will be a problem."

Despite these rapid developments, Cortés-Funes says that cancer treatment must never be only about drugs. "I think the really new advances will become stronger, but I hope that people will understand that to treat a cancer patient is very complicated. It not just about drug-related treatment. It is about early diagnosis and very good early orientation of the disease. Mutilating surgery will disappear and abdominal and thoracic surgery will become laparoscopic. Conservative treatment of the organ will become more frequent. Drugs will be used very early – chemotherapy and non-chemotherapy drugs – and the future will be in their combination. You will give a patient comprehensive treatment with radiotherapy plus chemotherapy, and surgery for diagnosis, restaging and second-look rescue surgery.

"Cancer is a genetic disease, and the genetics will become the basis of the treatment, although genetic treatment will not come at the present time. However, the genetic knowledge of the disease is very, very important." His unit recently joined the MINDACT trial to see whether the genetic profile of a breast tumour is more precise in guiding treatment than the clinical profile.

Although Cortés-Funes still has good links with oncology in Argentina, he is today thoroughly Spanish. He has three children by his first marriage. One is a journalist, the other is a clinical psychologist in his own oncology department, and the third is still at university. His first wife, Fabiola, was killed in a motor accident 13 years ago. Cortés-Funes remarried six years ago and he and his wife Blanca have two young children.

He is proud of the role that Spanish oncology plays in an evolving Europe, the credit for which must be partly his – the Spanish Society for Medical Oncology (SEOM), the Spanish Society for Cancer Research (ASEICA), the SOLTI cooperative research group, and the Madrid Breast Cancer Conference all form part of his legacy. "We are not in a leading position – the Anglo Saxon power is still running everything – but Spain is very well recognised in Europe, and participates in all the most important areas of oncology. We are a young country – we have the opportunity if we improve our politicians a little."

"We are standardising protocols, because how patients are treated depends on which door they come in"

What they never taught you at medical school

New curriculum offers online information on helping with distress, depression and more

➜ Marc Beishon

Interest in addressing cancer patients' emotional and psychological needs is far outstripping access to training all over the world. Now the International Psycho-Oncology Society and the European School of Oncology have clubbed together to fill the gap.

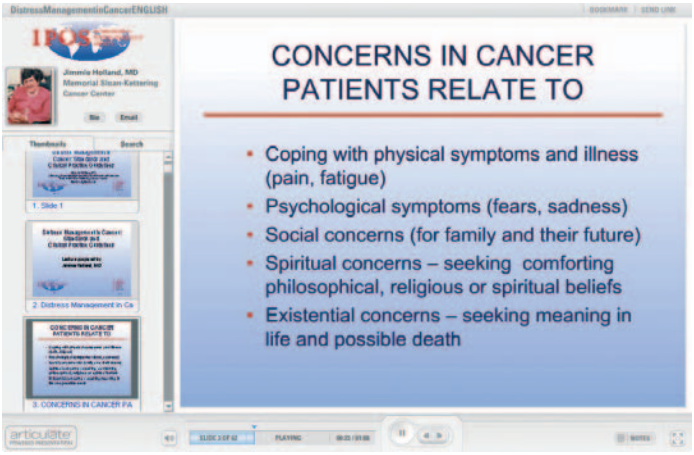
Psycho-oncology has been around for 30 years, but it is not yet established as a formal oncology or psychiatric speciality to the extent that standard, national training programmes exist, even in developed countries. While most major cancer centres do have a psycho-oncology unit – although not necessarily termed as such – there is great variation in the resources and approaches to hand. General hospitals and other parts of healthcare systems may have little to offer.

As Luigi Grassi, president of the International Psycho-Oncology Society (IPOS), comments, it is a fast moving discipline that is proving difficult to 'pin down'. Some consider it a true oncology specialty, but others see it as classical 'consultation-liaison' psychiatry (now known also as psychosomatic medicine – the interface between other medical specialties and psychiatry).

Then there is the wide spectrum of those other specialties it involves. Apart from oncology and psychiatry, there is of course clinical psychology, other social sciences and nursing, and general and palliative medicine.

As Grassi, whose 'day job' is professor of psychiatry at the University of Ferrara, Italy, adds, today's psycho-oncology now extends to all aspects of cancer, from prevention (such as screening campaigns and changing lifestyles), to a wide spectrum of psychosocial morbidity during diagnosis and treatment, to quality of life and end-of-life care, plus topics such as patient–doctor communications. "We have seen a tremendous increase in psycho-oncology research and training programmes in recent years, and it has become a model for intervening in other severe conditions such as heart disease and multiple sclerosis," he says. "But while there are some special fellowships and masters courses in psycho-oncology, no country yet has a specific national residency programme."

One of the goals of IPOS, says Grassi, is to encourage the development of core psycho-oncology curricula at a national level, building on current provision at places such as Ferrara and several other Italian universities, where medical students receive 20 hours training in psycho-oncology as part of their psychiatry module, with workshops and training for oncology and surgical residents.



Your window on psycho-oncology. This online lecture on distress management was prepared by Jimmie Holland, one of the pioneers of psycho-oncology. Holland narrates the English-language version, but it can also be listened to in French, German Hungarian, Italian and Spanish, with Japanese, Portuguese, Arabic and Chinese versions set to come online in the coming year

Italy also has at least four masters programmes in psycho-oncology, and there are training curricula in other countries. In Germany, for instance, training is organised by the country's two psycho-oncology societies, and is supported by charitable donations; 900 professionals have been put through basic and advanced courses in 10 years. The US – where psycho-oncology started – now has many and varied postgraduate training opportunities.

But while IPOS continues to lobby for such initiatives to be formally and widely supported, via its network of country societies and members, the organisation has decided not to wait, and recently it launched its own online core curriculum in psycho-oncology. The aim is to bring the latest knowledge from top psycho-oncology experts to a worldwide audience, and it has the obvious benefit of bringing training to healthcare professionals in countries and regions where national provision may not be available for some time.

Funded initially as a five-year project by the European School of Oncology (ESO), the IPOS programme is billed as 'a core curriculum in psychosocial aspects of cancer care'. It comprises a set of online lectures written by experts and delivered by narration and slides. The first set of five lectures went online in 2006, and another six are in preparation.

The first lectures cover some of the most pressing psycho-oncology topics, such as distress management, depression, and communication and interpersonal skills in cancer care. According to Christoffer Johansen, immediate past-president of IPOS and head of psychosocial cancer research at the Institute of Cancer Epidemiology in Denmark, the expert contributors who have both written and narrated the lectures are a real pull – in particular, he mentions Jimmie Holland of the Memorial Sloan-Kettering Cancer Center in New York, author of the distress management lecture, who is the pioneer of psycho-oncology and founding president of IPOS. Says Johansen: "We may have selected an old fashioned format – the lecture – but it's a model that can deliver a lot of information in a short time, in a format accessible to everyone."

Grassi, who has been involved in drawing together the content, says there are several important aspects of the programme. The most obvious is that each lecture has been translated into several languages from English. So far, most of the lectures are available in English, French, German, Italian, Spanish and Hungarian, and Grassi says, "We have a Japanese version coming soon and people are working on Portuguese, Arabic and Chinese too – just imagine how many more professionals that can involve."

While there are other online materials, in particular a number of presentations on the website of the American Psychosocial Oncology Society (APOS), Grassi emphasises that the IPOS curriculum has been designed as an integrated set of lectures with a commitment to update the material as developments take place, such as the

"It's a model that can deliver a lot of information in a short time, in a format accessible to everyone"

introduction of new drug treatments. Furthermore, each language translation has been assessed for quality and cultural factors by experts nominated by ESO. "Other lectures on the web may just be presentations taken from meetings, and are simply not part of an updatable curriculum," he points out.

Each lecture has an online evaluation form, from which IPOS has gathered an impressive volume of feedback. "We have had more than a thousand responses so far, and the indications are that the quality of the lectures is high," says Johansen. "However, we do need to put more thought into how people fill in the evaluation, as it is taking too long at present."

Of 995 evaluations received as of last October, the biggest professional grouping was 175 psychologists (21%), followed by patient advocates (11%), nurses (6%), and oncologists (4%). Quite a few other professions also took part, such as counsellor, psychiatrist, grief therapist and social worker. But there seems to be more information that can be gleaned about who wants the training, as 345 (42%) were 'others'. Of the 995 respondents, 55% worked in a clinical setting, 37% in 'other' settings, 7% in science and 5% in industry.

Maggie Watson, consultant clinical psychologist at the Royal Marsden Hospital in the UK, and an IPOS board member, feels the curriculum has achieved its aim to provide desktop teaching, and "consolidates current opinion into a single lecture for each topic, providing important overviews." She adds, "Many different professionals can access information on a discipline that is essentially multi-disciplinary" – which certainly seems to be the case judging by the mix of participants so far.

A core aim is to increase access to professionals worldwide, especially those in developing countries. And as Johansen adds, the curriculum could also play an important part in helping to reach decision-makers who may be able to unlock more funds for vital psycho-oncology services.

Awareness around this issue does seem to be growing. IPOS had a record attendance of 1,350 people from 58 countries at its world congress in Venice last year, and it is busy forging links and holding joint symposia with other oncology societies. Johansen says that, thanks to IPOS involvement, the World Health Organization is including psychosocial aspects of care in its cancer control work for the first time (see *Cancer control: knowledge into action, WHO guide for effective programmes*, at www.who.int).

"If we are going to get psycho-oncology onto the everyday agenda of hospitals, we have to get to the heart of the political issues involved in changing the treatment protocols for patients," says Johansen – not least the world population of 25 million cancer survivors and rising that health policy makers now need to take into account.

THE CORE CURRICULUM

The lectures presently available on the IPOS and ESO websites (www.ipos-society.org and www.cancerworld.org) are:

- Communication and interpersonal skills
- Anxiety and adjustment
- Distress management
- Depression and depressive disorders
- Psychosocial assessment

This year, the following topics will be added:

- Family and partner issues
- Palliative care
- Grief and bereavement
- Psychological intervention
- Psycho-pharmacology
- Ethical aspects

Does a new model improve decisions about mismatch-repair genetic testing and Lynch syndrome identification?

