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Once-only colorectal test is 'safe and practical'

A single sigmoidoscopy examination reduced colorectal cancer mortality by 43%, and incidence by one third, in a UK study.

The study included a total of 170,432 men and women between the ages of 55 and 64 years. They were followed for a median of 11 years; the researchers expect the reduction in incidence of colorectal cancer to increase over time (*Lancet, doi:10.1016/S0140-6736(10)60551-X*).

Participants had previously indicated that they would accept an invitation for screening and were randomly allocated to intervention or control groups. Intervention entailed flexible sigmoidoscopy with polypectomy for small polyps and referral for colonoscopy for high-risk polyps. Those with low-risk polyps, or none, were discharged.

The hypothesis – that a single flexible sigmoidoscopy is a cost-effective and acceptable method to reduce incidence and mortality – is based on observation: most people with a distal colon cancer will have developed an adenoma by 60 years of age, and removal of adenomas by sigmoidoscopy provides long-term protection against distal colorectal cancer.

In the rectum and sigmoid colon, incidence was reduced by half in those who were screened. There was no effect of screening on the upper colon, which is not examined in sigmoidoscopy.

The researchers write: 'Economic analyses suggest that... a once-only flexible sigmoidoscopy screen at age 55 or 60 years would be cost-saving, largely because of the avoided costs of treatment resulting from the reduction in incidence.'

Flexible sigmoidoscopy 'is a safe and practical test', they conclude, which 'confers a substantial and long-lasting protection from colorectal cancer.'

An accompanying editorial states: 'this size of benefit is large for any cancer screening test, certainly compared with mammography for breast cancer or assay of prostate-specific antigen for prostate cancer.' (*Lancet, doi:10.1016/S0140-6736(10)60626-5*).

The Lancet report is published against a backdrop of increasing concern about the fall-out from screening programmes. A group of US researchers are calling for clinical and research strategies to quantify, recognise, and manage the overdiagnosis of cancer.

'THIS SIZE OF BENEFIT IS LARGE FOR ANY CANCER SCREENING TEST'

Based on data from large randomised screening trials, Drs. Gilbert Welch and William Black (Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire) found that 25% breast cancers detected on mammograms and 60% prostate cancers detected with prostate-specific antigen (PSA tests) could represent overdiagnosis. In a lung cancer screening trial of chest X-rays and sputum tests, 50% of the cancers detected represented over diagnosis.

Incidence and mortality data from the past 30 years in thyroid, prostate, kidney and breast cancer, and melanoma has demonstrated an increase in incidence but not in mortality. In each of these cancers, increased screening has been associated with more new diagnoses, they say (*doi:10.1093/jnci/djq099*).

In accompanying editorial, Dr. Laura Esserman (University of California, San Francisco, USA) says the article 'should serve as a clarion call to acknowledge the spectrum of cancer behaviour and the need to reclassify 'indolent' lesions with a term other than 'cancer' and to improve the specificity of our screening tests' (*JNCI 2010;102(9):582–3*).

Physicians and scientists of all disciplines must come together to reduce the burden both of cancer death and of diagnosis, she says: 'We must advocate for and demand innovation in diagnosis and management, fuelled by science, harnessing modelling, molecular, and immunology tools to address this problem.'

She acknowledges that it will take courage for radiologists to redefine what they call 'suspicious' on imaging, but writes, 'We need to make it an explicit goal to raise the threshold for what we biopsy and diagnose.'

Patients need to understand that not all cancers have the potential to kill. The challenge 'is to work alongside our patients to make care more appropriate, more tailored, less resource intensive and less morbid,' she concludes.

● The European Association of Urology (EAU) reiterated at its 25th Annual Congress (Barcelona; 16–20 April, 2010) that it does not recommend population screening for prostate cancer in Europe.

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BATTLE in lung cancer

The phase II BATTLE (Biomarker-Integrated Approaches of Targeted Therapy for Lung Cancer Elimination) trial used molecular signatures to individualise treatment for non-small cell lung cancer (NSCLC), delegates heard. The study demonstrated 'the feasibility of a biopsy-based, hypothesis-driven biomarker trial,' Professor Roy Herbst said.

The study, at the MD Anderson Cancer Center, Texas, used a statistical model to match four drugs to specific molecular signatures in the tumours of 255 stage IV NSCLC patients. Each of the drugs – erlotinib (Tarceva), sorafenib (Nexavar), vandetanib (Zactima) and erlotinib/bexarotene (Targretin) – is designed to target specific molecular pathways.

