Population screening and genetic testing

A briefing on current programmes and technologies

August 2005
British Medical Association
Board of Science

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- Ms Joanne Harcombe, National Education Lead NSC Antenatal Programmes, National Screening Committee
- Dr Sally J Nelson, Director of Public Health, South Wiltshire Primary Care Trust
At the BMA’s 2004 annual representative meeting (ARM) the following resolution on screening was debated and passed:

‘That this meeting is concerned about the implications of population and genetic screening for patients, and requests that the Board of Science and Education investigates this matter.’

Introduction
Progress in medicine has historically been associated with increasing knowledge of disease, its causes and courses, and the application of this knowledge to improving the health of patients. In the past, this has depended upon a patient presenting to a hospital or GP with recognised symptoms. Population screening is a significant departure from this clinical model of care, because it involves apparently healthy individuals being approached proactively or opportunistically by the health service. Screening is essentially an exercise in risk reduction: an effective screen detects either risk factors for developing a disease, or the disease itself at an early stage where treatment can improve patient outcomes. It has the potential to save lives, but it cannot offer any guarantee of protection. As screening programmes gain prominence within the medical community and the media, there is a need to ensure a better understanding of screening as a whole, on the part of both health professionals and the public.

Many screening programmes in the UK have only recently begun national rollouts and data on them are currently limited. Availability of information also varies across different regions and diseases. Many of the tests which could potentially be part of a screening programme are in use outside formal screening programmes and used in an ad hoc manner without central coordination.

This briefing paper discusses the main issues regarding population and genetic screening including areas of controversy; outlines current programmes in operation; and directs readers to useful sources of information. The aim is to provide healthcare professionals and other interested parties with the information needed to understand and explain screening programmes.
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Definitions and principles of screening

Screening is a public health service in which members of a defined population, who do not necessarily perceive that they are at risk of, or are already affected by, a disease or its complications, are questioned or offered a test. The aim is to identify those individuals who are more likely to be helped than harmed by further tests or treatment to reduce the risk of a disease or its complications.

Screening is a whole system, not just a test. This takes into account the need to provide the patient with adequate information, as well as further investigation and treatment. The programme should be properly managed and monitored, with effective quality assurance in place to ensure that more good than harm results.

Systematic and opportunistic screening

There is a difference between systematic and opportunistic screening. Systematic programmes invite all members of a certain population to take a test. An example of this is the breast screening programme where all women between 50 and 64 routinely receive invitations to have a breast examination. Other examples of systematic screening include the cervical screening programme, and a national bowel cancer screening programme will start in April 2006. Other national programmes operate opportunistically. They are aimed more at individuals who are at risk, although these people may be reluctant to admit their eligibility for screening, and so may be harder to reach. The most prominent example is sexually transmitted infection (STI) screening where the test is offered to the target population as and when they are in contact with the health service at the primary care level. For example, all pregnant women are offered HIV testing as part of their antenatal care, with a target uptake of 90 per cent. The majority of these women would not perceive themselves to be at risk of infection. Chlamydia screening is another example of an opportunistic screening programme; government plans to extend the current programme are discussed further on page 9. The BMA paper, Sexually transmitted infections, produced in January 2005, discusses the current situation with regard to STIs.

Formal versus ad hoc screening

It is important to differentiate between formal screening programmes which aim to evaluate the entire population, and more informal arrangements where clinical guidance and/or patient choice creates a situation where an ad hoc, non-evidence based screening programme is in operation, outside national policy and recommendations and central coordination. Patients often request such screening tests; for example, women may request Group B Streptococcus antenatal screening, privately purchasing testing kits for a medical practitioner to carry out the test. These ad hoc programmes have resource implications, and potentially put patients at risk of harm: there may be a lack of evidence underpinning the tests on offer, and the service is unlikely to be properly quality assured or coordinated. Patients are also unlikely to receive sufficient information to enable them to make an informed decision as to whether or not to undertake the screen (see page 10).
**False positive and false negative results**

A *false positive* or *false negative* occurs when the test results do not correlate with the presence of disease. With all screening tests there is a compromise between the sensitivity and specificity of the test. If the sensitivity is set high to avoid missing cases and thus avoid false negatives, the specificity will be low, with large numbers of false positives. The consequences of false positives include participation in unnecessary and sometimes costly medical procedures, as well as the psychological harm that arises when patients believe themselves to have a serious illness. The importance of lowering false positive rates is highlighted by the Down’s syndrome screening programme. Those who have a result indicating high risk are offered invasive investigation such as amniocentesis or chorionic villus sampling, which involves a 1 per cent risk of miscarriage. It is therefore vital to keep false positives as low as possible. The target for false positive rates is currently set at 5 per cent or less, and this is due to be lowered to 3 per cent by 2007. Conversely, a false negative means that the condition might only be caught at a later stage. As a consequence, the cost of treatment will be increased, the efficacy of treatment may be diminished and patients may suffer excess psychological distress from finding themselves afflicted with a condition they previously thought they were unlikely to acquire.

