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'Value for money' requirement in treatment choices

Physicians need to change their approach and choose the treatment options which offer most value for money, a conference concluded. This is the only way that all cancer patients will receive the treatment they deserve, without overburdening the health care financial system.

The International Health Economics Forum (Vienna, 20–21 April 2002) was hosted by the Central European Cooperative Oncology Group (CECOG). CECOG is an international group of clinicians which aims to educate physicians in Central and Eastern Europe and the Middle East. The Forum included 25 decision-makers from across the region, who are currently involved in establishing therapeutic guidelines for oncology in their countries.

Many practitioners are unable to use novel anticancer therapies, despite strong medical evidence for their efficacy. This is usually attributed to the slow adoption of these agents into national formularies and, hence, lack of reimbursement for their use.

However, the conference concluded that physicians themselves need an improved understanding of health economic evaluation. This would help them find better ways of coping with economic restraints which limit their provision of healthcare.

"PHYSICIANS MUST SELECT COST-EFFECTIVE TREATMENTS"

Economic evaluations go further than comparing the costs of drugs and should include the burden and management of the disease. For example, in the treatment of non-small cell lung cancer (NSCLC) drug costs for gemcitabine–cisplatin are higher than for standard therapy. Health economist Adrian Kielhorn (Eli Lilly & Co) said that once hospitalisation and administration costs were taken into account as part of an economic evaluation, both treatments cost essentially the same but the new treatment provides patients with a better quality of life.

Improved outcomes associated with novel therapies include prolonged survival for certain patients, but also improved quality of life and reduced side-effects. Policy-makers need to take this into account.

Physicians also need to develop a frame of mind in which they select the treatment options that offer most value for money; and which they are most likely to be able to afford. Continuous education is a key factor in increasing awareness of applied health economics to healthcare providers worldwide. The standard of healthcare for cancer patients must not be compromised.

Professor Dr Christoph Zielinski Director of the Clinical Division of Oncology, University Hospital,Vienna

PET "prevents unnecessary lung surgery"

One in 5 patients with suspected non-small cell lung cancer (NSCLC) could be spared unnecessary surgery by having a PET scan along with conventional workup, says the PLUS study group in the Netherlands (*Lancet* 2002, **359**, 1388–1392).

A group of patients with NSCLC were scheduled for surgery after conventional workup. Half were randomly allocated to receive a PET scan, and all patients were followed for a year. The researchers found that 41% of those who did not have the PET scan had a futile thoracotomy, compared with 21% of those who received the scan.

The main effect of PET was to upstage patients. More than 1 in 4 who had the PET scan were upstaged as a result. "Obviating surgery in such patients improves patients' management," the researchers said. "Non-curative surgery unnecessarily increases burden of disease and risk."

"NON-CURATIVE SURGERY UNNECESSARILY INCREASES THE BURDEN"

The researchers concluded that the addition of PET "can strikingly reduce the number of futile thoracotomies in patients with suspected potentially resectable non-small-cell lung cancer."

An accompanying editorial (*Lancet* 2002, **359**, 1361–1362) said that the findings were "not unexpected" and noted that justified surgery was not decreased by the PET scan result because "PET improved identification of patients who would benefit from thoracotomy".

"Future work should include the determination of the lower limit of nodule size that FDG-PET can accurately characterise and whether FDG-PET can replace other staging procedures," it concluded.

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Endogenous sex hormones "raise breast cancer risk"

High levels of oestrogen and testosterone can double the risk of breast cancer among postmenopausal women, according to the results of an international study (*JNCI* 2002, **94**, 8). Researchers say that, in future, measurement of endogenous hormones might help to identify women at increased risk.

The study was a re-analysis of nine prospective studies, from the UK, Italy, US and Japan. It included individual data on 663 women who developed breast cancer, and 1765 controls.