Statistician Jack Lee said, 'BATTLE employed an adaptive randomisation approach that allowed the statistical model to learn as the clinical trial progressed.' The first 97 patients were equally randomised to BATTLE's four arms. As information from patients' biopsies and outcomes became available, it was employed by the model to guide assignment of drugs to new patients. Later patients were then more likely to receive a drug that had worked for earlier patients with the same tumour biomarkers.

The study found that sorafenib was best suited to tumours with a KRAS mutation; erlotinib to EGFR mutations; vandetanib for high VEGFR-2 expression; and erlotinib-bexarotene with cyclin D1 defects or amplified numbers of the EGFR gene.

The model leads to greater use of successful drugs and minimisation or dropping of those less successful. Vandetanib helped those with VEGFR overexpression but was dropped for patients with the KRAS mutation.

Overall, 46% of patients in the trial had disease control at 8 weeks, compared with historical experience of around 30% for late-stage lung cancer.

[Proc AACR 2010 # LB-1]

An early marker for breast cancer?

Levels of epidermal growth factor receptor (EGFR) may rise in the 17 months preceding a diagnosis of breast cancer, the meeting heard.

Dr. Christopher Li (Fred Hutchison Cancer Research Center, Seattle) said the results suggest that there may be detectable changes of proteins in blood in the 2 years before a clinical diagnosis: 'Identification of these proteins could have a major impact on our ability to detect breast cancer early, when it is most treatable.'

The study included 420 oestrogen receptor-positive breast cancer patients whose blood had been drawn within 17 months prior to their diagnosis. They were compared with an independent set of 198 cases and controls from the Women's Health Initiative database.

Researchers found that women with the highest levels of EGFR had a 2.9-fold increase in their risk of developing breast cancer, compared to those with the lowest level.

EGFR could not be used as a single marker, and the results need confirmation. But Dr. Li said, 'No prior studies have validated a single breast cancer early detection biomarker specimen to the degree we have here.'

[Proc AACR 2010 # 4815]

Statins 'do not protect against colorectal cancer'

Statins did not protect against colorectal adenomas and, in a high-risk population, may have increased the risk of benign colorectal tumours, Dr. Monica Bertagnolli (Harvard Medical School, Boston, Massachusetts) said.

Presenting a secondary analysis of the Adenoma Prevention with Celecoxib (APC) trial, she said, 'Given our results, we do not think that is it reasonable to further study statins for chemoprevention of colorectal cancer, as the chance that they have this activity is very small.'

The APC trial included 2035 adenoma patients randomised to receive placebo or two different doses of celecoxib. Among the 679 on placebo, patients who used statins at any time had no benefit in tumour growth over a 5-year period compared with those who never used statins.

The results were surprising, since pre-clinical studies had indicated that statins would be beneficial. However, Dr. Bertagnolli stressed that people at risk of cardiovascular disease should not stop taking statins based on this data.

[Proc AACR 2010 # LB-173]

Risk assessment in prostate cancer

A refined prostate-specific antigen (PSA) test is a step towards identifying those men with prostate cancer who will need treatment, Dr. Robert Veltri (Johns Hopkins Hospital, Baltimore) said.

He and colleagues tested 71 patients undergoing proactive surveillance for low-grade, low-stage, non-palpable prostate cancer. They used the Prostate Health Index, which incorporates pro-PSA, free PSA and total PSA, along with an annual surveillance biopsy and a 6 monthly digital rectal examination.

Of the group, 39 patients developed an unfavourable biopsy. The Prostate Health Index predicted cancer progression, as did DNA content measurements – performed by image analysis – of the biopsy. Serum pro-PSA level alone did not predict biopsy conversion.

'The overall objective of the Proactive Surveillance project is that baseline levels of molecular and morphologic biomarkers or other risk factors can identify men with prostate cancer who can safely forego curative intervention based upon monitoring clinical parameters and quantitative biopsy pathology,' Dr. Veltri said.

An expanded study by the same team is evaluating other potential biomarkers that predict unfavourable biopsy conversion.

[Proc AACR 2010 # 2731/13]

EUROFILE

An overhaul of the Clinical Trials Directive

European cancer organisations have submitted evidence to the European Commission substantiating claims that the clinical trials directive is hampering academic cancer-related clinical trials in Europe. They have rejected a Commission idea to withdraw the law for non-commercial and academic trials.