**Genetic screening/testing**

A distinction needs to be made between *genetic screening* and *genetic testing*. Screening involves testing members of a population for a disorder for which there is no prior evidence of the condition, although they may be part of a higher risk group, such as Ashkenazi Jews who are at risk of developing Tay Sachs disease. Testing relates to those who know that they are at risk, such as people belonging to families that may carry high penetrance genes associated with breast cancer, or with a history of Huntington’s disease. Genetic testing can mean carrying out a genetic test for a condition, such as Alzheimer’s and coronary heart disease. It can also be testing for a genetic disease, which may or may not involve identifying the genetic makeup. Examples include cystic fibrosis and sickle cell disease. Genetic screening raises specific concerns where a hereditary condition is being tested for, as it will have implications not only for the individual, but also for family members. Genetic screening and testing are discussed in more detail on page 12.

**The balance of harms versus benefits**

Screening has the potential to save lives. For example, a study by the World Health Organisation in 2002 estimated that there was a 35 per cent reduction in mortality among women who participated in screening programmes. The major *benefits* of screening are that it allows for early diagnosis, prevention, care and treatment. An example is screening for phenylketonuria (PKU) through the UK Newborn Screening Programme. Babies suffering from PKU are unable to breakdown the amino acid phenylalanine, which is found in food. This can lead to severe brain damage. However, if detected early enough, a low phenylalanine diet is prescribed, which will prevent this, and the child will be able to lead a normal life.

Early diagnosis means that treatment has a greater potential for success than at a later stage in the disease. Those who are identified as at risk of developing a condition are able to make lifestyle
changes to reduce this risk. For example, those identified through the Diabetes, Heart Disease and Stroke (DHDS) Prevention Project as being at risk of these diseases may be encouraged to lose weight and offered treatment for high blood pressure and cholesterol. Screening therefore also has the potential to make people more aware of their health.

Screening can be relatively inexpensive when compared with treatment for chronic illnesses. The cost-effectiveness of a programme must be considered to ensure that the resources could not be better spent on other means of prevention or treatment. This is outlined in the criteria used to approve a screening programme (see appendix 1). Screening also has the potential to control diseases at a population level; the extension of the chlamydia screening programme is part of the English government’s strategy to improve sexual health and reduce the rate of STIs. Identification of carrier status through genetic screening allows couples to make informed decisions with regards to family planning.

There are however potential harms inherent in screening that must be weighed against the benefits; indeed, the balance between good and harm can be very fine. It is important to remember that screening is a programme and not merely a test, and so any potential harms relate to the entire programme. As mentioned above, there are the risks of false positives and false negatives associated with the screening test, and the issues that arise from them. Some tests used in screening may be of an invasive and potentially dangerous nature, exposing patients to risks when they may not even have the disease. For example, there is a risk of perforation of the colon during colonoscopy, which may be used to detect colon cancer.

There is a danger of over detection of symptomless diseases, which leads to unnecessary treatment. An example of this is prostate cancer (see pages 7 and 10). A positive test result, be it a true or false positive, will result in further interventions and possibly treatment. There are controversies about over detection in both the breast and cervical screening programmes. While a test result may show an increased risk of developing the disease, this does not mean that the patient will go on to develop it. A study into cervical screening in Bristol found that in one screening round, of the 225,974 women tested, 15,000 were found to be at risk. After follow-up smears, 5,500 of these women went on for further investigation and treatment. However, estimates based on the number of deaths before screening began, put the number of women who would have died from cervical cancer at only 220. This shows that a very large number of women were unnecessarily treated for a disease which they would never have developed.

Positive results, whether true or false, can also be psychologically traumatic for the patient. Screening can raise anxiety levels among participants: those who receive a positive result are likely to experience some anxiety, and for some, even participating in a programme can be worrying. Many people consider themselves to be healthy, and attend screening without properly thinking through the consequences. An unexpectedly unfavourable result will create uncertainty and anxiety about their health status. The issue of informed consent is discussed on page 10. Genetic screening may impact on the family of the individual being tested, raising further issues as discussed above.
### Potential benefits versus potential harms

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Current programmes

The National Screening Committee (NSC) is responsible for issuing guidance to the NHS on national screening programmes. It maintains an online listing of its current policies as well as timetables for both reconsidering current practice and considering new screening campaigns. The NSC assesses proposed new screening programmes against a set of 22 internationally recognised criteria covering the condition, the test, the treatment options and effectiveness and acceptability of the screening programme. Assessing programmes in this way is intended to ensure that they do more good than harm and at reasonable cost. Since 1996, the NHS has been instructed not to introduce any new screening programmes until the NSC has reviewed their effectiveness. The criteria are listed in appendix 1.

Much of the NSC’s work is planned through the work of the NHS Health Technology Assessment (HTA) Programme. The role of the HTA programme is to ensure that high quality research information is produced on costs, effectiveness and the broader impact of health technologies, in order to assist those who manage the NHS. It commissions research on designated priorities. The resulting reports are rigorously peer reviewed and all ongoing projects are closely monitored. The HTA has a Diagnostic Technologies and Screening Panel, which plays a major role in determining the work of the NSC.