Dimitrios Roukos, Michael Fatouros, Epameinondas Tsianos, Angelos Kappas

A new predictive model developed by clinical geneticists in Edinburgh offers a useful tool for physicians making decisions relating to genetic testing, although its clinical application in patients with colorectal cancer for the identification of Lynch syndrome requires caution.

Hereditary nonpolyposis colorectal cancer, also called Lynch syndrome, is caused by a mutation in one of the DNA mismatch-repair (MMR) genes.[1] Pretreatment identification of these carriers among patients with colorectal cancer is critical because it may alter surgical and adjuvant therapeutic decisions. Instead of segmental resection, patients with Lynch syndrome may benefit from prophylactic surgery including total colectomy or proctocolectomy (and hysterectomy with salpingo-oophorectomy for women who have completed childbearing).[2] Ideally, genetic testing of all at-risk patients could identify mutation carriers. The low rate of Lynch syndrome among patients diagnosed with colorectal cancer (2%)[3] and the high costs of testing (about US$3,000 per patient) have led to the development of algorithms based on family history and clinical and pathologic criteria. Currently, based on Bethesda guidelines, tumour immunohistochemistry and microsatellite instability (MSI) are recommended as prescreening tests; patients with abnormal immunohistochemistry or high MSI in tumour analysis are considered for mutational analysis in MMR genes.[4] Even this strategy combining clinical criteria and prescreening misses an appreciable number of mutation carriers, however.[3]

Based on a prospective study in Scotland (see opposite), Barnetson et al. provide a new model for identifying carriers of mutations in the MMR genes *MLH1, MSH2* and *MSH6*. The innovative features of their investigation include population-based recruitment without preselection according to family history or a prescreening with immunohistochemistry or MSI before genetic testing, and a validation approach. This strategy allowed the development of a two-part model predictive of Lynch syndrome, thereby reducing the likelihood of bias. Stage 1 of the model incorporated only clinical variables with significant predictive value: age, sex, location of the tumour, presence of synchronous or metachronous tumours and first-degree relative with colorectal or endometrial cancer. Combining this first stage with immunohistochemistry at stage 2 indicated, with a specificity of 80%, that only 3.4% of patients with colorectal cancer should have mutation testing. This is an excellent finding because immunohistochemistry for MLH1, MSH2, MSH6 and PMS2 protein expression is highly sensitive and associated with several advantages over MSI analysis; it is easily performed, inexpensive, does not require a molecular laboratory and as gene-specific prescreening allows mutational analysis, if abnormal, only for the specific gene.[5] Thus, the overall costs can be reduced substantially. The model is available on the Internet (http://www1.hgu.mrc.ac.uk/Softdata/MMRpredict.php) and is easy to use, helping physicians in making genetic testing decisions for various thresholds of likelihood that a given

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patient with colon cancer has a mutation.

The application of this model in clinical practice requires caution, however, because of several study weaknesses. There were only 38 mutation carriers, and participants were under 55 years of age. A recent study, which left out probands and considered only mutation-positive relatives, showed the median age of onset of colorectal cancer to be 61.2 years.[6] Furthermore, mutation in the *PMS2* gene (although admittedly controversial as a cause of Lynch syndrome) was not investigated by Barnetson et al., and the interpretation of many mutations of unknown clinical significance is challenging.

Strategies for identification of healthy carriers and carrier patients are extremely complicated and have not been standardised. It is our professional challenge to provide individualised and efficient management of Lynch syndrome.

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Synopsis

RA Barnetson, A Tenesa, SM Farrington, et al. (2006) **Identification and survival of carriers of mutations in DNA mismatch-repair genes in colon cancer.** *N Engl J Med 354:2751–2763*

Background. It is important to identify any mutations in germline mismatch-repair (MMR) genes at the time of diagnosis of colorectal cancer, as this affects management. Pragmatic and cost constraints often lead to 'prescreening' for microsatellite instability (MSI) or DNA MMR proteins, or both, being performed to select patients for genotyping, but this can cause mutations in DNA MMR genes to be missed.

Objective. To undertake mutational analysis of germline DNA MMR genes without considering the family history or results of tumour testing among cases of early-onset colorectal cancer in order to construct a predictive model.

Design and intervention. In a prospective, population-based series, all patients in Scotland with early-onset colorectal cancer diagnosed between February 1999 and July 2003 were identified and invited to participate within a few weeks after diagnosis. Family history was established and tumour and blood samples were taken. Tumour samples were analysed by immunohistochemistry and tests for MSI, and staged using Tumour–Node–Metastasis criteria and Dukes' classification. Germline DNA from leukocytes was examined for *MLH1, MSH2* and *MSH6* mutations. A two-stage model to detect the presence of germline mutations of DNA MMR genes was constructed using logistic regression. Stage 1 used exclusively clinical variables to identify subgroups more likely to include carriers, and stage 2 involved MSI and immunohistochemistry testing. The model was validated in a separate retrospective series of patients.

Outcome measure. Survival was analysed according to genotype using Kaplan–Meier analysis.

Results. Among the 870 patients originally studied, 38 mutations were identified (4%): 15 mutations in *MLH1*, 16 in *MSH2* and 7 in *MSH6*. Carrier frequencies were higher in men than in women (6% vs 3%; $P<0.04$). Most carriers would have been identified using Bethesda criteria, but only 42% had characteristics concordant with the Amsterdam criteria. Clinical variables that were predictive of mutational status were having a first-degree relative with colorectal cancer ($P<0.001$) or endometrial cancer ($P=0.006$), age ($P<0.001$), sex ($P=0.03$), tumour location ($P<0.001$), and the presence of synchronous or metachronous tumours ($P=0.001$). Addition of immunohistochemistry in stage 2 of the model provided a sensitivity of 62% (95% CI 0.46–0.77%) and a positive predictive value of 80% (95% CI 0.66–0.95%). Addition of immunostaining of biopsy specimens in the 17% of the population enriched for mutation carriers indicated a requirement for mutational analysis in only 3.4% of all cases. In the validation group of 155 patients, mutational analysis of germline DNA identified 19 mutations in *MLH1*, 13 in *MSH2* and 3 in *MSH6* (35 mutations overall; 23%). Survival did not differ between carriers and noncarriers over 2,938 patient-years of follow-up.

Conclusion. The authors suggest that this model would be a highly efficient means of identifying patients who should receive mutation testing.

*Acknowledgement:*The synopsis was written by Petra Roberts, Associate Editor, *Nature Clinical Practice*.

Is breast conservation a reasonable option for women with BRCA-associated breast cancer?

Mark Robson

A recent study has shown that women with *BRCA* mutations are as likely to achieve local control with breast-conserving treatment as women without mutations, but have increased long-term risk of ipsilateral and contralateral breast cancer.

When considering *BRCA1/2* testing, patients and physicians usually concentrate on defining and managing future cancer risks, but what about the woman with recently diagnosed breast cancer? Should germline *BRCA* status be taken into account when decisions are being made about her local and systemic treatment? Does the presence of a germline mutation have enough of an impact on treatment choices that peridiagnostic testing should be offered to women of unknown mutation status who are at a significant risk for these mutations, such as young women with 'triple-negative' disease? The paper by Pierce et al. (see opposite) bears strongly upon these questions.

Ten years after the discovery of *BRCA1* and *BRCA2*, breast-conservation therapy (BCT) for *BRCA*-associated breast cancer (BABC) remains controversial.[1] Studies examining the question are limited by ascertainment biases, small size and relatively short follow-up. Despite these limitations, most reports broadly agree that the short-term (five-year) risk of an in-breast tumour recurrence (IBTR) event after breast conservation for BABC is 12–15%, and that the actuarial risk over this time frame is not significantly greater than that for women without mutations; however, there are reports of higher rates of metachronous ipsilateral cancer with longer follow-up. Groups in the US and the Netherlands described actuarial risks as high as 49% at 12–15 years.[2,3] These alarming estimates might not be robust given the small number of patients at risk for more than 10 years in these studies, and it is reassuring that larger series from North America[4] and the Netherlands[5] confirm the findings of Pierce et al. – a 12% ipsilateral risk at 10 years. Even so, longer follow-up may yet reveal a greater risk. In the report by Pierce et al., for example, the rate of IBTR in carriers and non-carriers appeared to separate after 10 years of follow-up, and rose to 24% at 15 years in carriers. This increase is likely to reflect an ongoing risk of developing second ipsilateral primary cancers, a risk that may be deferred, but not eliminated, by adjuvant radiation.

Is breast conservation, therefore, appropriate for women with *BRCA* mutations? It seems that BABC and non-hereditary breast cancer are equally likely to be sterilised by local excision and adjuvant radiotherapy. So, for treatment of the established breast cancer, BCT is indeed a reasonable option; however, the significant risk of contralateral cancer and late ipsilateral metachronous primaries is not completely ameliorated by oophorectomy or tamoxifen. The substantial

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contralateral cancer risk, in particular, could lead carriers who are otherwise candidates for BCT to choose to undergo bilateral mastectomy to reduce these risks, recognising that the impact on survival is uncertain. Since adjuvant radiation may compromise reconstruction options, early genetic testing could benefit women who would consider preventive mastectomy if they were shown to carry a mutation, even if they may require postmastectomy radiotherapy on other grounds such as extent of nodal involvement. Successful communication of genetic prognostic information in the peridiagnostic setting remains a critical challenge, because of the psychological risks of 'information overload'.

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Synopsis

LJ Pierce, AM Levin, TR Rebbeck et al. (2006) **Ten-year multi-institutional results of breast-conserving surgery and radiotherapy in BRCA1/2-associated stage I/II breast cancer.** *J Clin Oncol 24:2437–2443*

Background. There is no consensus on the usefulness of a breast-conservation approach for *BRCA1/2* mutation carriers

Objective. To compare the outcomes of treatment with breast-conservation therapy (BCT) and radiotherapy in *BRCA1/2* mutation carriers with breast cancer compared with matched controls with sporadic breast cancer. The potential impact of oophorectomy and tamoxifen on rates of in-breast tumour recurrence (IBTR) and the development of contralateral breast cancer (CBC) was also studied.