Researchers found that the risk of breast cancer increased significantly with increasing levels of all sex hormones examined. For oestradiol, the fifth of women with the highest levels had double the risk of the fifth with the lowest levels. For free oestradiol, women with the highest levels had 2.5 times the risk of women with the lowest levels.

"THIS IS THE FIRST EVIDENCE FOR A DIRECT LINK"

Women with raised levels of sex hormone binding globulin were at reduced risk of breast cancer.

Dr Tim Key (Cancer Research UK Epidemiology Unit, Oxford, UK) said that reproductive and hormonal factors are known to be involved in the development of breast cancer, but that this study provides the first strong evidence for a direct link between blood levels of natural hormones and risk of the disease.

"Our study confirms that high levels of sex hormones can raise risk. In the future, our research may allow testing to predict a woman's risk of breast cancer and could provide leads for improved drugs to help prevent the disease. But meanwhile it's important that women try to maintain a healthy weight, since this will reduce their blood oestrogen levels and breast cancer risk."

Conservative treatment in high risk breast cancer

Conservative surgery and radiotherapy is a viable treatment option for women with breast cancer at high risk of developing second primary tumours in either breast, say US researchers (*Lancet* 2002, **359**, 1471–1477). This includes young women with early breast cancer and established genetic vulnerability.

A group of 127 women who were diagnosed with breast cancer before the age of 42, had lumpectomy followed by radiotherapy at Yale University School of Medicine, New Haven. Genetic analysis established that 105 had sporadic disease and the remaining 22 carried deleterious mutations in *BRCA1* or *BRCA2*.

"A SUBSTANTIAL PROPORTION WILL NOT ACCEPT BILATERAL MASTECTOMY"

After 12 years of follow-up, almost half of the genetic group (49%) had ipsilateral cancer, compared with 21% of the sporadic group. Rates of contralateral cancer were also much higher (42% versus 9%). Even faced with the high risks of a second event, they say that "a substantial proportion of patients" will not accept bilateral mastectomy.

None of the group was treated with tamoxifen or had undergone prophylactic oophorectomy, and the researchers suggest that use of these measures "seems prudent" in the genetic group. Careful monitoring should allow early detection of new cancers and effective management should mean that survival is not compromised. "There is no evidence from this or others reported to date that overall or cause-specific survival is compromised for patients with *BRCA1* or *BRCA2* mutations by choosing conservative surgery and radiotherapy over mastectomy," they say.

"MOST CONSIDER AN AGGRESSIVE SURGICAL APPROACH TO BE REASONABLE"

An editorial (*Lancet* 2002, **359**, 1451–1452) is sceptical. This statement is "technically true" it says, but not reassuring since the study did not report on mortality, and there has been no previous work. Author Dr Steven Narod (Sunnybrook and Women's College Health Sciences Centre, Toronto, Canada) says his experience is the opposite. "Most women will consider an aggressive surgical approach to be reasonable when told that their risk of contralateral breast cancer is 40% over the next decade."

He claims that women may not be presented with accurate risk figures, do not have bilateral mastectomy discussed, and that physicians provide unrealistic expectations of mammography.

Screening for pancreatic cancer in diabetic patients

Screening for pancreatic cancer may be possible among selected patients with diabetes mellitus, say Japanese researchers (*Cancer* 2002, **94**, 2344–2349). They found that more than 1 in 8 of a group of diabetic patients had pancreatic cancer.

The study group included patients who had developed diabetes after the age of 55, without obesity, alcoholism or a family history. They demonstrated deterioration of pre-existent glucose intolerance, body weight loss, elevation of serum amylase, high CA19-9 levels and pancreatobiliary abnormalities on routine ultrasonography. They underwent endoscopic retrograde pancreatography (ERP).

Of 86 patients who met the study criteria, 7% had pancreatic cancer. Among those diagnosed with diabetes within the previous 3 years, the rate was even higher, at 13.9%. This compares with only 2% among those diagnosed less recently. The 3-year period after the onset of diabetes is critical, the authors say.