The UK health departments set targets for participation in screening programmes. While data reported to the departments are broken down by disease and geographic region, such data are typically presented to the public as a national number. Good information and coverage data are available at the local level for breast and cervical cancer screens, which are subject to quality assurance. The health departments also publish annual reports for these two screening programmes. However, this level of coverage information is not available for the whole range of programmes endorsed by the NSC because not all are supported by national programmes.

The NSC recognises four major age categories of testing: antenatal, child, adult and old age. Currently, screening programmes (at various stages of development) exist in the following areas:

- Down’s Syndrome Screening Programme: www.nelh.nhs.uk/screening/dssp/home.htm (England)
- Antenatal Screening Wales: www.screeningservices.org/asw/index.html (Wales)
- NHS Sickle Cell & Thalassaemia Screening Programme: www.kcl-phs.org.uk/haemscreening/ (England)
- UK Newborn Screening Programme Centre: www.newbornscreening-bloodspot.org.uk/ (UK wide)
- Newborn Hearing Screening Programme (NHSP): www.nhsf.info/ (England)
  Universal Newborn Hearing Screening: www.show.scot.nhs.uk/nd/services/hearing/ (Scotland)
  Newborn Hearing Screening Wales: www.screeningservices.org/nbhwsv1/index_eng.html (Wales)
- NHS Cancer Screening Programmes: www.cancerscreening.nhs.uk/ (England)
  Scottish Cancer Screening Programme: www.show.scot.nhs.uk/ldononline/cancer/screening/screening.htm (Scotland)
  Cervical Screening Wales: www.screeningservices.org/csw/index_eng.html (Wales)
  Breast Test Wales: www.screeningservices.org/btw/index_eng.html (Wales)
• Diabetes, Heart Disease & Stroke Pilot Programme:
  www.nelh.nhs.uk/screening/diabetesproject/home.htm (England)
• National Screening Programme for Sight Threatening Diabetic Retinopathy:
  www.nscretinopathy.org.uk/ (UK wide)

Screening in Europe and the United States
The European Union recommends that cancer screening should only be offered within the context of coordinated programmes, and has published guidelines on the implementation of screening. There are, however, wide variations in the organisation of programmes between different European countries. Some countries operate national programmes, while others are organised on a regional basis. This variation can be seen in a study of cervical screening programmes in 18 countries in Europe, which showed that six countries (or regions) had programmes inviting all women for smear tests, and nine invited only those who had not had a smear recently. The rest operated an opportunistic programme, with no invitation.

Screening practices differ in the United States. There are no centrally coordinated national programmes, but screening for some diseases can be more regular than elsewhere. Many Americans view screening as a right in safeguarding their health. This is illustrated by breast cancer screening. In 1997 the National Institutes of Health recommended that mammography should not be extended to women aged 40-50. (This is because evidence shows that in younger women, small cancers are very hard to find, and screening may result in large numbers of false positives, leading to further invasive treatment, and possibly even breast removal.) This provoked a campaign in the media and the Senate voted to extend mammography, forcing the National Institutes of Health to change their decision. The US programme operates by a mammography registry system, with screening for all women aged over 40, every one to two years. In comparison, the UK operates a national screening programme for all women aged 50-64, every three years.

To screen or not to screen
Not all major cancers are subject to screening, as many tests available do not meet the NSC criteria. The most noteworthy example is prostate cancer. The prostate specific antigen (PSA) test are used to detect prostate cancer by testing for high levels of PSA in the blood. This indicates a likelihood of cancer. However, men with prostate cancer may not have a raised PSA, and two out of three men with raised PSA do not have cancer. This test is therefore of low specificity and low sensitivity. It is not only the limitations of the test that determine whether a screening programme goes ahead; screening tests must lead to beneficial intervention. For prostate cancer, there is also little evidence that intervention does more good than harm. Based on the current body of evidence, the NSC was unable to recommend routine PSA testing for the general population or any sub-group. It has however introduced an informed choice campaign, Prostate Cancer Risk Management.

NSC decisions are not permanent. As science changes, tests which once did not meet the criteria, or screenings which were not cost-effective can become so. The recent NSC review of bowel
cancer screening is just such an example. A pilot in Faecal Occult Blood Test (FOBT) screening was run in the UK from 2000-2002. The results of this pilot were submitted to the NSC and the English and Scottish health departments for consideration, and in October 2004 the health departments announced that a national bowel cancer screening programme would be launched in April 2006.

Cost-effectiveness
It is important that the cost-effectiveness (ie value for money) and opportunity costs of any screening programme in comparison with prevention and treatment are taken into account before the programme is implemented. In considering opportunity costs, it is necessary to determine whether the resources used for screening (including staff as well as money) would not be better invested in alternative methods of intervention in controlling the disease. The NSC states in its criteria that all other options for managing the condition should have been considered to ensure that no more cost-effective interventions could be increased or introduced as an alternative to screening. It also states that the opportunity cost of a programme should be economically balanced in relation to expenditure on medical care as a whole. Many of the HTA research projects that examine potential screening programmes consider cost-effectiveness and opportunity costs. The HTA lists all its published reports on its website: www.nchta.org.

The 2004 White paper Choosing health: Making healthy choices easier from the English Department of Health sets out plans to create the National Institute for Health and Clinical Excellence (by merging the National Institute for Clinical Excellence and the Health Development Agency). This institute will have responsibility for integrating prevention and treatment, providing information and guidance, thus allowing comparison of evidence of the cost-effectiveness of early prevention programmes against later treatment.