Design and intervention. In this retrospective cohort study conducted in 11 institutions in the US, Canada and Israel, women with deleterious germline *BRCA1/2* mutations treated with BCT for a first primary breast cancer (stage I/II) were matched by age (within 2 years) and date of diagnosis (within 6 months) to controls with sporadic breast cancer (stage I/II). Patients who had a low probability of having a detectable mutation in either gene (<5%) were defined as having sporadic disease. Clinical data were retrieved through record review.

Outcome measures. Rates of IBTR and CBC were assessed.

Results. A total of 160 women with a deleterious germline *BRCA1/2* mutation and 445 controls were followed for median observation times of 7.9 and 6.7 years, respectively. No significant difference was found between carriers and controls for IBTR: 10-year and 15-year estimates were 12% (95% CI 9–15%) and 24% (95% CI 17–33%) for carriers and 9% (95% CI 7–10%) and 17% (95% CI 12–21%) for controls, respectively (hazard ratio [HR] 1.37, P=0.19). On multivariate analysis, excluding carriers who had undergone oophorectomy, *BRCA1/2* mutation status was an independent predictor of IBTR (HR 1.9; P=0.04). No significant difference was found between carriers who had undergone oophorectomy and sporadic controls for incidence of IBTR (P=0.37). Rates of CBC were greater in carriers versus controls: 10-year and 15-year estimates were 26% (95% CI 22–30%) and 39% (95% CI 31–47%) for carriers and 3% (95% CI 2–4%) and 7% (95% CI 5–10%) for controls, respectively (HR 9.57; P<0.0001). In mutation carriers who had not undergone oophorectomy, there were no local failures following tamoxifen treatment, in comparison with rates of 8%, 17% and 31% at 5, 10 and 15 years, respectively, without tamoxifen treatment. Tamoxifen use also reduced risk of CBCs in mutation carriers (HR 0.31; P=0.05).

Conclusion. The authors recommend considering bilateral oophorectomy and tamoxifen use in individuals with the *BRCA1* or the *BRCA2* mutation who prefer breast conservation, although additional risk reduction interventions are needed in these patients, particularly for long-term prevention of CBC.

Acknowledgement: The synopsis was written by Petra Roberts, Associate Editor, *Nature Clinical Practice*.

NEWSROUND

Selected press reports compiled by the ESO Cancer Media Centre

Assertive patients get better treatment

→ Journal of Clinical Oncology

Women who take greater control over choosing their breast cancer surgeon are more likely to be treated by more experienced breast surgeons and at a hospital affiliated with an accredited cancer programme, compared to women who are referred by another doctor or their health plan, according to a recent study.

A total of 1,844 women were surveyed about how their breast surgeon was selected, with choices such as 'I was referred by another doctor,' 'I chose this surgeon because of his or her reputation' or 'I wanted a surgeon who practiced near my home.'

Nearly two-thirds of the patients said they were referred to their surgeon by another doctor, with another 15% referred by their health plan. About a quarter chose their surgeon based on reputation – women with more education and higher incomes were more likely to be in this group.

The researchers found that only a third of the women were treated by a high-volume surgeon, defined as one with more than 50% of their practice devoted to breast cancer surgery. Two-thirds of the women were treated in hospitals designated as cancer centres by the National Cancer Institute or the American College of Surgeons.

Women who said they chose their own surgeon were twice as likely to see a highly experienced surgeon as were those referred by another doctor or by their health plan.

Commenting on the findings, author Steven Katz said, "Women with breast cancer should be aware that referrals from another doctor or their health plan may not connect them with the most experienced surgeons or the most comprehensive practice settings in their community. Patients might consider seeking a second opinion, especially if they are advised to undergo a particular treatment without a full discussion of the options."

■ Patterns and correlates of patient referral to surgeons for treatment of breast cancer. SJ Katz, TP Hofer, S Hawley et al. *J Clin Oncol*, 20 January 2007, 25:271–276

New tool to screen for ovarian cancer

→ Cancer

A symptom survey may provide doctors with a quick and cost-effective screening tool to detect early-stages of ovarian cancer, according to a new study. The findings reveal that early ovarian cancer may be identified by a specific set of symptoms, their frequency and duration.

Ovarian cancer is often misdiagnosed by general practitioners. There is no effective screening test to detect early-stage disease in the general population or in high-risk groups. The lack of recognised, early clinical signs and symptoms delays diagnosis until the disease is advanced. These factors combine to make ovarian cancer one of the deadliest malignancies in the world.

Recent evidence suggests that early-stage symptoms may be recognisable and could be used to develop a symptom index for early disease. Researchers led by Barbara Goff, of the University of Washington School of Medicine and the Fred Hutchinson Cancer Research Center in Seattle, compared the clinical history of women at high risk for developing ovarian cancer with that of women already diagnosed with ovarian cancer, to develop a basic symptom index.

They found "that a relatively simple evaluation of symptoms of recent onset and significant frequency" was sufficient to function as a potential screening tool. The symptom profile of 'any complaint of pelvic/abdominal pain, increased abdominal size/bloating, or difficulty eating/feeling full, that is present more than 12 days per month and for less than one year' was found to be present in 57% of cases of early disease and 80% of advanced cancers (sensitivity). Ovarian cancer was present in 90% of women over 50 years of age who identified these symptoms and in 86.7% of women under 50 years of age (specificity).

Goff plans to evaluate a simple three-question screening in a multi-year study in general clinical practice. Sherry Salway Black, from the Ovarian Cancer National Alliance in Washington, DC, explains in an accompanying editorial that, "a symptom index is only one of a number of promising research tracks the ovarian cancer advocacy community actively supports." Although years away, the development of a screening blood test would be "the real key to early detection". She continues, "Until there is a valid screening test, the symptom index could serve an important role in detecting cancers, and after a test is identified, the index could be a tool used in combination with other methods to

contribute to early detection."

In the meantime, health organisations need to continue to educate women and physicians about the symptoms of ovarian cancer. Awareness of the symptoms offers women the best hope for early detection and successful treatment of the disease.

■ Development of an ovarian cancer symptom index: possibilities for earlier detection. BA Goff, LS Mandel, CW Drescher et al. *Cancer* 15 January 2007, 109:221–227

Eating less fat may cut risk of breast cancer recurrence

→ JNCI

Women who have been treated for early-stage breast cancer may lower the chance of their cancer recurring if they reduce the amount of fat in their diet, according to a recent study.

Lead author Rowan Chlebowski, at the Los Angeles Medical Center in California, and his colleagues conducted a trial to determine whether a low-fat diet could prolong disease-free survival in women who had had early-stage breast cancer.

Between February 1994 and January 2001 nearly 2,500 women who had been treated for early-stage breast cancer were enrolled in the trial. Forty percent of the women were randomly assigned to a dietary intervention group and 60% made up the control group. Data were collected until 31 October 2003, a median follow-up of 60 months.

The goal of the women in the intervention arm was to reduce their dietary fat to just 15% of their total calorie intake. They attended counselling sessions twice a week for eight weeks and kept records of their daily fat intake. Dieticians contacted or met with the women every three months and the women could attend optional monthly dietary group sessions. The control group met with a dietician when they started the trial and were contacted by dieticians every three months.

At the beginning of the study, both groups consumed 56–57 g fat per day. After one year, the women on the diet consumed an average of 33 g per day, while the control group consumed 51 g per day). The two groups' body weight was similar at the beginning of the trial. Five years later, the women on the diet weighed an average of six pounds less than the women in the control group.

Women in the dietary intervention group had a 24% lower risk of relapse than those in the control group. Nearly 10% of women on the diet had some form of recurrence compared to 12% of the women in the control group. The researchers concluded that a lifestyle intervention designed to reduce dietary fat intake may improve relapse-free survival of breast cancer patients receiving conventional cancer management.

■ Dietary fat reduction and breast cancer outcome: interim efficacy results from the Women's Intervention Nutrition Study. RT Chlebowski, GL Blackburn, CA Thomson et al. *JNCI* 20 December 2006, 98:1767–76

Trastuzumab improves early survival in HER2+ breast cancer

→ The Lancet

Treatment of women with HER2-positive breast cancer with trastuzumab (Herceptin) for one year following standard chemotherapy can improve survival according to the two-year follow-up data of the HERA (Herceptin Adjuvant) study, which was published recently in the *Lancet*.

A total of 1,703 women were randomised to receive treatment with trastuzumab for one year after surgery and chemotherapy, and 1,698 women were assigned to the control group (observation only). After two years of follow-up it was found that more deaths occurred in the observation group than in the group of women treated with trastuzumab (90 versus 59), which corresponds to an absolute survival benefit of 2.7% (92.4% vs 89.7%) after three years.

Of the 172 women who stopped trastuzumab early, only 115 (6.8%) stopped because of safety issues. There were no cardiac deaths in the trastuzumab group; however, severe and symptomatic congestive heart failure occurred in more women on trastuzumab than in the observation group. Seventy-two women (4.2%) discontinued trastuzumab because of heart problems.

According to the paper's main author Ian Smith, from the Royal Marsden Hospital in London, "The survival benefit that has emerged over such a short period emphasises the potential of this approach and underlines the importance of developing further specific targeted therapies in breast and other cancers."

■ Two-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomised controlled trial. I Smith, M Procter, RD Gelber et al. *Lancet* 6 January 2007, 369:29–36

Gemcitabine can delay pancreatic cancer recurrence

→ JAMA

A recent study has shown that adjuvant use of gemcitabine can significantly delay the recurrence of pancreatic cancer following surgery. Helmut Oettle, from the Charite School of Medicine, Berlin, Germany, and colleagues, conducted an open-label, randomised, controlled trial that compared the use of gemcitabine with observation in 368 patients who had undergone complete surgical resection for their pancreatic cancer (R0 or R1) and received no prior chemotherapy or radiotherapy. Patients in the gemcitabine arm received, on average, six cycles of treatment.

More than 80% of the patients had gross complete resection of their pancreatic cancer. With a median follow-up of 4.5 years, cancer had recurred in 74.3% of patients in the gem-

citabine group and 92% of patients in the control group. The median disease-free survival was 13.4 months and 6.9 months in the control group. Grade 3 or 4 toxicities rarely occurred and there was no difference in quality of life between the two groups.

Subgroup analyses showed that the effect of gemcitabine on disease-free survival was significant in patients who had had a gross complete surgical resection. However, there was no difference in overall survival between the gemcitabine group (median, 22.1 months) and the control group (median, 20.2 months).

