vidual patient.[6] But the proliferation of instruments that have been developed for screening and for clinical prediction leaves open a temptation to confuse the two, and to misapply them in circumstances for which they were not designed. Tools designed to be used for screening are not necessarily effective in cases of individual decision making. This is not to say that there can never be circumstances in which screening tools are appropriate for individual assessment, but the onus must be upon those who wish to use tools in novel ways to justify such use in a systematic fashion.

Rosendal and colleagues address an important issue. Improved diagnosis of somatisation will help clinicians to provide appropriate support and understanding for patients with this disorder. Better diagnosis will help to avoid unnecessary investigations, referrals, and invasive procedures with the attendant problems of cost, delay, and distress for all concerned. The challenge for studies of somatisation that seek to address these important issues is to find definitions of the disorder that can be explicitly related to decisions about therapy, investigation, and referral. Diagnostic categories that can be related to these pragmatic questions will make the greatest difference to patients and clinicians in primary care.

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References

1. Rosendal M, Bro F, Fink P, *et al*. General practitioners' diagnosis of somatisation. *Br J Gen Pract* 2003; **53:** 917-922.
2. Starfield B. *Primary care: balancing health needs, services, and technology.* New York: Oxford University Press, 1998.
3. Burton C. Beyond somatisation: a review of the understanding and treatment of medically unexplained physical symptoms (MUPS). *Br J Gen Pract* 2003; **53:** 231-239.
4. Gilbody AM, House AO, Sheldon TA. Routinely administered questionnaire for depression and anxiety: systematic review. *BMJ* 2001; **322:** 406-409.
5. Beich A, Thorsen T, Rollnick S. Screening in brief intervention trials targeting excessive drinkers in general practice: systematic review and meta-analysis. *BMJ* 2003; **327:** 536-540.
6. McGinn T, Guyatt G, Wyer P, *et al*. Clinical prediction rules. In: Guyatt G, Drummond R (eds). *Users' guides to the medical literature: A manual for evidence-based clinical practice.* Chicago: American Medical Association, 2002: 471-85.

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The potential and limitations of personalised medicine in primary care

THE White Paper *Our Inheritance, Our Future* emphasises the government's intention to move molecular genetics into mainstream health care.[1] There are significant implications for primary care, in particular for detection of breast, ovarian and colorectal cancers, prevention of ischaemic heart disease, and screening for antenatal risks. A more surprising implication is the commitment to a personalised medicine approach through the use of pharmacogenetics to tailor prescriptions to the individual.

Pharmacogenetics is the study of the variation in drug responses between individuals due to genetic differences. The subject has existed for several decades with the observation of phenotypes (expressed biological characteristics), such as slow acetylation of some antihypertensives, differential responses to antitubercular drugs, and familial clustering of adverse reactions to anaesthetics.[2-4] Drugs exert their action through receptors and have their blood levels determined by the activity of metabolic enzymes. Receptors and enzymes are proteins, which are coded for by DNA. DNA molecular analysis should therefore reveal patient-specific information about the receptors and enzymes for a given drug, and consequently the effect of that drug at an individual patient level before the patient has taken the drug. The potential benefits are the prediction and avoidance of side effects, prediction of response to treatment and individually tailored advice on lifestyle and disease prevention: the right drug, for the right patient, at the right dose.

This bold statement sounds like unrealistic exaggeration. Indeed, 48% of MEDLINE-cited entries for pharmacogenetics are review articles, with only 11% of articles being original research examining the clinical validity of pharmacogenetic tests.[5] The technology promises much, but appears to be delivering little. However, there are a small number of papers that demonstrate association between pharmacogenetic test results and primary clinical endpoints, and this offers an enticing view of the future. Moving to prospective testing to improve the efficacy and safety of prescriptions is likely to change the consultation fundamentally. For example, DNA is inherited, therefore if an individual is unable to take a given drug then it is likely that some family members will also be unable to do so. The best example of pharmacogenetics in current practice is the use of the thiopurine methyltransferase (TPMT) genotype to guide the prescription of azathioprine, methotrexate and other mercaptopurines in childhood leukaemia, transplants and, potentially, rheumatoid arthritis.[6] It allows accurate dosing to provide maximum effect with minimal side effects. This, like many other pharmacogenetic genotypes, codes for a single metabolic enzyme. The natural role of such enzymes is to metabolise environmental toxins and carcinogens. Therefore, it is possible that predictive disease associations with cancers may become apparent after a pharmacogenetics test has entered the marketplace.[7]

