issue. It will take into account the service contribution provided by the doctors within structured training programmes, guidance from the Department of Health on the recruitment of doctors, equal opportunities legislation and policy, the arrangements for registration with the General Medical Council, and current immigration regulations. Options to be considered by the panel include a wholesale revision of the Overseas Doctors Training Scheme and the criteria for direct placement and possibly limiting direct placement to certain specific training placements or stopping it completely.

There is anecdotal evidence that a number of overseas doctors successfully complete the examination of the professional and linguistic assessment board but find it difficult to get training grade posts afterwards. In some cases doctors have waited for more than a year despite applying for many jobs. The supply of training placements for overseas doctors has been outstripped by the demand. Training opportunities in the NHS can meet the needs of overseas doctors, which include basic and higher specialist training and preparation for examinations. Improvements in managing and delivering training are needed to maximise the training opportunities; these improvements could include offering an induction course about the NHS and specific training placements and assessing the doctor's training needs and agreeing objectives. Immigration regulations allow overseas doctors to stay in the United Kingdom to complete postgraduate training to the standard of the Certificate of Completion of Satisfactory Training. This certificate is granted by the Specialist Training Authority of the Medical Royal Colleges and confirms that the doctor has completed specialist training.

While we await the recommendations of the review panel, overseas doctors who are considering travelling to the United Kingdom for training must be given appropriate information from British embassies and consulates, from the British Council, and from the GMC. The information must clearly state that success in the professional and linguistic assessment board examination does not guarantee employment in the NHS, and that there is competition for placements in training grades. Overseas doctors should be warned, as those who train in the United Kingdom should also be, that in certain specialties gaining a training post at a higher specialist level is intensely competitive.

Christopher Welsh *regional postgraduate dean*

NHS Executive Trent, Sheffield S10 3TH
(chris.welsh@doh.gsi.gov.uk)

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Molecular stool screening for colorectal cancer

Using DNA markers may be beneficial, but large scale evaluation is needed

Colorectal cancer is the most common fatal malignancy among non-smokers in North America and Europe. Better tools are needed to improve the accuracy, compliance rates, safety, and affordability of screening. Stool testing has several important advantages over structural screening methods and warrants more investigation. Stool testing is non-invasive, avoids unpleasant cathartic preparation, can be performed on transported specimens without people having to visit their physicians, and, unlike sigmoidoscopy, reflects the state of the full length of the colorectum. Screening for stool markers that are more accurate than occult blood could substantially improve screening outcomes, and there is a strong biological rationale for targeting the DNA alterations that are exfoliated from neoplasms.

Faecal occult blood testing, used to screen for colorectal cancer for nearly three decades, continues to be the most widely used tool. Although controlled trials have shown that is of significant benefit, deaths from colorectal cancer have only been reduced by 15-33% after 10-14 years, and it has had no real impact on reducing the cumulative incidence of cancer.[1–3] These outcomes are consistent with a tool that misses many early stage cancers and most premalignant adenomas.

Because neoplasms that could be caught by screening often do not bleed and occult bleeding from trivial sites is common, faecal occult blood is an inherently insensitive and non-specific marker. When compared with endoscopy, faecal occult blood tests detect <30% of cancers and <12% of large adenomas.[4] The specificity of the faecal occult blood test averages about 95% (range 88-98%); this translates into an average false positive rate of 5%, the equivalent of an unnecessary colonoscopy on 1 in every 20 people screened.[4] Non-specificity increases the costs of screening programmes and morbidity from diagnostic interventions. These limitations of faecal occult blood tests are biologically inescapable and cannot be remedied by technological advances in measuring faecal occult blood.