The authors concluded that adjuvant gemcitabine offers a good, and currently perhaps the best, chance for delaying the development of recurrent disease in patients who have undergone certain types of surgical resection for pancreatic cancer.

An accompanying editorial pointed out that "It is unlikely that these small steps alone will provide the necessary enhancements of benefit beyond the improvements in surgery to profoundly alter the course of this most challenging of cancers."

■ Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. H Oettle, S Post, P Neuhaus. *JAMA* 17 January 2007, 297:311–313

IARC issues warning on rising cancer burden

→ IARC

The latest figures released by the International Agency for Research on Cancer (IARC), and published online in the Annals of Oncology, reveal that 3.2 million new cases of cancer were diagnosed in Europe in 2006. The equivalent figure for 2004 was 2.9 million, indicating a rise of 300,000 new cases over the two-year period.

IARC director Peter Boyle, who prepared the report with colleagues, warned that despite better prevention and treatments, Europe faces a major increase in the cancer burden because of the ageing population. He said urgent action is needed now to tackle cancer, particularly in Central and Eastern Europe.

Breast cancer incidence has increased by 16% since 2004. It has now overtaken lung cancer as the most common cancer diagnosis, with 429,900 new cases reported in 2006 (13.5% of all cancer cases). Though much of this increase is due to better early detection, death rates continue to rise.

The number of new cases of colorectal cancer rose to 412,900 (12.9% of all cancer cases), making this the second most common cancer in Europe. Colorectal cancer remains the second biggest killer, with mortality rates increasing by 1.8% since 2004.

Lung cancer is now the third most common cancer diagnosis, with 386,300 new cases reported in 2006 (12.1% of all cancer cases); however, it remains the biggest killer.

Commenting on the report, Boyle said, "urgent action is particularly vital now to take preventive action against cancer, especially in Central and Eastern Europe, with strong and effective measures to curb the tobacco epidemic and more widespread screening programs for breast, cervix and colorectal cancers."

■ IARC press release no 174, www.iarc.fe, and Estimates of the cancer incidence and mortality in Europe in 2006. J Ferlay, P Autier, M Boniol et al. Ann Oncol published online 7 February 2007, doi:10.1093/annonc/mdl498

Zoledronic acid can protect against bone loss from hormone treatment

→ Journal of Clinical Oncology

Two recently published studies suggest that zoledronic acid can prevent loss of bone mineral density (BMD) in both pre- and post-menopausal women. BMD loss is a side-effect of aromatase inhibitors, which are used to treat early hormone-receptor-positive breast cancer in post-menopausal women, leaving them more susceptible to bone fractures. The results could therefore be important to this group of patients.

In one of these studies, known as Z-FAST, scientists looked at the effect of adding zoledronic acid to adjuvant endocrine therapy with the aromatase inhibitor letrozole, to see whether this protected against loss of BMD.

A total of 602 post-menopausal patients receiving treatment with letrozole were randomly divided into two groups. The first group was given zoledronic acid from the beginning of their letrozole treatment. The second group was given a delayed dose of zoledronic acid after their BMD had reduced (when lumbar spine or total hip T score decreased to less than –2.0 or when a non-traumatic fracture occurred). The researchers measured the BMD in the lumbar spine and hip to compare the results.

The study found that after 12 months the lumbar spine BMD was 4.4% higher in the group that received zoledronic acid straight away compared to the delayed group, and total hip BMD was 3.3% higher. The upfront group also had less enzymes, which show up active bone disease, whereas concentrations of these enzymes increased significantly in the delayed group. The authors concluded that within one year of follow-up, results indicate that upfront zoledronic acid therapy prevents BMD loss in the lumbar spine in post-menopausal women receiving adjuvant letrozole for early-stage breast cancer.

The other study looked at using zoledronic acid to prevent bone loss associated with adjuvant hormone therapy in pre-menopausal women – a group of patients in whom use of aromatase inhibitors is still under evaluation. This randomised phase III trial compared tamoxifen plus goserelin with or without zoledronic acid against anastrozole plus goserelin with or without zoledronic acid for three years in pre-menopausal women with hormone-responsive breast cancer.

A total of 401 patients underwent BMD

measurements at intervals throughout the three-year period. The results showed that hormone treatment without zoledronic acid led to significant overall BMD loss after three years of treatment. The loss was significantly greater in patients receiving anastrozole/goserelin compared with patients receiving tamoxifen/goserelin.

However, BMD remained stable in both groups of patients treated with 4 mg zoledronic acid every 6 months. No interactions with age or other risk factors were noted. The authors conclude that patients undergoing hormone therapy should have regular BMD measurements, and zoledronic treatment should be considered for patients experiencing bone loss.

■ Zoledronic acid inhibits adjuvant letrozole-induced bone loss in postmenopausal women with early breast cancer. A Brufsky, WG Harker, JT Beck et al. *J Clin Oncol* published online 11 December 2006, doi: 10.1200/ JCO.2005.05.3744 Zoledronic acid effectively prevents cancer treatment-induced bone loss in premenopausal women receiving adjuvant endocrine therapy for hormone-responsive breast cancer: a report from the Austrian Breast and Colorectal Cancer Study Group. MFX Gnant, B Mlineritsch, G Luschin-Ebengreuth. *J Clin Oncol* published online 11 December 2006, doi: 10.1200/JCO.2005.02.7102

ICMJE trial registration standards starting to pay off

➜ New England Journal of Medicine

Eight percent of the 2,983 clinical trials sponsored by pharmaceutical companies in 2006 and entered into the ClinicalTrials.gov website did not include information on the outcomes being measured, compared with 26% of 5,355 trials registered prior to 2006, according to an editorial published recently in the *New England Journal of Medicine*. In 2006, none of the filings omitted the name of the drug being tested, compared with a small number that excluded drug names from the registry before 2006.

The editorial, written by *NEJM* Editor in Chief Jeffrey Drazen and Deborah Zarin of the National Library of Medicine, praised the increase in quality of registration but called for researchers to avoid registration duplication. Evidence of such duplication came to light after an article about the treatment of renal cancer with sunitinib was considered for publication by the *NEJM*.

The journal's staff routinely check the quality of registrations in ClinicalTrial.gov to see whether they meet the standards set by the International Committee of Medical Journal Editors (ICMJE). The registration for the sunitinib study did not meet these standards because information filed by the study's sponsor Pfizer was missing from the outcome-measured field.

However, further investigation revealed that one of the co-authors had also registered the trial through one of the cancer centres. This second registration did meet the ICMJE standards.

The editorial sent a message to investigators: "Before you enrol a patient in a study, be sure that there is a full and appropriate registration of the trial in a public database approved by the ICMJE (www.icmje.org). It could salvage a study report that otherwise would not be published."

■ Salvation by registration. JM Drazen, DA Zarin. *New Engl J Med* 11 January 2007, 3562 184–185

Radiotherapy cuts risk of recurrence after breast-conserving surgery

➜ Cancer

Radiotherapy after breast-conserving surgery for breast cancer reduces recurrence and prevents development of additional breast tumours in older women with early-stage breast cancer, according to a new study. The findings also suggest that women benefit from the recommended five years of tamoxifen treatment for hormone responsive tumours.

Women over 65 are at highest risk for breast cancer and make up half of those diagnosed. However, they are less likely than younger women to receive standard therapy, particularly radiotherapy after breast-conserving surgery. Making treatment recommendations for older patients is complicated because of the under-representation of older women in clinical trials and prognostic studies.

A total of 1,837 women over 65 years of age who were operated for early-stage breast cancer were followed for 10 years to examine the impact of choice of treatment on the occurrence of recurrent and additional breast tumours.

The researchers found that, regardless of age or comorbidities, women who underwent breast-conserving surgery but no radiotherapy were more likely to have recurrence of disease or develop additional breast tumours compared to women who received breast-conserving surgery and radiation or mastectomy alone. The risk was highest for local and regional recurrence. These results held, regardless of whether the women were treated with tamoxifen, suggesting that adjuvant radiation treatment was highly effective.

The researchers also found that women who received less than one year of tamoxifen were more likely to have disease recurrence or develop additional breast tumours compared to women who completed the recommended five-year course.

Based on these study findings, the authors recommend that mastectomy or breast conserving surgery with radiation therapy, along with adequate duration of adjuvant hormonal therapy for hormone-responsive tumours, be considered standard therapy in women of all ages and comorbidities, excepting those with very limited life expectancies.

■ Recurrences and second primary breast cancers in older women with initial early-stage disease. AM Geiger, SS Thwin, TL Lash et al. *Cancer* published online 22 January 2007, doi: 10.1002/cncr.22472

No one told me I had a choice

Claire Laurent

The right of every patient to play a full role in decisions relating to their treatment remains more of an aspiration than a reality, according to a recent survey of breast cancer patients. For the situation to improve, doctors will need to take more time and learn better ways to communicate, particularly with their more elderly and less educated patients.

