unplanned surge in demand, patients are not being treated within the evidence based time period. FRISC-II and TACTICS-TIMI 18 randomised patients to invasive or non-invasive treatment within a few days of presentation, and ISAR-COOL⁹ shows that treating patients earlier than that is beneficial. Perhaps we are simply selecting out a group of patients at lower risk. Thirdly, we are also practising postcode medicine. A patient who has an acute coronary syndrome without ST elevation and is admitted to a hospital with facilities for revascularisation is likely to receive treatment quicker than a similar patient admitted to a hospital without such facilities.¹⁰ Similarly, in one hospital, a troponin positive patient with an acute coronary syndrome may be admitted for a few days and, if asymptomatic, be sent home, whereas in another hospital such a patient may be kept in hospital pending transfer. How can both strategies be correct?

Has measuring troponins in patients with acute chest pain been a clinical success? This measurement is flawed as a clinical tool. Firstly, our interpretation of the data may be overenthusiastic. Of studies showing a correlation between troponin concentration and outcome, the event rate, even in cohorts with the highest band of troponin is around 20%. Many centres currently refer all patients with acute coronary syndrome who have elevated troponin concentrations for early angiography. Thereafter, all these patients (fewer than 70% of whom will have an event during the follow up period) are considered for revascularisation on the basis of a reduction in the six month event rate from 12.1% to 9.4% for death or myocardial infarction in FRISC-II or 19.4% to 15.9% for death, myocardial infarction, or rehospitalisation in TACTICS-TIMI 18.^{4 5} Surely this represents a rather blunt screening tool. The second flaw in measuring troponin is that it is too eagerly perceived as a rule in or rule out test. The test has become, for many clinicians, the main component of their decision making. The final flaw is that elevation of troponin is reported in a myriad of clinical conditions that do not seem to be associated with myocardial ischaemia.

The solution is to refine the way we use the test to ensure that it is only one element of a clinically driven management algorithm. The meticulous derivation of clinical risk scores, particularly GRACE,¹¹ should be exploited. Furthermore, research that focuses on the identification of other markers of risk should be facilitated, in order to target revascularisation at those most likely to benefit. In addition, we should make use of the heterogeneous nature of current management by care-

fully observing outcome in patients who are not put up for inpatient angiography. Do such patients do badly? Recent data from the ICTUS trial¹² call our current strategy of early angiography for all patients with raised troponin into question.

Troponin measurement in patients with acute chest pain is a mixed blessing. We need to refine our current strategy to provide optimal treatment for such patients. Troponin is a blunt screening tool for the assessment of patients with acute coronary syndromes without ST elevation, and we should avoid compounding this by ignoring clinical factors. Above all, we need a realistic national management guideline to avoid inequity of access, pending better risk stratification tools.

N Curzen *consultant cardiologist*

Wessex Cardiac Unit, Southampton General Hospital, Southampton SO16 6YD
(nick.curzen@suht.swest.nhs.uk)

Competing interests: None declared.

- 1 Hamm CW, Ravkilde J, Gerhardt W, Jorgensen P, Peheim E, Ljungdahl L, et al. The prognostic value of serum troponin T in unstable angina. *N Engl J Med* 1992;327:146-50.
- 2 Lindhal B, Venge P, Wallentin L. Relation between troponin T and subsequent cardiac events in unstable coronary artery disease. *Circulation* 1996;93:1651-7.
- 3 Antman EM, Tanasijevic MJ, Thompson B, Schactman M, McCabe CH, Cannon CP, et al. Cardiac-specific troponin I levels predict the risk of mortality in patients with acute coronary syndromes. *N Engl J Med* 1996;335:1342-9.
- 4 FRISC II Investigators. Invasive compared with non-invasive treatment in unstable coronary artery disease: FRISC-II prospective randomised multicentre study. *Lancet* 1999;354:708-15.
- 5 Cannon CP, Weintraub WS, Demopoulos LA, Vicari R, Frey MJ, Lakkis N, et al. TACTICS-TIMI 18 Investigators. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with glycoprotein IIb/IIIa inhibitor tirofiban. *N Engl J Med* 2001;344:1879-87.
- 6 Fox KA, Poole-Wilson PA, Henderson RA, Clayton TC, Chamberlain DA, Shaw TR, et al. Randomised Intervention Trial of unstable Angina (RITA) Investigators. Interventional versus conservative treatment for patients with unstable angina or non-ST elevation MI: the BHF RITA 3 randomised trial. *Lancet* 2002;360:743-51.
- 7 Archbold RA, Curzen N. The role of revascularisation in the management of non-ST elevation acute coronary syndromes: who should you refer? *Clin Med* 2004;4:32-5.
- 8 Bellenger N, Eichhofer J, Crone D, Curzen N. Hospital stay in patients with non-ST elevation acute coronary syndromes. *Lancet* 2004;363:1399-4000.
- 9 Neumann FJ, Kastrati A, Pogatsa-Murray G, Mehilli J, Bollwein H, Bestehorn HP, et al. Evaluation of prolonged antithrombotic pre-treatment ("cooling-off" strategy) before intervention in patients with unstable coronary syndromes: a randomised controlled trial. *JAMA* 2003;290:1593-9.
- 10 Miller C, Lipscomb K, Curzen N. Are DGH patients with unstable angina at a disadvantage? *Postgrad Med J* 2003;79:93-8.
- 11 Eagle KA, Lim MJ, Dabbous OH, Pieper KS, Goldberg RJ, Van de Werf F, et al. GRACE investigators. A validated prediction model for all forms of acute coronary syndrome: estimating the risk of 6 month post discharge death in an international registry. *JAMA* 2004;291:2727-33.
- 12 De Winter R. Invasive vs. conservative treatment in unstable coronary syndromes (ICTUS) trial. Oral presentation, European Society of Cardiology Congress, Munich, August 2004.