Equity of access
As with other areas of the NHS, there are issues around equity of access to screening programmes. Independent assessment of screening programmes has revealed significant variation in access to services by geography, socio-economic status and ethnicity. For example, there is poorer uptake of breast and cervical cancer screening among women from black and ethnic minority groups. People with learning disabilities often do not have suitable information and support to help them to decide whether to attend screening. The English government has set targets of reducing health inequalities by 10 per cent by 2010, measured by infant mortality and life expectancy at birth. There are measures set out in the 2004 Choosing health white paper to tackle these inequalities and achieve this target. These include specific measures to increase screening take up. Primary care trusts (PCT) in England should use health equity audits to gain an understanding as to why some groups are less likely to attend screening, and use this information to implement ways of improving access. Services should be specifically targeted at groups from disadvantaged areas in order to meet their needs.
The white paper discusses chlamydia screening in particular, highlights the fact that women, young people, homosexual men, black and ethnic minority groups and those living in London are more likely to suffer from poor sexual health. Provision is made to extend the National Chlamydia Screening Programme across the whole of England by March 2007. Screening will be expanded to include pharmacies, shopping malls, sports centres, universities and work places, in order to improve access for those who are traditionally harder to reach. It is intended that the effectiveness of these innovations will be evaluated.
Screening has developed as a service to provide a net health gain in terms of the population, whereby the majority benefit, while some suffer adverse effects. The benefits have therefore been emphasised to achieve high coverage levels, as this was perceived as being best for the population. There is now, however, a movement towards viewing screening in terms of the individual (without losing sight of the benefit to the health of the population as a whole). As discussed, there are risks involved with screening, so it is important that participants are able to make an informed decision. Informed consent is seen as critical to establishing the credibility with which patients treat the results. There is a danger that any harm caused to individuals who have not been fully informed could lead to distress and potential litigation, and to inappropriate media interest that may jeopardise the programme. The BMA book, *Medical ethics today* discusses the issues around proper informed consent and those factors that should be taken into consideration.

**Empowering the patient**

Information should be available to allow people to appreciate both the benefits and the problems involved in being screened for a condition. Patients undertake a risk in undergoing screening, and they need to understand not only the issues associated with the actual test, but also the implications of a positive result with the ensuing investigation, treatment and psychological distress involved. It is important that they understand that the decision is theirs, and should not feel coerced into undertaking the test. It may be necessary to consider what the outcome for the patient would be if there were no screening. For example, as previously mentioned, prostate cancer can be non-aggressive, and many older men are unlikely to die from it. Unfortunately, the PSA test cannot identify those who will die, and it must be borne in mind that treatment of prostate cancer has side effects that can cause more problems than the disease.

Informed consent is advocated in the USA, and individuals are encouraged to take responsibility for their own health. In 2004, the US Preventative Services Task Force published a paper on the need for healthcare professionals and patients to work together in making decisions about preventative treatment including screening.

**The health professional’s role**

The onus should remain with the clinician to provide sufficient information to allow the patient to make an informed decision and guide him/her to further information if this is desired. To this end, the NSC has commissioned the development of professional training for informed choices in antenatal and neonatal screening. It is anticipated that the open learning materials will be available through the NSC in summer 2005. Information on the programme will be available via the National Electronic Library for Health. In England, NHS Direct provides guidance on assessing information and reaching a decision. A programme is due to be launched through the NHS Direct digital television service in 2005 that will provide information on screening in a variety of different languages.
There is some concern about doctors being offered target payments for screening, which may present a potential conflict of interest, and possibly affect doctors’ objectivity in recommending screening to patients. There is further discussion of this issue in the BMA book *Medical ethics today.*

Decision aids are a useful tool in assisting individuals in deciding whether to undergo screening and/or treatment. These are starting to be used, although research aimed at finding the best ways of conveying such information is relatively new. The Cochrane study, *Decision aids for people facing health treatment or screening decisions,* provides a comprehensive inventory of decision aids and systematically reviews randomised controlled trials of aids. The study found that using decision aids was more effective than usual methods in improving knowledge, and that their use enhanced realistic expectations about harm and benefits, decreased the number of people remaining undecided, and encouraged people to take a more active role in decision making. The study also highlighted the fact that there are many decision aids available on the internet, but these may not have been appropriately evaluated.

Doctors’ and patients’ roles in the decision-making process have evolved over recent years to the point where patients should be able to take more responsibility for their healthcare. This issue is discussed on the Resourceful Patient website. The site also highlights the amount of information now available, and considers ways in which patients can be better informed about screening.
Genetic testing and screening

With the developments in the use of genetic testing in screening, the NSC has adapted its criteria to include points relating to genetic aspects of a potential screening programme.

Genetic testing to establish disease development
Presymptomatic genetic testing, which establishes whether a disorder will develop, raises few concerns where effective medical intervention is available. However, if there is no effective treatment (in which case, a NSC-regulated programme would not progress) the issues are more problematic. Huntington's disease is one example. A positive test will result in the individual knowing that at some point they will develop a serious disorder, and there is nothing that they can do to prevent or cure it. This can clearly be traumatic, and genetic counselling should be available initially to help people in deciding whether to take the test, and later in coping with a positive result. This will provide detailed information, discussion of the implications and emotional support by trained professionals.