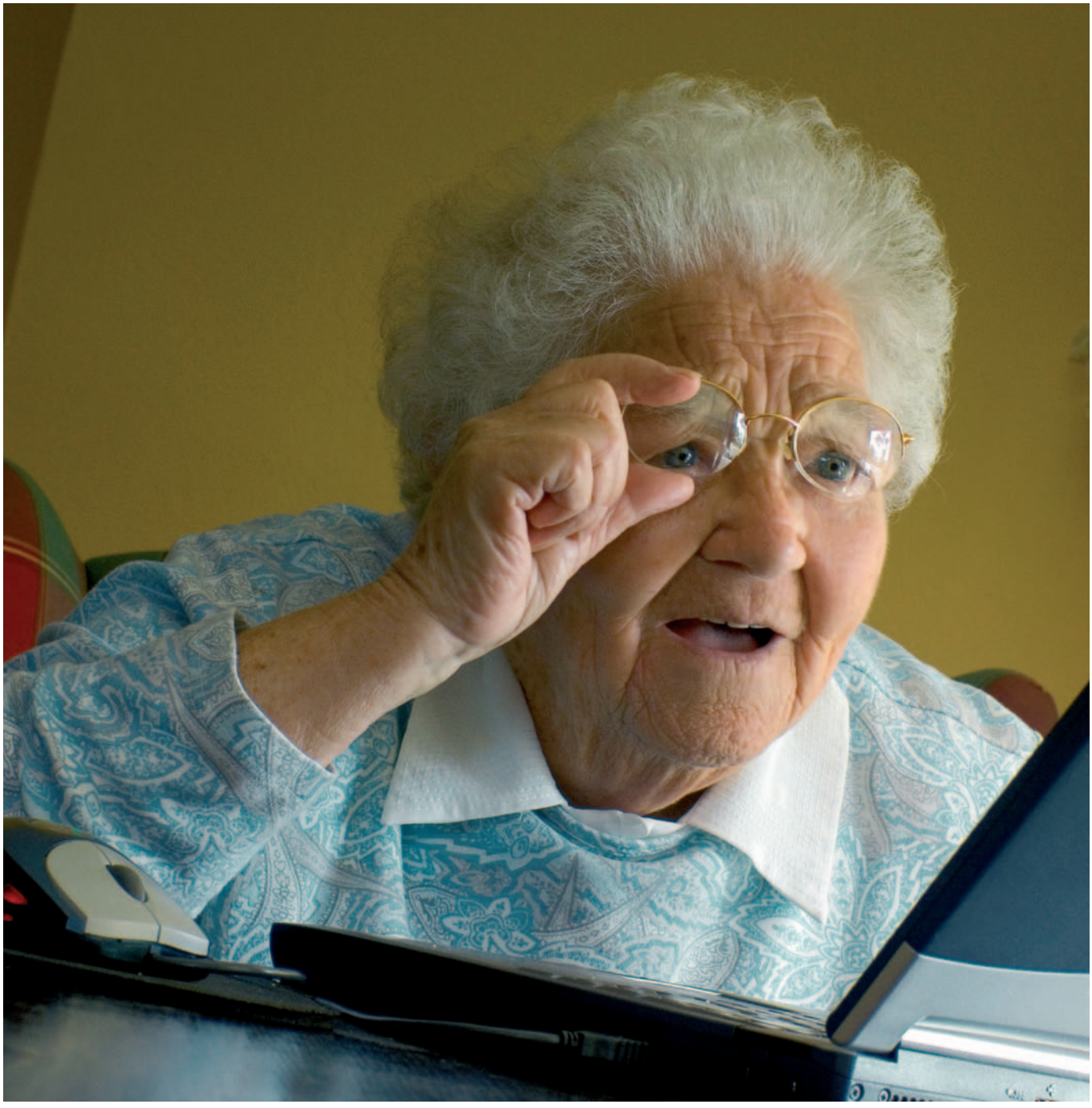
Many women with breast cancer are poorly informed about treatment and its consequences, with many not even being told about available treatment choices. As a result they are less likely to be involved in decisions that might affect their life expectancy and quality of life. Older women with a low level of education and without Internet access receive least information.

These were the principal findings of a survey conducted last year of European women with early breast cancer. The survey formed part of the GAEA (Gathering Information on Adjuvant Endocrine Therapy) initiative*, and involved 547 post-menopausal women with early breast cancer in nine European countries. It was designed to find out how much patients know and understand about adjuvant endocrine (hormone) therapy and about their risk of recurrence, their involvement in treatment decision making and their information and support needs.

Adjuvant endocrine therapy (AET) is given after breast cancer surgery to reduce the risk of recurrence, and is usually continued for at least five years. It is given as an insurance policy; most women who take it would never have gone on to develop a recurrence in anycase. For some, therefore, it is a life-saver, while for others it may mean years of suffering side-effects for no benefit.

There are two main therapeutic options. One is tamoxifen, which is associated with increased risk of stroke, thromboembolic events, uterine cancer, and uncomfortable and embarrassing side-effects such as hot flushes and vaginal bleeding. The other is an aromatase inhibitor (AI) – there are a number to choose from. These also cause hot flushes and vaginal bleeding, though not as badly as tamoxifen. The main problem with AIs, however, is that they cause pain in the joints and can weaken bones, leading to an increased risk of fractures. AET must be

* The GAEA (Gathering Information on Adjuvant Endocrine Therapy) initiative is a collaboration between the European School of Oncology (ESO), the European Oncology Nursing Society (EONS) and Novartis Oncology, with Europa Donna, the European Breast Cancer Coalition, acting as patient advocacy resource. Full results of the survey can be found at www.gaeainitiative.eu



"We tend to forget that the women we are treating today are not the ones brought up with the Internet"

Only 22% of patients were 'fully' or highly' involved in the decision to start adjuvant therapy

taken for at least five years – a long time for a women to cope with burdensome side-effects. Perhaps not surprisingly, women can find it difficult to adhere to their treatment.

Whether a patient would do best to opt for AET, and which AET would be best for them, depends on their attitude towards their particular risk of recurrence and the impact of the attendant side-effects on their quality of life. If they are not told, or don't understand, their level or risk or the nature of the possible side-effects, it will be impossible for them to take an informed decision.

The finding that only 46% of women surveyed said they had been told that there were treatment options is therefore rather worrying; 47% said they had not been told and a further 7% could not recall. Of equal concern is the finding that only 22% of patients reported being 'fully' or 'highly' involved in the decision to start AET; a figure that fell to 15% among women in their 60s. Among the over 70s, only 11% reported having been 'fully' or 'highly' involved, while 80% said they had had little or no involvement at all.

Ingrid Kössler, who has played a leading role in the Swedish Breast Cancer Association for many years, and is president of Europa Donna the European Breast Cancer Coalition, says the results of the survey match the experiences she has encountered amongst older women in Sweden. "Elderly women don't know enough about their diagnosis or treatment. They don't ask so many questions because they think the doctor's word is law and they are not used to interrogating and looking for better treatment."

Doctors, she says, must make sure that their patients have the information they need to be involved in the decision making. "It should not be up to the patient. It's the responsibility of the doctor. The patient needs to have enough information to understand why they are being offered a particular treatment."

She accepts, however, that there are many patients – and they are often older people – who want the doctor to tell them what they need. "Patients are different. Some of them want to know every detail associated with their illness, cure and treatment, and so on and some of them don't involve themselves in it. They are more fatalistic," says Kössler.

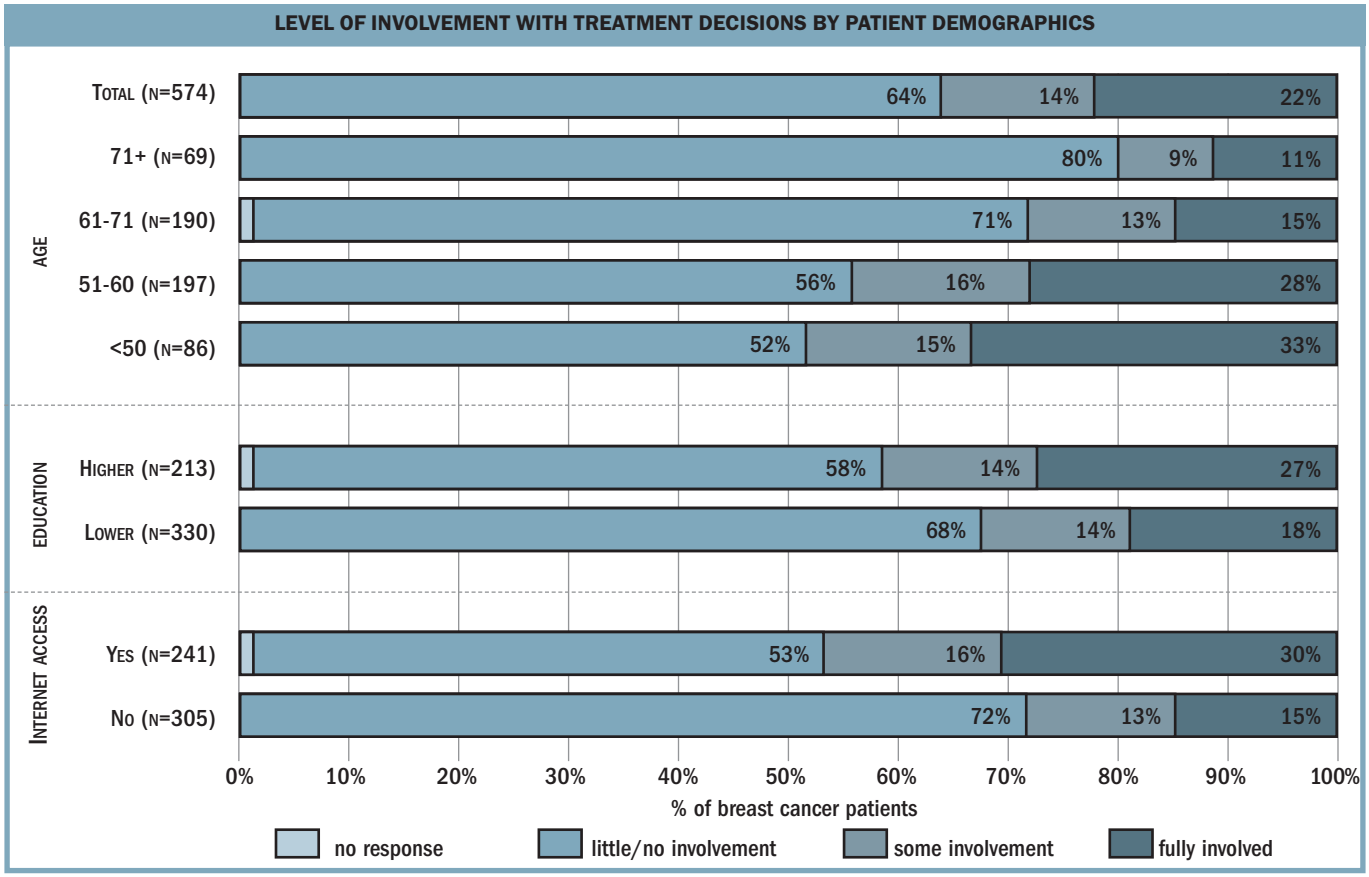
For such patients it is harder for health professionals to judge just how much information to give. It is likely a proportion of patients choose not to be involved in decisions about their treatment at the time, and it is only with hindsight, perhaps when they are feeling fitter, that they wish they had.