Patenting genes

May slow down innovation, and delay availability of cheaper genetic tests

Patents on genes have been granted for many years. Until January 2001, when the first patent for the first breast cancer gene (BRCA1) was granted by the European Patent Office to Myriad Genetics, a US company, most geneticists in Europe had never worried that genes and genetic tests could become exclusive property of a laboratory or a

company. A patent allows a company to develop commercial laboratory testing services based on the gene sequences and charge other laboratories wanting to run genetic tests. Myriad Genetics holds several patents on the breast cancer genes BRCA1 and BRCA2 and offers a specific test called BRACAnalysis to detect abnormalities in these genes. The company opted to

BMJ 2004;329:1358-60

Patenting the familial breast cancer genes

The familial breast cancer genes, BRCA1 and BRCA2, have been located on chromosome 17 and 13 respectively as a result of a large, international collaborative effort in the early nineties. The BRCA1 gene was eventually cloned by Myriad Genetics in 1994. The BRCA2 gene was sequenced in 1995, first at the Sanger Institute, and almost at the same time by Myriad Genetics.

Several patents on BRCA1 and BRCA2 have been granted by the United States Patent and Trademark Office between 1997 and 2000. In Europe, a total of five patents have been granted by the European Patent Office, between 2001 and 2004. In the meantime, many European laboratories had already set up BRCA1 and BRCA2 testing.

exert its monopoly right strictly on the genes, by requesting that all diagnostic testing be done at its laboratory in the United States. The Belgian, Dutch, French, and other European genetic centres and cancer institutes have filed oppositions against these patents.¹ Recently, the European Patent Office has revoked the first BRCA1 patent granted to Myriad Genetics.²

But earlier this year, the European Patent Office also granted a patent on the second breast cancer gene, BRCA2, to Cancer Research UK, the charity trust which has funded breast cancer research at the Sanger Institute in the United Kingdom.³ However, Cancer Research UK has immediately announced that it will allow public laboratories throughout Europe to use the patent for free.³ Even if the latter sounds like good news, it further illustrates the arbitrariness of patenting and licensing in the field of gene based diagnostics.

Patents are meant to reward the inventors but also to promote progress through the generation of useful new products. In this way, patents are thought to be beneficial to the public. Gene patents typically cover the clinical applications of mutation analysis, as well as the use of the gene sequences for the development of treatment. Under current patent law both in Europe and in the United States, genes can be patented "if their isolation from their natural environment involves a technical step."⁴ This is obviously controversial. The Nuffield Council on Bioethics has already concluded that the description of an association between a gene and a disease amounts to little more than a discovery.⁵ Similarly, the American College of Medical Genetics has taken the position that genes and their mutations are naturally occurring substances that should not be patented.⁶

For the time being, most European laboratories that established mutation analysis for BRCA1 and BRCA2 in the few years since the genes were discovered, continue to perform their own testing. If, nevertheless, a few samples are sent to the Myriad Genetics laboratories, it is because Myriad beats the European laboratories by offering speed for the analysis. However, together with the result comes an invoice of some \$2500 (£1400; €2100, if purchased directly from Myriad Genetics, or €3980 when purchased via Bioscientia, the European licensee for the BRACAnalysis). In general the European laboratories use more cost effective tests.⁷ The difference for the patients is huge, however, because the local tests are free or largely reimbursed and the overseas invoices are not.