Few people at risk of such conditions are screened: the uptake for testing for Huntington's disease is approximately 18 per cent of those at risk. However, for some, knowing for certain whether they will develop a disorder is preferable to the psychological distress of wondering if they will. Some people even experience a decrease in emotional upset on finding out their genetic status, even if this confirms that they are carriers. Further discussion on this issue can be found in the BMA book, *Medical ethics today*.

Genetic testing to establish increased risk of disease development
It is also possible to test for a genetic disposition for a disorder. This does not mean that an individual will necessarily go on to develop the disease if they test positive. Such testing is useful where there is a high risk, for example for carriers of mutations to the BRCA1 and BRCA2 genes. These greatly increase the risk of developing breast cancer, which increases with age: 50 per cent of BRCA1 carriers at age 50 are likely to have breast cancer; this increases to 80 per cent by age 80. A positive result would allow measures to be undertaken, such as more regular mammographic screening to detect cancer should it develop, or bilateral prophylactic mastectomy. It should be noted that BRCA1 and BRCA2 genes contribute to only a small minority of breast cancer cases. A larger proportion of cases are now thought to be attributable to multiple lower penetrance genes. The risk is unlikely to be as high as for BRCA1 and BRCA2, but it may be significantly higher than average.

Predisposition testing may show lower levels of risk. While this does not resolve issues of uncertainty about developing the disease, it may be useful where changes can be made to reduce the chance of developing the disease, for example lifestyle changes relating to heart disease. As the ability to identify such genetic patterns increases, there is growing opportunity for risk assessment for the individual. Information about the genetic impact on testing for a variety of diseases can be found on the Public Health Genetics Unit website.
Carrier status

Genetic testing may identify people as carriers of a genetic mutation, and while not actually suffering from the disease themselves, the discovery would have implications for their children, siblings and relatives of childbearing age. There are issues about what to do with this knowledge, and the appropriateness of passing it on to relatives who have not consented to testing, even though disclosure of information might be valuable. Genetic testing does allow couples to make informed decisions about family planning, and people at risk of a hereditary disorder may wish to consider testing before deciding to have children, in order to establish any risk to their offspring. There is further guidance on the issue of sharing genetic information with relatives in the BMA book *Medical ethics today*.

Population genetic screening

It is possible to screen members of a particular population who may be at risk of genetic disposition to a disorder. People may choose to be tested for autosomal recessive conditions prior to having children, thus identifying any risk to their offspring. For example, in a number of countries the Ashkenazi Jewish population is tested for Tay Sachs carrier status. Prior to implementation of a screening programme in the USA, Tay Sachs disease occurred in 1 in 3,600 births among Ashkenazi Jewish couples, with a carrier frequency of 1:30 in that population. Implementation of screening resulted in a 90 per cent reduction in births of children affected with Tay Sachs. There is also the potential for large-scale genetic screening of an entire population, for example those at risk of certain types of cancer. This would involve similar ethical issues as those for hereditary diseases, but on a larger scale and with the problems inherent to population screening programmes.

Preimplantation genetic diagnosis

Preimplantation genetic diagnosis (PGD) is ‘a technique which involves the genetic testing of embryos created in vitro for deleterious heritable genetic conditions which are known to be present in the family of those seeking treatment and from which the embryos are known to be at risk’. This process is regulated by the Human Fertilisation and Embryology Authority (HFEA), and may only be carried out in licensed centres, of which there are currently 13 in the UK. There were around 45 live births from PGD in the UK between 2001 and July 2004, from approximately 430 cycles. The number of diseases which may be screened for is growing, and includes Huntington’s disease, cystic fibrosis, and Beta thalassaemia. On 1 November 2004, the HFEA announced that it had licensed PGD for testing for Familial Adenomatous Polyposis Coli, an inherited predisposition to colon cancer.

A public consultation carried out by the HFEA and Human Genetics Commission (HGC), which reported in 2002, found that there was considerable public support for PGD, although there were also important reservations to be considered. There are deliberations surrounding the fact that the technology can also be used to create embryos of specific tissue type which can then be used to save siblings suffering from certain conditions. There are also fears in some quarters that the
procedure could be used to create ‘designer babies’. Moreover, there are ethical considerations about the disposal of the surplus embryos created. PGD is traumatic and involves the physical and emotional strains generally associated with all in vitro fertilisation (IVF) (including a relatively low success rate), but is more expensive than IVF due to the complex technologies necessary for testing the embryo. For those parents who know that they are at risk of passing on a genetic disorder to their children, PGD does however offer an opportunity to select embryos that are free of disease.

The BMA believes that due to the difficulties involved in PGD, only those couples who are at serious risk would consider undergoing it, and that the fears of its use for ‘frivolous’ reasons are unfounded.

The HGC has called for priority to be given to further work on the subject, involving key groups. This should consider and consult on the wider and longer-term ethical, social and human rights issues in the development of PGD technology.