Test results are probabilistic, not binary; i.e. there is a percentage chance of response and side effects. For example, there is reasonable evidence that possession of a cytochrome P450 (CYP) 2C9 variant allele is associated with an increased risk of major bleeds for those on warfarin (odds ratio = 3.68, 95% confidence interval = 1.43 to 9.50).[8] What is clear is that not everybody with the variant allele bleeds. Choosing a lower dose of warfarin or avoiding warfarin and taking aspirin instead leads to increased safety at the expense of efficacy. Informed choice regarding such treatment decisions will require the explanation of probabilistic test results to patients and decision rules probably based on health economics.

No health service in the world has ever tried to afford every

single intervention that might help. What DNA technology offers is a more personalised means of assessing the cost–benefit equation. Potentially, this means that some individuals could receive and some be refused the same treatment on explicitly defensible grounds, rather than the current indefensible ones such as postcodes. Health economic models will break down, however, if decision rules are not adhered to. This eventuality is possible in particular where the patient has a serious condition with major consequences, such as advanced breast cancer or resistant HIV infection, and small possibilities of efficacy are important to them. Recent pharmacogenetics advances, such as the human epidermal growth factor receptor (HER)-2 test for trastuzumab (breast cancer chemotherapy) or single nucleotide polymorphism (SNP) profiling for abacavir (an antiretroviral drug) would be rendered uneconomic if patients in whom the test predicts insufficient probability of efficacy and safety would want the drug anyway.[9,10] This raises the philosophical issue of the importance of the hope of a cure. Does hope have a measurable utility to patients and, if so, how much is society willing to pay for it?

Unwillingness to abide by pharmacogenetics results may not be limited to advanced cancer and HIV. There may be as many as 35% of the ischaemic heart disease population who do not respond to statins, as measured by changes in intimal wall thickness.[11] It is not clear that patients would accept the label of non-responder without trying the drug, particularly if no alternative treatment is offered specifically for their lipids. Nor is it likely that the National Health Service (NHS) would willingly fund statins for those patients with ischaemic heart disease whose tests suggest they are non-responders. A cost-effectiveness modelling analysis comparing the public health to the personalised medicine approach is likely to be the way forward.

Health economics can answer the clinical cost-effectiveness question; for example, whether the NHS should test CYP 2C9 status before warfarin prescription.[8] However, if tests are available direct to the public, doctors will have to decide how to take into account privately acquired test results during NHS consultations. Given the new nature of the technology and the likely educational requirements, the NHS may require pharmacogenetics information; for example, in the form of prescribing software, even if it does not provide the tests.

The pharmaceutical industry is currently using genotyping before trials to exclude individuals with a high risk of adverse events or to enrich trials with those who are more likely to respond, thereby allowing trial sizes to be smaller and more cost-effective to them.[12] However, such trials produce no evidence for efficacy in certain screened-out genotypes and it is doubtful whether the results of such trials can be generalised to the population as a whole. Clearly, pragmatic trials are needed in order to allow generalisation of pharmacogenetic data to the real world of primary care.

Pharmacogenetic testing would require an in-depth discussion of the probability of efficacy and side effects to a degree that almost certainly doesn't occur at present. The *British National Formulary* does not provide information on the frequency of side effects or the likelihood of a drug having a therapeutic effect. Therefore, pharmacogenetic testing is likely to introduce new dimensions to the consultation making it longer, with more complex decisions. Conversely, the holistic approach to a problem cannot be reduced to a single genetic test.