DNA is an intriguing alternative marker in the stool for reasons that are, theoretically, compelling. Firstly, DNA is released into the faecal stream continuously via exfoliation rather than intermittently via bleeding, which could enhance sensitivity and obviate the need for multiple stool tests during each screening. Secondly, DNA comes from the neoplasm itself rather than from the circulation, which could improve specificity. Thirdly, colonocyte exfoliation from cancers is quantitatively much greater than from normal mucosa.[5 6] Fourthly, the well characterised genetic alterations in colorectal neoplasms serve as potential targets for assays.[7] Fifthly, DNA seems to be stable during faecal transit and storage. Sixthly, proscriptions on diet and medications would probably be unnecessary with this test. Finally, sensitive laboratory techniques allow minute amounts of

DNA to be detected; recovered faecal DNA can be amplified more than a billion-fold by polymerase chain reaction before it is measured.

Early investigations targeting single mutations, usually K-ras, show that mutations in tumours can be detected in stools from the same patients.[8–10] Since colorectal neoplasms are genetically heterogeneous, however, no one mutation has been identified that is universally expressed. Mutant K-ras, for example, is present in less than half of all colorectal neoplasms; this would restrict the maximum sensitivity of this test for colorectal cancer to less than 50% if it was used as the sole marker for screening in a stool assay.[8–10] Also, since mutant K-ras may arise from non-neoplastic sources, such as pancreatic hyperplasia, this marker may lack specificity. Multiple DNA alterations should be targeted to achieve high rates of detection, and each component marker must be specific for a neoplasm to avoid false positive results.

Data from pilot projects suggest that the diagnostic yield improves when a stool assay with multiple targets is directed at a spectrum of DNA alterations commonly expressed by cancers.[11] The assay used in the pilot study included 15 mutational "hot spots" on K-ras, p53, and APC genes; BAT-26, a microsatellite instability marker (a genomic alteration present in 15-20% of colon cancers), and long (non-apoptotic) DNA. Using one stool per patient, which was tested blind, DNA alterations were detected in 20 of 22 (91%) patients with colorectal cancer, 9 of 11 (82%) patients with adenomas >1 cm, and 2 of 28 (7%) controls who had had normal colonoscopies. When K-ras was dropped from the assay, sensitivity for cancer was unaffected but it fell to 73% for large adenomas and specificity rose to 100%. Larger studies are clearly indicated to corroborate these early outcomes.

Preliminary data suggest that components of this assay panel may also detect cancers that occur above the colon, including in the lung, at sensitivities comparable to those for colorectal neoplasia.[12]

Thus, stool screening with DNA markers could have benefits beyond detecting colorectal neoplasms: it may be useful in controlling other cancers as well. It will be important to evaluate the implications of these findings using screening algorithms and evaluations of overall cost effectiveness.

Assay methods are labour intensive and must be streamlined for large scale testing, but exciting technologies are emerging to make this possible. While it is too early to know for certain, molecular markers may improve the effectiveness and efficiency of stool screening.

David A Ahlquist *professor of medicine*

Division of Gastroenterology and Hepatology, Mayo Clinic E-19, Rochester, MN 55905, USA (ahlquist.david@mayo.edu)

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Which clinical studies provide the best evidence?

The best RCT still trumps the best observational study

A common question in clinical consultations is: "For this person, what are the likely effects of one treatment compared with another?" The central tenet of evidence based medicine is that this task is achieved by using the best evidence combined with consideration of that person's individual needs.[1] A further question then arises: "What is the best evidence?" Two recent studies in the *New England Journal of Medicine* have caused uproar in the research community by finding no difference in estimates of treatment effects between randomised controlled trials and non-randomised trials.

The randomised controlled trial and, especially, systematic reviews of several of these trials are traditionally the gold standards for judging the benefits of treatments, mainly because it is conceptually easier to attribute any observed effect to the treatments being compared. The role of non-randomised (observational) studies in evaluating treatments is contentious: deliberate choice of the treatment for each person implies that observed outcomes may be caused by differences among people being given the two treatments, rather than the treatments alone. Unrecognised confounding factors can always interfere with attempts to correct for identified differences between groups.

These considerations have supported a hierarchy of evidence, with randomised controlled trials and derivatives at the top, controlled observational studies