**Pharmacogenetics**

Pharmacogenetics is the study of how a response to a drug is influenced by genetic makeup. At present, screening information that feeds into treatment informs practitioners of the need to follow a particular course of action. Interest and developments in pharmacogenetics is growing, and its future use could potentially lead to more people undergoing genetic screening.

Different people respond differently to drugs, which impacts on the efficacy and reliability of the drug. An example is warfarin, which is metabolised by an enzyme that may vary slightly. This variation depends on genetic profile, and affects the rate at which warfarin is metabolised. A slow metabolic rate would mean that the drug remains in the system for longer, and thus could have prolonged effects, with possibly serious implications. Doctors must therefore prescribe warfarin in relation to each individual. Pharmacogenetics can be used to target drugs at individuals’ genetic make-up, making them as safe and effective as possible. Widespread use of such techniques, however, has significant ethical, social and legal ramifications. The Royal Society launched a study into pharmacogenetics in September 2004, with the aim of providing a balanced assessment of the benefits and limitations of this technology. The report is due to be published in September 2005, and will make recommendations to the government and for research.

The major issues surrounding pharmacogenetics are consent, data management, and the cost of developing these drugs. They may prove to be extremely expensive both to produce, and for the NHS to use; conversely, if they are more effective, they could potentially reduce cost to the NHS. Pharmacogenetics has the potential to hugely improve treatment. The fact that drug prescribing can be tailored to individual genetic make-up can save time and resources by avoiding treatments that are ineffectual, or have an adverse effect on a patient.
The increased use of genetic screening will require robust adherence to current rules relating to consent, and possibly the strengthening of safeguards on data. A more fundamental issue is that while pharmacogenetics has the potential to offer more effective treatment, there is the risk that the medical community will place excessive weight on the results of genetic testing. A move towards clinical guidelines based (wholly or partly) on genotype (i.e., genetic makeup) would lead to difficulties for patients whose genotype is extremely uncommon. A further complication arises when consent is refused. In a world where drugs are tailored to meet the most common (or even all) genotypes, how does a physician treat a patient who will not allow himself to be genotyped?
Impact of screening on insurance

One of the controversies surrounding screening is how this may disadvantage individuals in relation to health and life insurance. This is particularly true for genetic testing, but may relate to other types of screening. There is concern that insurance companies will require information on the results of screening tests, which may affect cover for those with unfavourable results, and also their relatives. For example, insurance companies can be reluctant to provide insurance for those who have a history of treatment for abnormal precancerous cervical cells detected through screening.

Disclosure of genetic test results

With regard to genetic tests, there is concern that disclosing results will lead to those with a disposition for a disease having to pay higher or very high premiums. This in turn may lead to those who would benefit from testing declining through fear of discrimination. In order to resolve some of these problems, in March 2005 the Department of Health produced a concordat, which builds on existing codes of practice and guarantees that insurers’ use of genetic information is fair, transparent and subject to independent oversight. This policy framework was informed by discussion between the government, the Association of British Insurers (ABI), the Genetics and Insurance Committee (GAIC), the HGC and patient groups. There is currently a moratorium in the UK until November 2011 on the use of genetic information by insurance companies. During this period, companies are prevented from requiring the disclosure of adverse genetic test results for premiums up to £500,000 for life insurance and £300,000 for critical illness insurance. Beyond this value, they may only use test results approved by the GAIC which is an independent government committee. This is currently only the case for Huntington’s disease. Insurance companies may, however, take into account favourable test results, showing that the individual does not have the condition. The ABI in 1999 produced a code of practice (due to be reviewed shortly) which provides guidance on the use of genetic tests in insurance, taking into account legal requirements, ethics and commercial considerations. Insurance companies believe that they should have equal access to medical information as clients, otherwise those with positive test results could take out high value policies.

Other countries are similarly considering the impact of genetic testing on insurance. In the USA, the Senate has passed the Genetic Information Nondiscrimination Act of 2005, which is making its way through the legislative process. This would prohibit discrimination on the basis of genetic information with regards to insurance and employment. In Australia, the Human Genetics Commission of Australia was set up in 2003 to advise the government, insurers and the public on matters relating to genetics, including the use of tests for insurance purposes. Currently, no tests may be taken for insurance, although current results are used, with written consent. Family history can also be taken into account.

Another aspect to be considered is that of family history. Insurance companies can presently require the disclosure of family history, although this can in reality amount to genetic information; insurance companies tend to view genetic information as an extension of information currently...
required. For some diseases, such as Huntington’s disease, premiums are already raised if there is a family history, in much the same way as it is feared they would be if there was a positive genetic test. However, it has been pointed out that better knowledge of people’s genetic susceptibility might actually lead to individuals obtaining insurance where previously they had been unable to, for example, where there is a family history of a disease but the individual is proven not to be at risk. Where genetic test results may be used, geneticists and insurance companies will need to work together to ensure that premiums are based on accurate predictions of genetic risk. It is also important that the rights of other individuals potentially implicated in any test result are properly protected.

The BMA will continue to contribute to the debate on the use of genetics for insurance purposes. Its current position is that the period of the moratorium should be used to consider whether there are sound political or other logical and objective reasons for treating genetic information differently to other medical information in terms of insurance.