The clinical trials directive came into force in 2004 with the intention of providing a common set of standards to make it easier for member states to conduct pan-European trials, and simplify procedures to make the pharmaceuticals sector in Europe more competitive.

The Commission launched a consultation exercise at the end of 2009 after two separate EU studies published that year highlighted negative impacts. Both ICREL (Impact on Clinical Research of European Legislation), as part of the EU Framework and the High Level Group of Independent Stakeholders on Administrative Burdens, concluded that performing clinical trials in Europe had become more difficult and costly after the introduction of the law.

The Commission consultation asked for both qualitative and quantitative evidence on the impact of the directive. Of 106 replies received, 60 came from hospitals, non-commercial/academic investigators and sponsors. ECCO provided a bullet-point summary of areas requiring attention. Its individual member organisations gave detailed evidence and recommendations for improving the system.

The two main factors for the increase in cost of non-commercial pan-European cancer trials stem from the directive's requirement for a single sponsor to accept the legal and financial responsibility for running a trial across all study sites, and the increased cost of risk insurance. Research institutions had previously shared these costs.

The Commission proposed excluding non-commercial sponsors from the scope of the directive altogether. This would subject them only to the rules of the member state hosting the trial. It would also render the results of these clinical trials unusable for drug marketing authorisation applications in the EU.

Cancer organisations are almost unanimously opposed to the idea. EORTC feels 'this would marginalise academic research' and advises pragmatic implementation on a risk-based approach.

It clarifies its position in a joint position paper with ECRIN, the European Clinical Research Infrastructures Network and the European Medical Research Councils. 'Defining specific modalities for non-commercial trials tends to suggest that there are two levels of quality. This should be avoided, and in turn risk-based strategies should be used to improve the cost-effectiveness of clinical trials, especially for monitoring. Therefore developing regulatory requirements adapted to the risk associated [with] defined categories of clinical trials would be an alternative way,' it says.

'Most clinical trials sponsored by academic institutions correspond to categories of research associated with a lower risk: studies using marketed drugs within their labeled indication for treatment optimisation or combination trials, trials on off-label use of marketed drugs, pharmaco-epidemiology studies. Academic institutions are also involved in the development of drug treatments for rare diseases, where market incentives fail to drive industry investment. Public–private partnership is frequently used for co-funding or co-development. Specific modalities should be defined for all these categories of research, not for non-commercial trials as a whole.'

Jan Geissler, director of the European Cancer Patients Coalition proposes two main categories for a risk-based approach. 'For cancer, therapy-optimisation and follow-up studies with drugs or modalities where the efficacy and side effects are known through approval and daily practice, should follow a less strict framework than studies that aim at approval of a new compound or modality,' he says. 'The adequacy of insurance requirements should be reconsidered, also in long-term observational studies in oncology, for example – when following up for 10–15 years.'

Cancer Research UK proposes modifying the definition of a sponsor to allow for:

- A 'co-sponsorship' model; and/or
- Member state specific versions of an academic trial which are sponsored on a national level but for which meta-analysis of the data is specified within the protocol; and/or
- National sponsorship in individual countries with one named nominated sponsor retaining oversight of a trial without any legal responsibility.

Markus Hartmann, senior consultant at European Consulting and Contracting in Oncology says when considering risk for research participants, amendments to the directive 'should consider the sponsor as not relevant since the protection of patient rights and safety must be ensured in all cases.'

While the Society of Paediatric Oncology and Haematology for Germany and Austria believes that exclusion of academic sponsors from the directive may be better than the current situation, the proposal is rejected outright by the European Society for Paediatric Oncology (SIOPE). The cancer organisations' near-universal position received perhaps unexpected support from the European Federation of Pharmaceuticals Industry Associations (EFPIA). It advocates 'a review of the legislation to identify those provisions of the legislation that cause difficulty for 'academic' and other sponsors.'

'If, by excluding these provisions, there is no impact on the safety of clinical trial participants or quality of the data, the reasons for including those provisions in the CT legislation and applying them to all sponsors needs to be reviewed,' EFPIA says.