However, the cancer was invariably advanced. "A more aggressive diagnostic approach toward the diagnosis of pancreatic carcinoma in diabetic patients with our criteria may contribute to the earlier diagnosis of the disease," the authors conclude.

EUROFILE

Animal experiments under pressure

One of the most hotly debated ethical issues in biomedical science looks likely to tax the brains of European policymakers, lobbyists and pressure groups over the next few years. In November 2001, the European Commission announced its plans to revise the 1986 Directive on animal experimentation. This will require every EU Member State to amend its national legislation regulating the use of animals in experiments.

The revision, which is expected to be completed in the next 2 years, sets new standards for the housing and welfare of laboratory animals and will apply to all those countries that have adopted the Convention on animal experimentation. In 2000, the European Union itself adopted the Convention, obliging it to adopt the same changes into the Directive. However, the EU requires the approval of the European Parliament to amend any part of the Directive and it is extremely unlikely that Parliament will agree to make only these changes, without amending other parts of the Directive.

"MEPS SAID THE EC HAS FAILED TO PROMOTE ALTERNATIVE METHODS"

MEPs have strong views on animal experimentation and they are certain to propose amendments. Any changes to this Directive will have to be made under the co-decision procedure, where Parliament, the Council and the Commission have to agree, so the Commission cannot ignore amendments passed by Parliament.

The details of the revision are not yet known, but are likely to involve considerable tightening up of regulations on animal experimentation in most European countries. The new-look Directive will also apply to the 'accession' countries, currently waiting to join the EU.

The full-scale revision is not likely to start for 2 or more years, but the political manoeuvring has already begun. Within days of the Commission publishing its proposals, the European Parliament Environment Committee announced that it will prepare a report on the effectiveness of the Directive by December 2002.

"MUCH RESEARCH IS ONLY POSSIBLE USING LABORATORY ANIMALS"

The fate of the unfortunate official who represented the Commission at the first debate on this issue may give a pointer to what is to come. MEPs from all parties hauled him over the coals for what they saw as the failure of the Commission to protect laboratory animals. One MEP after another took the floor to express their dissatisfaction. They cited lack of action against Member States not complying with the current Directive, and the Commission's failure to promote the development of alternative methods.

Troops are also lining up on the other side of the fence. In a highly unusual move, the Scientific Steering Committee, set up to advise the European Commission's Directorate General Sanco (Health and Consumer Protection), issued a statement to "raise awareness of the Commission Services about the implications that would result from a complete disappearance of non-human primate research facilities".

The steering committee, which is comprised of 16 members from across the EU, is so worried by mounting opposition to tests using non-human primates, that it has warned of EU scientists having to rely on research done elsewhere, in countries where they would be unable to control standards of animal welfare. In the UK, Cambridge University's plans to develop a new research centre into brain diseases — which would have involved experiments on monkeys — were scuppered by the probability of animal rights demonstrations. It is an indication of the growing success of the protest movement.

Dr Mark Matfield, Executive Director of the Research Defence Society, the UK body which defends scientists using animals in their research says: "At the moment, the main challenge in cancer research is to understand the functions of all the genes that have been identified as involved in cell division, movement and invasiveness. When we understand which are the crucial genes and the exact roles they play, then we can start designing new treatments that will be specific for cancer. However, much of this research and certainly a lot of the development of treatments will be only be possible using laboratory animals."

Oncologists have also started to defend the need for animal research in the light of these developments. Breast cancer research is under threat from the "new ethics" — well-meaning but misguided attempts to protect the public from the work of the very people who are trying to advance the fight against cancer, said UK breast cancer surgeon Professor Michael Baum at the recent European Breast Cancer Conference (Barcelona, March 2002).

"These threats to research come from multiple directions — EU regulations on clinical trials, the revised Declaration of Helsinki, which is branding some legitimate clinical research unethical, and the activities of animal rights," he said.