The debate on disclosure of genetic information raises other questions about who should be responsible for meeting the cost of treatment of diseases: the individual through raised insurance premiums, or society and the government through the NHS. The possibility of knowing who is at risk of developing a disease through genetic testing makes this question more pertinent.

Another area which could potentially be problematic in the future is the use of genetic information by employers. Although currently this practice is rare, it is something that needs to be considered. A report by The Human Genetics Advisory Commission published in 1999 recommended that this issue should be monitored, with a thorough review in 2005, and that the Data Protection Act 1998 and the Disability Discrimination Act 1995 should be brought to bear where necessary. It also made several policy recommendations, including that individuals should not be required to disclose information about their genetic status to an employer, unless it would affect their ability to perform the job, or pose a hazard to others. The UK government accepted this position.
Private sector screening

There are many private health clinics that offer screening tests for a wide variety of conditions, and also basic health checks. These are marketed as a means of detecting illnesses or potential health problems earlier, thus allowing early treatment or implementation of risk-reducing measures, and so preventing the condition developing to a dangerous and potentially life-threatening level. There are questions about private sector screening. A Which? report in August 2004 examined five different clinics, and concluded that vital safeguards in relation to quality assurance and information provision were lacking. *Vitally, there is no continuity of care with private sector screening, whereas in the NHS, testing is part of a screening system which includes follow-up treatment, and is free of charge.* This is highlighted by the controversy surrounding a US online company which has recently started offering genetic testing for predisposition to breast and ovarian cancer directly to individuals. Following a telephone consultation with a genetic counsellor, women are able to buy the test kit online. The results are then available over the telephone or online, with no face to face genetic counselling. This has raised fears that people will not be receiving appropriate support and advice, which is essential in genetic screening. The biggest difference between private sector and NHS screening is that in the private sector, individuals choose to be tested, and are not systematically invited to do so. The one advantage of private sector screening may be that there is more time available with a doctor, something that is often limited within the NHS.
Ad hoc screening
- There is a need to address ad hoc, non-quality assured screening outside approved, evidence-based national programmes. Ad hoc programmes may put patients at risk, as tests may not be of a high quality or properly coordinated or regulated. They also divert resources from more useful services.

Information about screening programmes
- The NSC and DH should guarantee that there is comprehensive and regularly updated performance data available for all existing NSC approved programmes. This should include a detailed breakdown of figures geographically by SHA and demographically by socio-economic status and ethnicity. It should also provide an indication of plans for the expansion and/or modification of services in the future, as well as progress made towards previously stated goals. This would help to improve doctors' understanding of the availability of screening and services to patients.

- The NSC and DH should undertake that improved information is available to the public about: the aim of screening; who is eligible; what the screening process is; what the diagnostic process is; what the intervention is; the chances of benefit; the chances of harm. Existing information about each screening programme is insufficient and focuses only on the number of lives saved.

- The NSC and DH should ensure that improved information and a better comprehension exists about the limitations and harms of screening. Current inadequate information has resulted in a general lack of understanding about the complexities of screening among the public, journalists and politicians.

Screening and genetics
- That the special implications of testing for a genetic disease be considered, and the DH should guarantee that there are safeguards in place for third parties where genetic test information for one person has implications for family members.

- There is a need for consideration of the inherent uncertainty in predicting an outcome for an individual based on the detection of an abnormality. This is particularly relevant where genetic tests are concerned.

Insurance
- The DH should make sure that there is sound evidence-based medical advice to give insurance companies if they are to use information relating to inherited disorders. The BMA calls upon the DH and the Association of British Insurers to work together to undertake that where test results are used, premiums are based on accurate prediction of risk, and that people are not unfairly discriminated against. It would help to ensure that people do not reject screening due to fear of their information being misused and leading to inappropriately high premiums.
Further reading

This listing of organisations and publications is intended as a guide for those wishing to know more about screening and its uses in the UK. The BMA is not responsible for the content of external websites, nor does it endorse or otherwise guarantee the veracity of statements made in non-BMA publications.

National organisations

Department of Health
www.dh.gov.uk

National Electronic Library of Health (Screening)
www.nelh.nhs.uk/screening

National Services Division
www.show.scot.nhs.uk
Has responsibility for ensuring the provision of both national screening programmes and specialist services on behalf of NHSScotland. They also fund a number of specialist services in England on behalf of NHS Boards.

NHS Health Technology Assessment Programme
www.hta.nhsweb.nhs.uk

NHS Quality Improvement Scotland
www.nhshealthquality.org
NHS agency which monitors quality of care and treatment in NHSScotland. It issues authoritative advice on effective clinical practice and service improvements.

Scottish Executive Health Department (SEHD)
www.show.scot.nhs.uk

Scottish Health Statistics
www.isdscotland.org
Includes statistics on the breast, cervical and colorectal screening programmes.

The UK National Screening Committee
www.nsc.nhs.uk
Cancer

www.scotland.gov.uk/library5/health/cissc-00.asp

Cancer Research UK
www.cancerresearchuk.org.uk

Now largely out of date as various initiatives have been trialled, expanded and/or cancelled, the Cancer Plan still provides the most coherent picture to date on government plans for cancer screening.