Take it slowly, keep it simple

Some of the answers to this involve simplifying the language used, giving patients more time at appointments and involving trusted friends or family members, says Kössler. "Information is not what the doctor says but what the patient understands. It is easier for doctors to use common language than for patients to learn medical language. I think it's important for patients to get their family involved, maybe a son or daughter, if you are an elderly woman. They can help you find out more about your treatment and accompany you to the doctor.

"As a newly diagnosed patient you won't even know what questions to ask, and even if you try and find the information on the Internet you don't have the background to evaluate it. I think we need to spread the information that breast cancer is not just one disease. There are so many varieties and that's why treatment differs," she says.

The GAEA survey showed that less than half of the women (44%) received information on how AET works. Only 25% were told of the possible severity of side-effects, 20% of the duration of side-effects and 22% of the risk of their cancer recurring when AET was stopped. Elderly patients, patients without Internet access and those with a lower educational level were less likely to have



A picture of inequality. The survey results show that a majority of women of all categories had little or no involvement in the decision to start adjuvant hormone treatment for breast cancer. In older women, those educated to a lower level and those without Internet access, the figures reached 80%, 68% and 72% respectively

Source: The GAEA Initiative, www.gaeainitiative.eu

received this sort of information from a doctor or nurse. The three variables worked independently, meaning that younger women with lower education and no Internet access tended to receive more information than older women in the same situation, but less than women of their own age and education who did have Internet access, and so on.

There seems, therefore, to be a cycle whereby women who start off being poorly informed, continue to be so, leading to a reduced involvement in decision making about their treatment and a poorer understanding of the risk of side-effects and recurrence.

Yvonne Wengström, the president of the European Oncology Nursing Society, said it was clear that patients who took part in the survey wanted more information about treatment and especially about side-effects. She pointed out that while the patients tended to regard health professionals as a "highly trusted source of information," these health professionals often failed to give them comprehensive information about the rationale for treatment and the potential consequences of treatment.

Wengström believes the survey results also show that women don't know where to look for the information they need. "Many women were unaware of what options they had to inform themselves, such as patient groups for example. We tend to forget that the women we are treating today are not the ones brought up with the Internet – those are the patients of the future."

For those patients there are a myriad of websites about breast cancer. In the UK, for example, there are a number of big cancer charities that provide information via the Internet. In Sweden, the Swedish Breast Cancer Association is developing

"We have to consider the time spent explaining and answering questions as part of the medical activity"

a website to advise women on what questions they should ask their doctor regarding their treatment and care. But these information sources don't solve the difficulties that older women have about their treatment. And health professionals need to be imaginative in the ways they try and get information across to an age group that tends not to question the doctor.

Health professionals need to listen to patients, recognise their individual needs and take responsibility to ensure patients know where they can get information from, says Wengström. "We have to develop a professional approach to patient information and education and recognise the important role we play in the patient's treatment and decisions."

Doctors are key

Alberto Costa is a breast cancer surgeon based at Pavia, and Director of the European School of Oncology, one of the GAEA collaborating partners. He argues that doctors are crucial to ensuring that patients are involved with decisions about their treatment. "As doctors we are clearly failing some patients by not involving them in the decision about starting adjuvant endocrine therapy and by not giving them the information they need to make these decisions."

WHAT PATIENTS WANT

This is how patients in the GAEA survey summed up what they need from their health professionals:

- Explain things in simple terms
- Take time to explain my disease and treatment
- Encourage me to have faith in my treatment
- Make sure I understand the importance of taking medication every day
- Provide follow-up care and information when I leave hospital

The study findings, he says, are borne out by his own experiences. "Patients who are actively involved in decision making have better psychological adjustment, are more satisfied with their treatment, and are more likely to adhere to treatment."

The point is an important one, as studies have repeatedly shown that up to 40% of women on adjuvant treatment have problems sticking to their prescription, and that those who are well informed about their treatment are more likely to adhere to it. Patients are also more likely to report side-effects if they are better informed, because they will understand what they should be watching out for and can make the connection between the symptoms and the treatment. Accurate reporting of side-effects in turn helps doctors plan follow-up appointments. "There is a collaboration between doctor and patient to be accurate," says Costa.

He argues that doctors need to be taught communication skills, not just in the classroom but in the clinic too. "It's not considered something you have to teach. We all know of the senior surgeon teaching surgery in the theatre to the junior surgeon, but he doesn't generally teach them how to talk to the patient. This consultation is still very often a private affair between doctor and patient," says Costa. Teaching in the classroom remains theoretical; students need to witness conversations in practice and learn how best to ensure patients are informed and involved, he says.

Hospitals in general and cancer centres in particular need to reorganise in order to provide more time for discussion with patients, argues Costa. "Not just doctors but nurses and managers need to give much more importance to the moment of communication," he says. "We have to consider the time spent with the patient to explain and answer questions as part of the medical activity. Some people think medicine is only about doing surgery, visiting and writing. Talking to the patient is seen as a 'nice' thing, but really it is part of the treatment and the care."

Savings lives through changing systems and practices

Anna Wagstaff

There is no secret about the steps needed to improve cancer survival and revolutionise the patient experience. But change is a challenge for professionals and managers alike. The first ever *CancerWorld* conference focused on this challenge – how can you change systems and practices to improve quality of care across the board?

When *CancerWorld* magazine invited politicians, health policy makers and administrators, health insurers, clinicians, nurses and patients to the first ever *CancerWorld* conference, it took the risk that it might be organising a brainstorming session in the tower of Babel.

Though each might talk with great eloquence to others in their own field, differences in terminology, perspective and conceptual approach could make it hard to achieve coherent discussion and reach meaningful conclusions. Yet just such a dialogue is essential if Europe is to implement the changes to its cancer services necessary to achieve the best results at a sustainable cost.

Saving Lives in Cancer: Policies and Practices that Make a Difference looked at what is needed to move from the current patchy picture of cancer care in Europe to one in which high-quality, safe and patient-centred care is available to patients of all ages and backgrounds, whether they live on remote farms or in a bustling city.

The reasons for this focus were three-fold. The first was a question of fairness. One statistic widely quoted by those who argued for a national cancer plan in France was that cancer patients were up to six times more likely to survive if they came from an area with the best cancer services compared to the worst. That level of inequality is not acceptable between countries, and it's certainly not acceptable within a single country with a strong centralised health system.

The second reason was strategic. We have a good idea about what makes the best cancer services better than the worst. Bringing cancer services in the worst areas up to the level of the best could improve survival of some French patients by up to six fold. When was the last time that science delivered improvements on that scale?

The third reason is economic. The combination of an aging population and escalating costs in cancer care creates a risk that public health systems and health insurers will no longer be able to cover the costs. In identifying which policies and practices make a difference we also identify those policies and practices that do not, thereby identifying resources that could be put to better use.

Management issues rarely fire people up in the

Championing change. The story of how videotechnology came to be embraced by staff and patients throughout the South West Wales cancer network provided an interesting case study at the *Saving Lives* conference (p71), illustrating how good ideas and strong leadership can overcome resistance to change and how successful pilot projects can be rapidly spread. The picture below shows a colorectal cancer team meeting at Bronglais Hospital in a remote corner of West Wales. In the room are the consultant colorectal surgeon and his team, including the clinical trials nurse, the oncology nurse, and the lead clinician for cancer services. The right-hand screen shows the consultant radiotherapist and oncologist in his room at the cancer centre 75 km away in Swansea. The double screen allows people in the meeting room to see the image relayed to the remote location from the camera in front of them, but it can also be used to show X-rays, histopathology slides etc (see left)

DELYTH LEWIS

way that human stories from the frontline of cancer care can do. But system errors are deemed to account for around 90% of errors that result in cancer patients failing to get the right care at the right time from the right people. It is therefore to improvements in management that we should look if we are serious about improving the service for all cancer patients.

ORGANISATION – THE THIRD DIMENSION

The scene was set by Bruce Barraclough, President-elect of the International Society for Quality in Health Care, who oversaw a major reshaping of the safety and quality agenda in Australia's health systems. A surgeon by profession, Barraclough chaired the Australian Council for Safety and Quality in Health Care from 2000 to 2005 and now heads the New South Wales Clinical Excellence Commission.

Europe can learn from the Australian experience, not least on the issue of equal access. The Australian population is more dispersed than anywhere in Europe, but people in remote areas – including a high proportion of the aboriginal population – now have a cancer survival rate only 10% below the average. Compare that with the

six-fold difference in survival within the far more concentrated French population, and the four-fold difference in lung cancer survival between hospitals five miles apart reported for Scotland (see p 67), and it becomes clear that Australia must be doing something right.

Barraclough talked about four 'dimensions' of health care:

- The personal dimension – care of the individual patient, which must also involve their carers
- The professional dimension – the training, skills, experience of health care professionals, and the culture in which they work
- The organisational dimension – the structures and processes involved in deciding on and delivering care
- The political dimension – determining major policy decisions and whether there is political will to push through major changes to the status quo

Although all four play a role in determining the quality of patient care, *Saving Lives* focused on the organisation of services. This is the most complex dimension, going through the greatest change, and where there is the greatest scope for improving the service.

Barraclough argued that the way healthcare is delivered has changed radically, and demands a new management approach.

Perhaps the most significant change is due to increased specialisation. This has the potential to fragment services, with many patients likely to see 20–40 different health professionals at different locations throughout their cancer journey. It is a major logistical challenge to coordinate the patient journey while ensuring that all patients have access to appropriate specialists. Getting things wrong can cause the patient unnecessary frustration and stress, needlessly reduce their quality of life or even lead to the death of patients who, cared for properly, could have been saved.

The traditional 'doctor knows best' culture is also facing an increasing challenge. This is both because treatment decisions are increasingly subject to evidence-based guidelines and multidisciplinary discussion, and because patients demand more information and a greater say in the way they are treated.

The cultural change towards a more patient-centred approach is also opening health services to greater scrutiny on such key issues as waiting times, complications rates, and patient satisfaction.

No-one who has worked in health care over the past 20 years can be unaware of these changes, yet Barraclough argues that there has been a reluctance to grasp the implications for how health services are managed, leading to a sub-standard service, that puts patients in danger and wastes resources.