Mary Rice,
Brussels

In addition to freelance journalistic activities, Mary Rice is the newly appointed Chief Executive of the European Biomedical Research Association (EBRA) which promotes public understanding of the benefits to human and animal health and welfare resulting from the use of animals in research.

New European paediatric training programme

The training requirements for paediatric haematology and oncology in Europe have been defined by the Société Internationale d'Oncologie Pédiatrique Europe (SIOPE) and the European Society for Paediatric Haematology and Immunology (ESPHI). Their Education and Training Committee has set out the minimum requirements for the education of specialists who will practise within a specialised tertiary care unit.

The training programme is made up of a 3-year 'common trunk': training in basic paediatrics which serves as the basis for other training programmes. All trainees complete this before embarking on another 3 years' training in tertiary care paediatric haematology and oncology. At least two of these years must be spent in clinical training and additional training may be needed for certain career posts. Paediatric haematologists who run laboratories on top of their clinical role may need up to 2 years' extra training, for example.

Professor Jillian Mann (Birmingham University, UK), who chaired the Committee, said the programme was designed to be flexible, so that it will not prevent any potential trainees, such as those entering from adult haematology, from becoming fully trained specialists. "It's a very broad specialty. It covers non malignant haematological disorders, leukaemias, solid tumours, tumours of the central nervous system (CNS), and so on. A broad field of expertise is required."

"EVERYONE HAS TO HAVE AN UNDERLYING BASIC TRAINING"

Most consultants have a special interest and some work exclusively in bone marrow transplantation or in non-malignant haematology. "But everyone has to have an underlying basic training so that they can provide emergency cover across the whole range," she said.

The implementation of the programme will depend on the resources of individual European countries. Those with small populations may have insufficient patients to provide the full training, so that doctors will have to complete parts of their training elsewhere. A European final exam is still being considered.

"We want to improve training across Europe so that all specialists are fully trained. It should allow expertise to be transferable from country to country so that someone with a European qualification can work in any EC country. That is supposed to be the case now, but, in practice, training in one country is not necessarily accepted everywhere else," said Professor Mann.

The full document, The European Training Programme in Paediatric Haematology and Oncology, is posted on the SIOP website at www.siop.nl. Follow the menu through The Society; About SIOP; Continents; Europe; SIOP Europe; Other Committees; Education and Training Programme.

AACR Translational Research Prize

Dr Elwood Jensen and Dr Craig Jordan were jointly awarded the first Dorothy P. Landon-AACR Prize for translational research at the AACR Annual Meeting in April 2002. The selection committee said the symbiosis between their respective bodies of work "has resulted in a dramatic strategic change in the approach to the treatment of cancer, and is one of the most successful examples of translational cancer research." They shared the US $200,000 prize.

Dr Jensen (Vontz Center for Molecular Studies, University of Cincinnati) identified the oestrogen receptor (ER) and refuted the prevailing view of oestrogen action. He purified the receptor, made the first polyclonal and monoclonal antibodies, and contributed to the cloning of the oestrogen reception cDNA. His work led to later studies linking ER to prognosis and treatment response in breast cancer.

Dr Craig Jordan (left) *and Dr Elwood Jensen* (right)

Dr Jordan (Northwestern University, Chicago), a member of the *EJC* Editorial Board, defined oestrogen action at the cellular and molecular level, conducted seminal work on the function of oestrogen receptor antagonists, and recognised the potential of tamoxifen for the treatment and prevention of breast cancer. His further studies formed the basis for the potential clinical applications of selective oestrogen receptor modulators (SERMs).

The prize recognised that their research resulted in the first molecular targeting that has saved hundreds of thousands of lives and opened the door to practical chemoprevention.

Fulvestrant approved in US

Fulvestrant (Faslodex) has received marketing approval from the Food and Drug Administration (FDA) in the US for the treatment of hormone receptor positive metastatic breast cancer in post menopausal women with disease progression following antioestrogen therapy, such as tamoxifen. The drug is administered once a month by intramuscular injection.