There is other evidence that the costs for the genetic tests will increase as a result of patenting. A

survey about the effect of the patent on the hereditary haemochromatosis gene has revealed that Bio-Rad Laboratories, the current owner of the patent, requests up front payments of the order of \$25 000 per laboratory plus a per test fee of about \$20.⁸ This is a lot for a simple diagnostic test. Many laboratories in the United States have already refrained from offering this test.⁸ In the end patents will thus slow down biomedical innovation and delay the availability of cheaper tests.

One reason why the market system does not always operate properly in the case of patents on genes is because genes and genetic sequences are different from classical chemical compounds. Genes and genetic sequences have an informational content. One cannot "invent around" the sequence if it is patented, because each gene and each gene sequence is unique in its kind. Hence, through patenting, a "double" monopoly arises.¹

At first glance, this problem could practically be circumvented by the free licences, like the one offered to the European public laboratories by Cancer Research UK on BRCA2. However, this will be criticised by patent owners and supporters of the patenting system because it seemingly disregards the efforts and funds that the grantees have invested. In general, patent specialists and patents offices claim that the problem is in licensing, not patenting. I agree that Europe lacks a system that ensures guidance and surveillance of licensing of genetic inventions. Still, I believe that a claim to exclude gene based diagnostics from patenting is legitimate from the standpoint that the patenting system should not interfere with the availability of a genetic test for the patient. The basis for such an exemption has been laid years ago. Article 52(4) of the European Patent Convention of 1973 excludes "diagnostic methods, practised on the human body" from patenting.⁹ This definition dates back to the days when people did not want surgical methods and other medical practices to be patented. This could be updated to include genetic testing.

This is a way to avoid monopolies on the use of a genetic sequence for diagnostic purposes in humans, without interfering with patent protection of other genetic applications, including the development of therapeutics. The latter requires huge investments, but the first does not: once the relation between a gene and a disease is established, diagnostic tests can be developed at relatively low cost.¹

Several initiatives have recently been taken to deal with aspects of patenting and licensing of genes by international organisations like the Organisation for Economic Co-operation and Development (OECD), the Human Genome Organisation (HUGO), and the European Society for Human Genetics (ESHG), and by a few national governments. I wish to call on the medical community and the national and international medical associations also to take part in this important discussion.

Gert Matthijs *head, Laboratory for Molecular Diagnosis*

Center for Human Genetics, University of Leuven, Herestraat 49, Gasthuisberg, B-3000 Leuven, Belgium
(gert.matthijs@uz.kuleuven.ac.be)

Competing interest: GM is actively involved in the opposition procedure against the European BRCA patents, on behalf of several genetic and research institutes and societies. He will also be chairing the recently installed Patenting and Licensing Committee of the European Society for Human Genetics, which aims

to advance the discussion on patenting and licensing of genes, sequences, and genetic tests.

- 1 Matthijs G, Halley D. European-wide opposition against the breast cancer gene patents. *Eur J Hum Genet* 2002;10:783-5
- 2 European Patent Office. "Myriad/breast cancer" patent revoked after public hearing. Press release, 2004. www.european-patent-office.org/news/pressrel/2004_05_18_e.htm (accessed 18 May, 2004)
- 3 Cancer Research UK. Charities to make breast cancer (BRCA2) gene freely available across Europe. Press release, 2004. www.cancerresearchuk.org/news/pressreleases/breastcancergene_11feb04?version=1 (accessed 11 Feb 2004).
- 4 Directive 98/44/EC of the European Parliament and of the Council, 6 July 1998.

- 5 Nuffield Council on Bioethics. *The ethics of patenting DNA, a discussion paper*. www.nuffieldbioethics.org/publications/pp_0000000014.asp (accessed 3 Jun 2004).
- 6 American College of Medical Genetics. Position statement on gene patents and accessibility of gene testing. <http://genetics.faseb.org/genetics/acmg/pol-34.htm> (accessed 3 Jun 2004).
- 7 Sevilla C, Moatti JP, Julian-Reynier C, Eisinger F, Stoppa-Lyonnet D, Bressac-de Paillerets B, et al. Testing for BRCA1 mutations: a cost-effectiveness analysis. *Eur J Hum Genet* 2002;10:599-606.
- 8 Merz JF, Kriss AG, Leonard DG, Cho MK. Diagnostic testing fails the test. *Nature* 2002;415:577-9.
- 9 European Patent Convention. *European patent convention*. <http://www3.european-patent-office.org/legal/epc/index.html> (accessed 3 Jun 2004).

Trial protocols at the *BMJ*

Authors must submit the protocol with the trial

Moves to improve the conduct and reporting of clinical trials have gathered pace this year. One issue that the *BMJ* has long grappled with is what to do about protocols of trials, and we announce a new policy that begins in January 2005.