He characterised healthcare provision as highly complex and process-based, because it involves multiple interactions between people doing different activities in different environments, using different methodologies and communicating different types of information. It is also 'high-risk' because of the possible consequences of doing something wrong or failing to do the right thing. Barraclough argued that these characteristics are not unique to healthcare and that health managers can learn from industry.

He cited McDonald's as a provocative role model for standard operating procedures: "A promise of a free one if you don't get it on time, and if you don't like the fatty meat patty in between the bits of bun, then they offer you a salad." If people expect minimum standards and remedial action in their fast food, why should they not have the same rights in health care, where so much more is at stake?

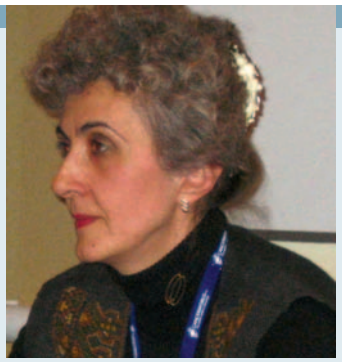
This is more than a rhetorical question. To assert this right is to challenge the traditional autonomy (some might say impunity) enjoyed by medical professionals and administrators, and to argue for key aspects of the service to be subject to evaluation, external audit and accountability.

Barraclough stresses that this is not an attack on health professionals – though it may feel that way to surgeons who see their complications and mortality rates published or to hospital administrators challenged about long waiting lists. It is intended to create an environment where health professionals can use their skills to maximum effect.

In complex enterprises, about 10% of errors are due to individual failings, while 90% result from systems failures. Getting the system right is the key to getting many other things right – correct

The cost of fragmented services

Serbia and Switzerland pay the price for poorly structured cancer services



Vesna Kesic

Patients do better if their care is in the hands of multidisciplinary teams of specialists who have the right equipment and who spend much of their working lives treating patients with their particular type of cancer. Smaller centres cannot provide this, because they treat too few patients. They can, however, reduce the distances patients need to travel by coordinating with larger centres to deliver some treatments – chemotherapy for instance – closer to home.

The previous issue of *CancerWorld* (January–February 2007) looked at the way some countries are restructuring their cancer services based around regional specialist centres, with links to local hospitals, and primary and community healthcare.

The *Saving Lives* conference heard two examples of what happens when patients are treated in more fragmented systems: Serbia, which, at $373 (2003 figures), has one of the lowest per capita spends on health in Europe, and Switzerland, which has a per capita health bill of $4,077.

Vesna Kesic, who chairs the Serbian Society of Gynaecological Oncology, told the conference how patients are paying the price in unnecessary suffering and death of a badly structured cancer service. The country does have a cancer network, consisting of two national centres, three regional centres and 28 outpatient centres. However, most patients do not undergo their initial treatment at these centres. A recent survey conducted by the Serbian Society of Gynaecological Oncology, found that patients are operated by 223 gynaecologists at 43 different hospitals. Each surgeon operates on an average of seven patients a year – little more than one every two months. Almost half the gynaecological departments care for fewer than ten patients a year.

One consequence of this highly fragmented service is that in almost half the cases, the surgeon decides on treatment without any multidisciplinary consultation. The quality of the surgery is also substandard. Radical surgery, the standard for cervical cancer, is not performed in 70% of regional hospitals; omentectomy, standard for ovarian cancer, is performed in just over half. Though Serbia has national clinical guidelines for gynaecological cancers, these are not followed in one-third of cases.

Switzerland also suffers from fragmented services. Swiss hospitals have far more staff and better equipment than their Serbian counterparts, but far too many hospitals try to do everything. The conference heard how, in the canton of Ticino, a population of 300,000 is served by four public hospitals and three main private hospitals, which between them care for around 240 women newly diagnosed with breast cancer every year. In 2005, 160 women were treated in the public sector by 21 gynaecologists, eight of whom performed only two operations a year. Only one performed more than 30 breast operations.

In this highly competitive environment, each hospital employs its own team of specialists, many working well below full capacity. This wasteful use of resources is mirrored on the equipment side: Ticino has three CT scanners within an area of a few square kilometres.

In Switzerland, the price of badly structured cancer services is paid by the people through their health insurance. Per capita health spending is not just ten times that of Serbia, it is almost 50% greater than in Sweden, where cancer survival rates are higher for women and only marginally lower for men.

Each surgeon operates on an average of seven patients a year – little more than one every two months

If people expect minimum standards for fast food, why should they not have the same rights in health care?

diagnosis, appropriate and timely referral, proper application of guidelines, response to symptoms, effective communication, and many other things that contribute to quality patient care.

Part of this, said Barraclough, citing Avedis Donabedian the guru of health policy analysts, comes down to delivering the care through appropriate 'structures', related to who (accredited to what level) does what and where, and how different bodies relate to one another (see The Cost of Fragmented Services p 65). Barraclough focused on the larger and harder part, which relates to getting the 'processes' of care delivery right – how things are done.

Guidelines and performance agreements

Barraclough argues that health care facilities should have a legal responsibility to ensure that services are provided in an environment where the safety and quality of the delivery of health care is properly addressed. Performance agreements should spell out what is expected of the facility, with external review, incentives and penalties to promote compliance. Agreements can cover ethical practices, treating patients with respect and dignity, maximum waiting times and compliance with clinical guidelines, but are at their most effective if they can also tie in with national disease management guidelines on agreed standards of care for particular cancers or procedures.

These guidelines already exist in some parts of Europe, notably in the UK where the *Improving Outcomes Guidelines* specify agreed standards of care for each cancer, including, for instance, diagnostic and staging procedures every patient has a right to expect, or the requirement that treatment decisions are made in a multidisciplinary meeting at which specified disciplines should be present, or that certain procedures be carried out by doctors with a minimum accredited level of expertise. They also include the right, for example, to breast conserving therapy, to specialist palliative care, to join appropriate clinical trials and so on.

Greater use should also be made of performance agreements between facilities, to ensure a smooth passage for patients on their cancer journeys from one provider to another. An example given from Denmark was an agreement between general practitioners and a regional cancer centre over where each diagnostic test should be done – to prevent identical procedures being carried out twice, an irritating, time-wasting and costly problem.

If this sounds very 'top down', Barraclough was unapologetic about the need for external levers of control to deliver the best quality care. He did make the point, however, that this sort of regulation is increasingly operating at a network rather than a national level, "less reliance on top-down government action, more on mobilised networks of power". This approach was neatly illustrated in a contribution about how the Christie hospital in Manchester, UK, had gone about reducing waiting times that were beyond their immediate sphere of control (see Targets Help You Focus, p 69).

Measures should be taken to set minimum standards, benchmarks and targets and to evaluate healthcare facilities, and reward or penalise them on the basis on their performance. However, Barraclough stressed that the key to improving services lies in the ability of staff and the organisation to detect where things are going wrong, to understand why and to make the necessary changes to set them right.

Much of the effort towards improving healthcare services in Australia went into changing the culture. The Australian Council for Safety and Quality in Health Care promoted a no-blame system of open disclosure of adverse effects, using 'root cause analysis' (imported from the US Veterans Administration) to identify underlying

Audit as a key to improvement

How Scotland improved its lung cancer survival for the first time in 30 years

Noelle O'Rourke

Scotland has long been near the top of the European league table for lung cancer incidence, and near the bottom of the table for survival. While other countries saw small steady improvements in survival during the 1980s and 1990s, in Scotland the 5-year survival rate hovered obstinately around 6–7%.

Noelle O'Rourke, lead clinician for the West of Scotland Lung Cancer Network, was therefore delighted to bring good news to the *Saving Lives* conference: statistics just published for one-year survival for 2003–2004 showed an improvement of 5% on the '97–'98 figures, from 23% to 28%. The true survival increase may prove to be even higher once the statistics are adjusted for cause of death, and will improve further following recent efforts to increase the proportion of patients treated surgically.

O'Rourke attributes this success to 10 years of a very active cancer strategy. A retrospective audit of all patients registered in 1995 documented the cancer stage, what treatments were given where, and survival. This 'highly labour intensive' exercise revealed significant undertreatment of patients, with 41% offered only 'best palliative care'. Only 10% of patients were offered surgery, compared to the 15–20% that would normally be expected. The three-year survival rates most clearly showed the need for improvement. Patients were four times more likely to survive if they were referred to one hospital than if they were referred to a neighbouring hospital five miles down the road. A closer look revealed big differences in the use of radiotherapy, chemotherapy, surgery and palliative care only.

Turning this situation around involved three main steps.

1. Targets were published outlining what the service should be aspiring to in terms of treatment rates, based on national clinical guidelines adapted to the realities of the local situation.
2. Lung Cancer Networks were formed within each of Scotland's cancer networks, bringing together all health professionals involved in the treatment of lung cancer, as well as patients and carers. Network protocols for diagnosis and treatment were put in place to ensure that every patient is offered the same treatment for the same stage of disease and access to the same clinical trials. All patients have access to multidisciplinary teams, which have been set up at almost every site. Every patient now gets a folder of information developed by a patient-led group, relevant to their own case and telling them what they should expect in terms of treatment.
3. An audit of every facility is carried out annually to detect weak spots and anomalies and to identify areas for improvement. One thing that recently came to light is that multidisciplinary teams often cannot get surgeons to their meetings, and that the less frequently surgeons are present the smaller is the chance that a patient will be offered surgery. Ensuring there is a surgeon at every team meeting is therefore a major target for the coming year.

There is no miracle cure for lung cancer, but to O'Rourke, there is something miraculous about what the Scottish lung cancer service has achieved. "This is the first time in 30 years there has been a change in lung cancer survival in Scotland, and I cannot tell you how good it feels to stand up here and publicise that," she said.

Ensuring there is a surgeon at every team meeting is therefore a major target for the coming year

With 'seamless' coordination, the patient will be unaware that care is provided by different teams

problems. In New South Wales, this led to a 30-fold increase in adverse event reporting in the first year, which in turn led to important changes in practice. The discovery, for instance, that the majority of serious errors in drug administration take place around shift changes led to significant risk reduction simply by ensuring that dangerous drugs such as anticoagulants are administered well before the end of the day.

The Council encouraged a culture of internal review and audit so that teams and departments could measure how they were doing against agreed standards and compare this with what was happening elsewhere. (For an impressive example of how a similar system was used to improve lung cancer survival rates in Scotland, see Audit as a Key to Improvement, p 67).