NHS Cancer Screening Programme www.cancerscreening.nhs.uk
Current information on breast and cervical cancer screening programmes, and information regarding the situation with prostate and bowel cancer.

Genetics

This review provides practitioners with evidence-based information and advice on the provision of genetic counselling both before and during pregnancy, as well as advice on increasing the use of pre-pregnancy counselling to help improve birth outcomes.

Association of British Science Writers
www.absw.org.uk/Briefings/future_of_genetic_screening.htm
This website provides a useful summary of the issues surrounding genetic screening.

Consultation document from the Human Genetics Commission. It considers the developments of genetics, and the impact this will have on individuals and society as a whole. The HGC intends to report the findings by late 2005.
Human Fertilisation and Embryology Authority
www.hfea.gov.uk

Human genetics: choice and responsibility, BMA (1998)
An assessment of the ethical issues raised by human genetics, which discusses choice and responsibility, suggesting practical solutions for doctors, counsellors, patients, and policy makers.

Human Genetics Commission
www.hgc.gov.uk


Our inheritance, our future – realising the potential of genetics in the NHS, Department of Health (2003)
www.dh.gov.uk/PolicyAndGuidance
Department of Health white paper, setting out ways in which the public may benefit from genetics in the future and raising awareness of the potential of genetics in healthcare. It sets out a plan for preparing the NHS, and safeguards against inappropriate use of genetics.

www.nuffieldbioethics.org/publications

Public Health Genetics Unit
www.phgu.org.uk
Website providing information on advances in genetics and their impact on public health and disease prevention.


This study provides insight into the impact of genetic testing on adults and discusses the information and confidentiality issues involved.
General

Article outlining critically important issues in the development and use of decision aids for screening.

Department of Health white paper setting out actions the government will take in providing information, support and opportunities to enable people to improve their health.

Article discussing various issues around screening.

Laitner S *Screening*
Learning tool on screening on Health Knowledge website, part of the Public Health Electronic Library. Please note that this web address may change in June 2005.

UK National Screening Committee Criteria for appraising the viability, effectiveness and appropriateness of a screening programme

Ideally all the following criteria should be met before screening for a condition is initiated:

**The condition**
1. The condition should be an important health problem.
2. The epidemiology and natural history of the condition, including development from latent to declared disease, should be adequately understood and there should be a detectable risk factor, disease marker, latent period or early symptomatic stage.
3. All the cost-effective primary prevention interventions should have been implemented as far as practicable.
4. If the carriers of a mutation are identified as a result of screening the natural history of people with this status should be understood, including the psychological implications.

**The test**
5. There should be a simple, safe, precise and validated screening test.
6. The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed.
7. The test should be acceptable to the population.
8. There should be an agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to those individuals.
9. If the test is for mutations the criteria used to select the subset of mutations to be covered by screening, if all possible mutations are not being tested, should be clearly set out.

**The treatment**
10. There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment.
11. There should be agreed evidence based policies covering which individuals should be offered treatment and the appropriate treatment to be offered.
12. Clinical management of the condition and patient outcomes should be optimised in all health care providers prior to participation in a screening programme.

**The screening programme**
13. There should be evidence from high quality Randomised Controlled Trials that the screening programme is effective in reducing mortality or morbidity. Where screening is aimed solely at providing information to allow the person being screened to make an ‘informed choice’ (eg Down's syndrome, cystic fibrosis carrier screening), there must be evidence from high quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened.
14. There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/intervention) is clinically, socially and ethically acceptable to health professionals and the public.

15. The benefit from the screening programme should outweigh the physical and psychological harm (caused by the test, diagnostic procedures and treatment).

16. The opportunity cost of the screening programme (including testing, diagnosis and treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (ie value for money).

17. There should be a plan for managing and monitoring the screening programme and an agreed set of quality assurance standards.

18. Adequate staffing and facilities for testing, diagnosis, treatment and programme management should be available prior to the commencement of the screening programme.

19. All other options for managing the condition should have been considered (eg improving treatment, providing other services), to ensure that no more cost-effective intervention could be introduced or current interventions increased within the resources available.

20. Evidence-based information, explaining the consequences of testing, investigation and treatment, should be made available to potential participants to assist them in making an informed choice.

21. Public pressure for widening the eligibility criteria for reducing the screening interval, and for increasing the sensitivity of the testing process, should be anticipated. Decisions about these parameters should be scientifically justifiable to the public.

22. If screening is for a mutation the programme should be acceptable to people identified as carriers and to other family members.
References

1. UK National Screening Committee at www.nsc.nhs.uk (accessed September 2004).
30 Raffle A (2004) This house believes that HPV testing is in the best interests of women. Proceedings of the Annual Scientific Meeting of the British Society for Colposcopy and Cervical Pathology (BSCCP), 23 April, Cardiff.
34 Department of Health press release (27.10.2004) Reid announces new national screening programme to tackle bowel cancer.
37 Raffle A (2001) Information about screening – is it to achieve high uptake or to ensure informed choice? Health Expectations 4: 92-8.


*Bioethics* (2004) 18 is dedicated to all of these issues.