Saffina Rana
Brussels

http://www.efgcp.be/icrel/ and *http://ec.europa.eu/enterprise/admin-burdens-reduction/highlevelgroup_en.htm*

US court sparks debate on cancer gene patents

US District Court Judge for New York, Robert Sweet, ruled in favour of the American Civil Liberties Union and College of American Pathologists on March 29, invalidating seven gene patents on *BRCA1* and *BRCA2* held by Myriad Genetics and the University of Utah (*New York Times*, March 30, 2010). *BRCA1* and *BRCA2* mutations are associated with breast and ovarian cancer risk. With at least a fifth of human genes under patent, the decision sent shockwaves through the multibillion-dollar biotechnology industry. But restrictions on individual gene patents could hasten innovation in genome-wide diagnostic cancer testing and research, said experts contacted by *The Lancet Oncology*.

Myriad argued that isolated genes are 'markedly different' from genomic DNA in structure and function to justify patenting their use as diagnostic and prognostic tools. But Sweet dismissed Myriad's argument as 'lawyer's tricks', and ruled that simply isolating and purifying a product of nature is not, alone, a sufficient innovation for patent protection in the case of genes, because of DNA's unique quality of carrying information. Myriad's 20-year patents on *BRCA1* and *BRCA2* will expire in 2014 and 2015, respectively.

'It was an extremely sophisticated decision, involving an impressive and nuanced understanding of genetics', Jim Evans (University of North Chapel Hill, NC, USA), told *The Lancet Oncology*. 'The very essence of a gene is in its information content. That sets it apart from other biological molecules, because the gene does the same thing in a test tube as in a cell.' The case is destined for appeal at the Federal Circuit Court, and an appeal will probably be lodged at the Supreme Court by the losing party, although it is unclear whether the Supreme Court will agree to hear the case.

'The value of these patents lies in the information the gene encodes', Rochelle Dreyfuss (New York University, New York, NY, USA) told *The Lancet Oncology*. 'In the name of freeing the information encoded in these genes for diagnostic purposes, the court removes genes from the realm of patentable subject matter for all purposes. That could diminish incentives to invent therapies.'

Patents ensure that inventors are granted temporary market monopolies, allowing them to recoup costs and rewarding risk taking. The ruling implicitly threatens thousands of gene patents in the US, and might affect transcriptional gene product (RNA) patents as well. Patents on many proteins would also be threatened, warned patent lawyer Richard Gold (McGill University, Quebec, Canada; *Financial Times*, April 6)—a concern not shared by most experts contacted by *The Lancet Oncology* because of the importance given in the ruling to DNA's unique informational characteristics. Nor will the ruling affect genetically engineered products that are different from genes found in nature, Dreyfuss said. But the threat of lawsuits by the holders of gene patents stifles research, Evans said. Geneticists and those developing diagnostic tests avoid working not only with genes already patented by others, but even with genes 'with patents around them', Evans said. That concern is increasingly important in the emerging era of genome-wide microarray testing and complex gene-pathway-based research into potential cancer therapies, he noted. 'Such barriers to research are antithetical to the entire patent system', Evans said. 'The constitutional function of patents is to promote progress in science and the useful arts. To put tollbooths so far upstream, at the level of individual genes, is hard to justify. It significantly dampens research and clinical utility.'

One solution to that problem would be a research exemption from patent liability, Dreyfuss said. US gene patents are held largely by universities and result from publicly funded research, but exclusive licences to those patents do more to block competition in the diagnostic testing market than to hasten diagnostic innovations, Robert Cook-Deegan (Duke University, Durham, NC, USA) told *The Lancet Oncology*. In April, Cook-Deegan's team published case studies of genetic risk testing for ten clinical conditions, including breast and colon cancer. The studies were prepared for the US Health and Human Services Secretary's Advisory Committee on Genetics, Health and Society.

The pricing, availability, and for the most part, quality of diagnostic tests were not affected much by diagnostic market monopolies—although exclusive licensing decreased incentives to openly share test quality data, complicating assessment, Cook-Deegan noted. 'But exclusive licences are difficult for other companies to develop around,' he said. 'Patient rights should trump patent rights if a company engages in practices that undermine the purpose of patents in the first place.'

The case has been followed closely in Australia, where a Senate inquiry is expected to conclude in June its investigation into the effects of gene patents on patients (*Sydney Morning Herald*, March 31, 2010).

Bryant Furlow

For more on **genetic risk testing** see *Genet Med 2010*; published online April 14 DOI:10.1097/GIM.0b013e3181d694b0

For more on the **US Health and Human Services Secretary's Advisory Committee on Genetics, Health and Society** see http://oba.od.nih.gov/SACGHS/sacghs_home.html

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'Substantial differences' in lung cancer survival

Survival from lung cancer is significantly higher in Sweden and Norway than in England, a study has found (*Thorax 2010;65:436–41*).