Medical research should begin with a protocol that details the hypothesis, objectives, and methodology to be used in the study. Ideally the study should not deviate from the protocol, but in reality it often does. Sometimes deviating from the protocol is unavoidable—for example, when new evidence is published independently during the trial which invalidates the specified outcome. In other instances, protocol deviation may represent suppression of unfavourable findings in favour of reporting favourable ones.

Evidence of bias has been limited to case reports,^{1,2} but now we have research that begins to quantify the problem.³⁻⁵ Chan et al compared the completeness of outcomes reported in protocols versus outcomes reported in published research.⁴ Their cohort study showed that about 50% of efficacy outcomes and 65% of harms per trial were incompletely reported, and 62% of trials had at least one primary outcome that was added, changed, or removed compared with the protocol. That 86% of the authors surveyed denied the existence of unreported outcomes implies that the extent of reporting bias may be even greater. These findings are supported by two further studies, which show that selective and incomplete reporting of outcomes in published randomised controlled trials is common.^{3,5}

The desire to eliminate bias in reporting research has prompted important initiatives over the last decade. These have culminated in the use of the CONSORT statement (the Consolidated Standards of Reporting Trials) and other guidelines such as QUOROM (Quality of Reporting of Meta-analyses).^{6,7} The CONSORT checklist stipulates that deviations in the protocol should be described including reasons for doing so. Randomised controlled trials submitted to the *BMJ* must be reported in accordance with the CONSORT statement and checklist. We require a declaration that the decision to publish was controlled by the authors and not the trial sponsor.⁸ From July 2005 all trials will also need to be registered with a suitable trial registry.⁹ Now authors must submit the trial protocol with their manuscript submission, and we will not

send the manuscript to an external reviewer unless we have the protocol.

Our experience of chasing authors for trial protocols, when we have suspected deviation in the protocol or found it hard to fathom what the authors set out to do, has been miserable. Authors are reluctant to send us the protocol, and the review process can be considerably delayed. Our electronic manuscript submission system allows additional documents to be uploaded as supplementary data files, and we ask authors to add the protocol to their manuscript submission in this way. *BMJ* editors and reviewers of that particular manuscript will be able to see the protocol on our system and refer to it as necessary. We do not intend to publish the protocols at this stage.

We are not offering peer review of protocols as the *Lancet* does,¹⁰ although we may offer this in future. We are currently conducting research into what kind of protocol review trialists favour. In the meantime, we believe that identifying deviation from the protocol is another important step in ensuring that the findings of a study are reported with honesty and transparency.

Giselle Jones *assistant editor BMJ*

Kamran Abbasi *acting editor BMJ*

Competing interests: None declared.

- 1 West RR, Jones DA. Publication bias in statistical overview of trials: example of psychological rehabilitation following myocardial infarction [abstract]. In: Proceedings of the Second International Conference on the Scientific Basis of Health Services and Fifth International Cochrane Colloquium, Amsterdam, Netherlands, 8-12 October, 1997.
- 2 McCormack K, Scott NW, Grant AM. Outcome reporting bias and individual patient data meta-analysis: a case study in surgery [abstract]. In: Abstracts for Workshops and Scientific Sessions, Ninth International Cochrane Colloquium, Lyons, France, 9-13 October, 2001.
- 3 Chan A, Kriebitz-Jeric K, Schmid I, Altman D. Outcome reporting bias in randomized trials funded by the Canadian Institutes of Health Research. *CMAJ* 2004;171:735-40.
- 4 Chan A, Hróbjartsson A, Haahr M, Gøtzsche P, Altman D. Empirical evidence for selective reporting of outcomes in randomized trials: comparison of protocols to published articles. *JAMA* 2004;291:2457-65.
- 5 Chan A, Altman D. Outcome reporting bias in randomised trials on PubMed: evidence from publications and trialists. *BMJ* (in press).
- 6 Begg CB, Cho MK, Eastwood S, Horton R, Moher D, Olkin I, et al. Improving the quality of reporting of randomized controlled trials: the CONSORT statement. *JAMA* 1996;276:637-9.
- 7 Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF, for the QUOROM Group. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. *Lancet* 1999;354:1896-900.
- 8 Smith R. Maintaining the integrity of the scientific record. *BMJ* 2001;323:588.
- 9 Abbasi K. Compulsory registration of clinical trials. *BMJ* 2004;329:637-8.
- 10 McNamee D. Protocol reviews at the *Lancet*. *Lancet* 1997;350:6.

BMJ 2004;329:1360