There are countless more questions. Is it possible to increase the popularity of older drugs, such as tricyclics, if efficacious dose and adverse events were predictable?[13] Will the pharmaceutical industry find the fragmenting of the marketplace with pharmacogenetics profitable, or will they only use it when it suits them; for example, to increase the chance of an ineffective drug getting a licence by defining a genetic subgroup in whom it does work?[14] How will uncertainty regarding the comparability of different genetic assays for the same genotype be handled in economic models and by government licensing agencies? How will the significant fixed costs of developing pharmacogenetics testing facilities and a skilled workforce be handled by the NHS? Who will fund post-marketing surveillance if DNA testing for adverse drug reactions is required?

A sensible first step to untangle the research and policy questions is to carry out modelling studies and to work out the expected value of information from different research and service strategies. Only then can we sensibly proceed to pragmatic clinical trials of prospective pharmacogenetic tests, of which there have so far been none.[5] The vision of the White Paper is a long way down the road.

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References

1. Department of Health. Our inheritance, our future: realising the potential of genetics in the NHS. London: The Stationery Office, 2003. http://www.doh.gov.uk/genetics/whitepaper.htm (accessed 29 Oct 2003).
2. Denborough M, Foster J, Lovell R, *et al.* Anaesthetic deaths in a family. *Br J Anaesth* 1962; **34:** 395-396.
3. Iselius L, Evans DA. Formal genetics of isoniazid metabolism in man. *Clin Pharmacokinet* 1983; **8:** 541-544.
4. Evans DA, Mahgoub A, Sloan TP, *et al.* A family and population study of the genetic polymorphism of debrisoquine oxidation in a white British population. *J Med Genet* 1980; **17:** 102-105.
5. Hapgood R. A systematised search for evidence of 'real' pharmacogenetics tests. Society of Academic Primary Care Annual Scientific Meeting. Manchester, 2003.
6. Relling MV, Hancock ML, Rivera GK, *et al.* Mercaptopurine therapy intolerance and heterozygosity at the thiopurine S-methyltransferase gene locus. [See comments]. *J Natl Cancer Inst* 1999; **91:** 2001-2008.
7. Nebert DW, Ingelman-Sundberg M, Daly AK. Genetic epidemiology of environmental toxicity and cancer susceptibility: human allelic polymorphisms in drug-metabolizing enzyme genes, their functional importance, and nomenclature issues. *Drug Metab Rev* 1999; **31:** 467-487.
8. Aithal G, Day C, Kesteven P, Daly A. Association of polymorphisms in the cytochrome P450 CYP2C9 with warfarin dose requirement and the risk of bleeding complications. *Lancet* 1998; **353:** 717-719.
9. Hetherington S, Hughes AR, Mosteller M, *et al.* Genetic variations in HLA-B region and hypersensitivity reactions to abacavir. *Lancet* 2002; **359:** 1121-1122.
10. Vogel CL, Cobleigh MA, Tripathy D, *et al.* Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer. *J Clin Oncol* 2002; **20:** 719-726.
11. Kuivenhoven JA, Jukema JW, Zwinderman AH, *et al.* The role of a common variant of the cholesteryl ester transfer protein gene in the progression of coronary atherosclerosis. *N Engl J Med* 1998; **338:** 86-93.
12. Roses AD. Pharmacogenetics and the practice of medicine. *Nature* 2000; **405:** 857-865.
13. Kirchheiner J, Brosen K, Dahl ML, *et al.* CYP2D6 and CYP2C19 genotype-based dose recommendations for antidepressants: a first step towards subpopulation-specific dosages. *Act Psychiatr Scand* 2001; **104:** 173-192.
14. Rothstein MA, Epps PG. Ethical and legal implications of pharmacogenomics. *Nat Rev Genet* 2001; **2:** 228-231.

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