Based on registry data, researchers estimated 5-year age-standardised survival in Sweden as 11.3%, compared with 9.3% in Norway and 6.5% in England.

Differences in death rates were mostly in the year after diagnosis and the authors say that access to healthcare and population awareness drove the discrepancy. However, management approaches differed. In England, 48% patients were not offered active antitumour treatment, compared to 40% in Norway and 19% in Sweden.

PODIUM

EORTC: Fit for the Future

Professor Jean-Yves Blay (Université Claude Bernard, Lyon, France) chairs the French Sarcoma Group and is Network Director of the EC's Conticanet, dedicated to novel treatment approaches in sarcoma. At EORTC, he has been active on the Protocol Review and Translational Research Advisory Committees; he took over as President of the organisation in 2009.

What are the key challenges facing EORTC today?
EORTC is a mature organisation which has, of necessity, evolved over the years. The focus now is on the types of clinical trials we conduct. Today's molecular clinical trials can be carried out at centres with the capacity to undertake translational research. EORTC is moving in this direction; all new clinical trials will include translational research, and all need to be practice changing.

That's a very high standard?
The increase in the administrative burden of each clinical trial following the Clinical Trials Directive has meant that we have had to reduce the number of trials we conduct. We're now focusing on high quality, practice changing trials, which will be conducted rapidly. We need to match the standard of our partners in industry.

How well-placed is EORTC to be carrying out this research?
EORTC is in a central position for clinical trials in cancer in Europe, and has an important role to play in international trials. It is one of the few organisations with the capacity to integrate other research groups through our intergroup clinical trials. We have the experience necessary to organise and implement trials, taking the specific requirements of each country into consideration. But we also need to interact with other active networks in Europe and beyond. Some trials need to be conducted at the global level, and a common strategy for addressing multiple questions in some disease types requires EORTC to interact widely.

Is the structure of EORTC changing?
It is evolving. The 20 or so disease-oriented groups and task forces – in breast, gastrointestinal cancer and so on – remain a core activity which needs to continue to expand. They integrate small and medium-sized centres and they're important in accrual and in extending research activity into different centres and different parts of Europe. But we also need the Network of Core Institutions (NOCI) to carry out modern trials rapidly. It is comprised of 26 large institutions with excellent facilities for surgery, clinical research, molecular biology, pathology and so on. They can pilot clinical trials which are multi-disease and target-oriented, the type of clinical trial which is based on a true understanding of the biology of disease. At the moment, we're setting up a trial on the inhibition of ALK in different diseases: lymphomas, sarcomas, etc.

Are you being charitable by continuing with the smaller institutions?
It's a balance. EORTC used to work with institutes which contributed a couple of patients a year into trials. It was expensive, had implications for the quality of research, and is no longer feasible, but there's a huge reward for engaging with smaller centres and actively trying to help them accrue more significant numbers. There must be commitment on both sides; where they commit to substantial participation, we can help them become established on the European scene.

The picture is not static. Participation is researcher-oriented and institutions may become more or less actively involved in the EORTC depending on the interests of individuals. This is a good thing; we have to be flexible and allow some to arrive and others to leave. It's much better than leaving things unchanged for 20 years.

You are concerned about the lack of young investigators?
We have a shortage of molecular oncologists, pathologists and other specialists worldwide. EORTC is an important route on to the European scene for young investigators; it is exactly the right place to develop a career in research.

Our fellowship program has so far involved more than 120 young researchers who have benefited from working at the Data Centre and participating in EORTC's activities. But the more conventional route is via involvement with a group. Young investigators who put in the time and commitment can really develop their scientific career. There is a lot of room for them in EORTC groups; they can progress rapidly and take on positions of responsibility. It's particularly true right now because of our culture of translational research; young researchers have the molecular knowledge which is critical for the activities of every group.

What do you hope to achieve during your presidency?
We will remain a high quality, independent, academic clinical research organisation which, through NOCI and the whole of EORTC, will stress the importance of molecular trials. Targeted therapies need to be adapted to the molecular portrait of tumours, and we need a shift from the current standard inclusion criteria, which are disease-oriented, to molecular-oriented criteria. This is not trivial; our mind-set needs to change, so that molecular biology becomes integral to clinical trials. I want EORTC to become the central platform for clinical research in Europe. It's a promising time for an open and thriving network.

Helen Saul