INTERVIEW

Professor Louis Denis is director of the Oncology Centre Antwerp, Belgium. He has devoted his career to urological oncology, and introduced transrectal ultrasonography in Europe in 1976. He was the first managing director of EJC. *He was President of EORTC and a founding member of its urological group; and has held office at FECS, ESO, EIO, ESSO. He is chairman of the International Prostate Health Council and treasurer of the International Consultation of Urological Diseases and the UICC.*

Professor Louis Denis

Where did you train?
Initially in Ghent with my specialist surgical training in Colon, Antwerp, and the Medical College of Virginia in Richmond, Virginia, USA.

Who inspired you?
I was an only child growing up in Belgium during the Second World War, and I read a lot of library books, especially history books on the ancient world. I became attached to such inspiring characters as Alexander the Great, Herakleitos and Hippocrates. This interest continued in high school as a classical Latin–Greek education was required to enter medical school.
My three-year stint in the US was the turning point in my urological career. My training under Professor George Prout, later Professor of Surgery of Harvard University, left me enthusiastic for research and clinical trials. Participating in the first prostate cancer trial led by the great W.W. Scott of John Hopkins introduced me on a first name basis to the famous urologists of the era.

Why did you choose to work in the field of cancer?
It looked like the biggest challenge then — and it still is. I dreamed of finding a cure but unfortunately progress comes in very small steps, not one giant leap.

Did any other branch of medicine appeal?
I was interested in paediatrics and gynaecology, but neither was possible in the Belgian army where I started my career. I chose urology because it is a focused specialty and I thought it was possible to know everything. It wasn't and I still have difficulty grasping all the research and clinical developments.

Might you have done something else altogether?
No. I always wanted to help people as a doctor, or perhaps a male nurse. My family had a simple background and were always laughing at me for it, but I knew it was what I wanted to do.

What has been the highlight of your career to date?
A number of highlights in my career involve the successes of some great teamwork in multiprofessional groups. First the EORTC genitourinary group with excellent trials in prostate and bladder cancer. Later, the European School of Oncology, the European Journal of Cancer and the global collaboration with the UICC. Among all my medals and citations, I am most proud of becoming an honorary member of both the Japanese and American Urological Associations; it meant recognition by my peers and that is special.

. . . and your greatest regret?
That the efforts of all the major European Cancer Organisations (including FECS, OECI, EORTC, among others) over the last two years to produce a European Cancer Control Plan failed in front of the finishing line. Europe is still divided but I believe that the professional organisations have found each other.

If you could complete only one more task before you retire, what would it be?
To keep this collaboration on track, and push through the European Cancer Control Plan somehow. Also, to bring patient support groups on board and ensure that they are treated as equals. Finally, through UICC, to develop a strategic plan for cancer in Eastern Europe, Latin America and in Africa, where the situation is most painful of all.

What is your greatest fear?
That in the face of high technology and developments in molecular biology and genetics, we lose our focus on the patient.

What impact has the Internet had on your working life?
Five years ago I was hoping I could retire before the communications revolution took off, but it wasn't to be. I can write a 3-line e-mail but only survive because of the dedicated staff around me!

How do you relax?
With friends in nice places. I like nature, animals and people in our multicultural society, I only wish we could be more harmonious. We've been extremely lucky in this universe, I love this planet!

Who is your favourite author?
We have great writers in Dutch as Claus, Boon and many others. Of course one has a larger choice in English, from Jacob Bronowski's *The Ascent of Man* to Len Deighton or Tom Clancy.

What do you wish you had known before you embarked on your career?
How to plan long-term management and strategy. Medicine without economic management doesn't work in our capitalistic society.

What piece of advice would you give someone starting out now?
You have to like what you do, whether nurse, receptionist, cleaner, doctor. We all have a role. You also have to remain optimistic at all times. And when you need something from the authorities, you have to be prepared to ask 3 times. That's life.

What is your greatest vice?
Good food and drink. There are 450 different brands of beer in Belgium, and they're all good!