The Council identified various ways to achieve changes in behaviour and practice: audit and feedback to address a mismatch between staff perceptions and results; educational courses and aids to decision making where lack of knowledge was the problem; leadership, sanctions and incentives to address lack of motivation; and so on.

They also drew up an action plan to implement national cancer guidelines at local levels giving leadership responsibility to 'clinical champions', staff who are convinced of the need for change and can enthuse those around them. They introduced audit to compare guidelines or new procedures to current practice, to build an understanding of the need for change and to review progress (see also Don't Sideline the Guidelines, p 14).

Simplifying the patient journey

If it is difficult to ensure that everyone within a single health facility works to agreed standards and guidelines, understands their role and responsibilities, and communicates effectively with colleagues, patients and carers, the challenge is far greater where more than one facility is involved.

This is always the case in cancer, where most patients start their cancer journey by being referred for tests by a primary health care practitioner. These tests may be done at a local hospital, with the results then being sent to a tertiary facility with a specialist cancer unit. Following the diagnostic workup and staging, and decisions over the treatment package, the patient may be referred to yet other facilities for the actual treatment. They may have their chemotherapy or palliative care delivered at clinics closer to their home or they may have to travel elsewhere for radiotherapy. Several specialists, community health workers and family carers may all play a significant role in their care.

Ingvar Karlberg, from the Gothenburg Centre for Health Systems Analysis, told the conference that health providers should be aiming for a 'seamless' coordination, so tight that the patient is unaware that different elements of their care are provided by different teams and institutions.

Sadly, he said, the reality is often very different, with patients and information frequently getting lost in a 'Bermuda triangle' at the interfaces between facilities.

Patient tracking procedures may be poor or non-existent. Cultural differences and a lack of understanding about roles can create problems. Karlberg cited the tendency for hospitals to refer patients to home or community care with detailed notes about the medical procedures they have carried out, while failing to mention critical functional information such as "this patient is unable to walk," or "cannot eat unaided".

Inflexible financing and reimbursement systems can lead to patients being cared for in an inappropriate setting – receiving unnecessary medical intervention in a hospital bed when they would do better receiving care and rehabilitation in a community or home setting.

Lack of integration can lead to lack of clarity over lines of responsibility and accountability, with the danger that healthcare facilities play 'Old Maid', trying to duck their responsibilities or pass them on to others.

Targets help you focus

How Christie's slashed waiting times and helped other parts of the cancer network do the same

Caroline Shaw

When Christie's cancer hospital in Manchester, UK, was set a target of treating 100% of patients within 31 days of a decision to treat, and within 62 days of the patient being urgently referred by a general practitioner, staff said it couldn't be done. They were wrong.

Within 13 weeks, the proportion of patients treated within the 31-day target rose from 39% to close on 100%. The only additional resource was an extra 30 minutes of linear accelerator time, two days a week.

Faced with financial penalties if the target was breached, staff examined the patient pathways through the various hospital departments and systems, and they found ways to cut out much of the complexity by changes to working practices.

Caroline Shaw, Chief Executive at Christie's, told the *Saving Lives* conference that the new arrangements had proved hugely popular, not just among patients, but also among staff. "Our medical director said, 'It's fantastic – I don't have to give any more excuses. I can give my patients a treatment date when they need it, and make sure that they get their treatment on time.'"

The 62-day target was harder to tackle, because patients are often referred for tests to any one of 15 hospitals in the Greater Manchester and Cheshire cancer network before being referred to Christie's. As an incentive to get things right, Christie's faces shared penalties for breaches of the 62-day target, even if the fault lies elsewhere in the system.

They took the time to look at what was happening to patients during this part of their journey, and again unnecessary complexity became apparent. "We have too many hospital transfers. We make systems far too complex. We make things difficult for patients and clinical staff."

Redesigning the patient pathway proved to be the key to meeting the 62-day target.

- There is now a single waiting list for the whole Greater Manchester and Cheshire cancer network – "This is really important. It means that as a tertiary hospital we can pull patients into our system – we can we can track a patient from a GP referral. I know the names and details of patients, where they have been transferred and where the problem is."
- Negotiations have started to make care pathways much simpler and to reduce the number of transfers – "We are now very clear who is responsible for performance."
- Monthly meetings are held with all the hospitals in the network to share results, looking in depth at each case where the 62-day target has been breached.

Shaw told the conference that strong leadership, a 'can do' approach, and 'a culture of managing performance' had been essential to getting results. But she also strongly endorsed the use of targets and penalties for breaching targets – including shared penalties when waiting times involving more than one facility are breached.

"I think targets are fantastic. Quite often doctors in my organisation don't like targets. But targets make us focus and achieve things better for our patients. Hospitals shouldn't be paid for activity if they breach targets." She is very keen to work with the health authorities that commission and pay for patient care to improve care pathways and clinical outcomes and to develop an incentive-based commissioning framework.

"We can pull patients into our system – we can track a patient from a GP referral"

Regional centres have drawn up disease management guidelines covering a patient's entire cancer journey

A number of steps have been taken to improve integration in Sweden. These include simple measures such as putting together local directories of people who need to cooperate. Regional oncology centres have drawn up clinical guidelines on disease management, which extend over the full length of the patient's cancer journey. Sweden has also started making legislative changes to allow co-financing between health care, social insurance and social services, giving a single regional organisation responsibility for handling each care package as a whole.

The patient perspective

Lynn Faulds Wood, President of the European Cancer Patient Coalition (ECPC) reminded conference of what management issues mean in human terms. Her closest friend had recently been diagnosed with metastatic stomach cancer and was referred to a major London hospital, where she was to receive four cycles of aggressive chemotherapy. "She goes in once every three weeks for her chemo. They don't know when she is coming. They tell her to lie across three chairs because she can't sit up and they don't have a bed for her."

Faulds Wood got her friend moved to another hospital, where things improved dramatically. "They consult her; they write within days with her next appointment; they know she is coming; they give her a bed. They smile, introduce themselves, say what they are doing and why. It is just simple stuff, but the previous hospital did none of that."

The ECPC has almost 300 member organisations from more than 30 countries. Surveys conducted by keypad voting or a show of hands at ECPC master classes established a rough picture of the effectiveness of cancer care delivery across Europe.

- Around half of the patients said there were no disease management guidelines for treating cancer patients in their country
- Patients are, more often than not, provided with no information on their disease and its treatment – two-thirds of respondents said they had to find the information themselves
- Many patients are still not given a full say in matters concerning their treatment – 66% said patients in their country are 'sometimes' allowed to be involved
- Waiting times were deemed unacceptable or 'sometimes' unacceptable by three-quarters of respondents
- Half the patients said timely access to palliative care was not available in their country
- Only a tiny minority of respondents had been made aware of clinical trials they might be eligible to join

The ECPC surveys show that poor management practices in cancer care lead to loss of quality of life and widespread unnecessary suffering. Putting serious political will and leadership into improving structures and processes for cancer care is a relatively simple way to get results on three fronts: healthcare, economics and political popularity. It is the easiest way to improve survival rates, quality of life and patient experiences throughout their cancer journeys. It will deliver more effective care for the resources, without breaking the bank. And probably, in the long run, it is better appreciated by the electorate than simply opening state-of-the-art facilities.

French President Jacques Chirac chose to make the overhaul of cancer services a major part of his legacy. Restructuring the UK's cancer services will also be one of the positive factors in the legacy of UK Prime Minister Tony Blair. Given the escalating cost of health care, political leaders who fail to take action now risk being remembered for being the one who oversaw the beginning of the demise of Europe's public health systems and erosion of the principle of high-quality and affordable healthcare for all.

The power of local solutions

How a local team raised the standards of care for a highly dispersed population

Alan Axford

Speedy access to quality diagnosis, treatment and care has been steadily improving in the South West Wales cancer network, ever since one isolated district hospital turned to video technology to help solve its problems.

The region's one million population is dispersed over a large area with poor transport links. Now many will benefit from access to palliative cancer care, 24/7, thanks to a pilot scheme linking general practitioners and community-based palliative care nurses to a specialist palliative care service by video.

The network recently implemented an electronic tracking system from referral to treatment, helping to avoid unnecessary waiting times and loss of information through the cancer journey. It is piloting an electronic referral scheme for general practitioners (GPs), which cuts out postal delays. It is also using videoconferencing to conduct seminars for clinicians and nursing staff at district hospitals and to offer distance learning programmes to GPs. Pathologists routinely consult one another on camera for second opinions.

One of the best changes means that all cancer patients receive care from multidisciplinary teams that include specialists from the main cancer centre in Swansea on the south coast. These specialists are able to take part in discussions with clinicians and nurses who deliver much of the treatment closer to home.

It all started when the Bronglais hospital in Aberystwyth was asked to refer all cancer patients to Swansea. Although Aberystwyth is only 117 kilometres from Swansea, it is tucked away on the West Wales coast, two hours away by car and four hours by bus. To travel by train means crossing into England – the journey is more than five hours each way and hardly possible in a day.

Alan Axford, cancer lead clinician at the Bronglais hospital, put together a working party to look at how care could be shared between the Swansea centre and his unit to minimise unnecessary travel. The team travelled to the US to get ideas for using communication technologies, and used charity money to purchase equipment to link the district hospital with the cancer centre. This enables video link discussions about the diagnosis, treatment plan and delivery of treatment to be carried out in multidisciplinary meetings involving the local team, specialist teams at the cancer centre and staff elsewhere in the network.

Axford told the conference: "There was a great deal of scepticism among some of my colleagues at the time. The secret is to identify the sceptics and harness the enthusiasm of those who you feel will be prepared to accept the challenge. Some of the greatest sceptics in our hospital and the Swansea centre are now so enthusiastic about this technology that you would imagine they had invented it."

Impressed by this pilot, the South West Wales Network appointed a telemedicine project manager, who rolled it out across the area, mobilising clinicians from every hospital to promote the scheme and organise needs assessments, training, equipment, technical backup, directories and user guides. Communications technology has been quickly embraced throughout the cancer service, and staff and patients are coming up with new ways it could be used to improve services – such as the improvement to palliative care services and smoothing cancer journeys through electronic patient tracking. But it all started with local efforts to solve a problem at an isolated hospital in a small corner of the network.

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