Leading Article

Who should be offered genetic screening?

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General

The conditions dealt with here are those where detection of women or couples at risk of having children with burdensome disorders with little or no curative treatment, is feasible. One objective of screening is avoidance of birth of affected individuals by identifying those at risk, prospectively. As important is the reassurance which can follow negative tests. Voluntary participation of well-informed clients is a vital prerequisite. Screening may increase couples' options, one of which may include prenatal tests and termination of affected pregnancies.

All screening programmes have their enthusiastic supporters and opponents. Some of the arguments are so philosophical and paternalistic as to be incapable of resolution. Others rightly attract careful appraisal, such as knock-on effects on clinical and laboratory services and those which follow on false-positive and negative screening results.

It is important to devote a great deal of thought to the groups who should be made aware of screening or testing. The guiding principle of whom to choose is that the offer is seen as useful by the individual or family. Sometimes individuals themselves have made enquiries about tests, or mentioned the existence of one of the diseases in the family. Any doctor who does not respond by offering to organize tests when a family story of any of these severely disabling conditions is forthcoming, is neglecting the patient.

A practical aspect is whether tests can be offered before or only in pregnancy.

Pregnancy screening

To screen for Down's syndrome or neural tube defect in the fetus there must be a pregnancy in existence.

The current commercial atmosphere in the

National Health Service means that certain organizers of such tests are beginning to market their products rather aggressively. This includes the advertising campaign of writing to district managers and purchasers and by producing glossy literature for use by professionals and prospective patient clients. In this respect I refer specifically to biochemical screening tests for Down's syndrome, the so-called Triple or 'Triple +' Test. There was no similar campaign when α fetoprotein (AFP) screening was originally introduced for neural tube defect detection and certainly no glossy literature was produced. Whatever the motives, however, the existence of client/patient orientated literature for all screening programmes is important and its preparation deserves great care.

In introducing triple screening for Down's syndrome/neural tube defect, adequate attention to the knock-on effects on counselling, ultrasound, obstetric and cytogenetic services has not been paid. Centres which offer such tests without the added back-up of dating ultrasound scans before 16 weeks do so at their peril, with the predictability of AFP and to a lesser extent the other biochemical markers being highly dependent on accurate timing of the tests in pregnancy. False reassurance rates and false-positive rates rise if tests are performed too late or too early in pregnancies. Simple offers of tests in antenatal clinics without good explanations and patient literature and counselling services also court problems.

Though couple screening for carrier status for the autosomal recessive disorders, cystic fibrosis, sickle cell disease, thalassaemia and Tay-Sachs disease in groups of relevant ethnic background, is feasible in pregnancy (and this is the reproductive turnstile where those about to produce affected offspring can be 'caught'), there are serious reservations about choosing pregnancy as the time to test when earlier testing was feasible. Some added degree of anxiety is inevitable. Petrou and colleagues¹ write about poor uptake of prenatal diagnosis for sickle cell disease following pregnancy carrier testing. They advocate education and offers of testing before pregnancy. The King's Fund forum in the consensus statement after their

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1987 meeting on screening for genetic disease reached the same conclusions.² The same objections would apply to screening for fragile X carriers in pregnancy.

Even in the case of Down's syndrome and neural tube defect screening, one would wish individuals to be aware of tests before there are pregnancies and where possible to have made the decision to have tests prospectively. This requires education. When the Health Department decides that it is the turn of genetic disorders to receive priority in respect of development monies, the exceptionally important aspect of education must not be forgotten. One need not wait until there is special funding to implement the education process in professionals and the public, alike. The very recent publication of the booklet 'Population needs and genetic services' (HMSO, Dd DH004322, 6/93), aimed at non-specialists, is to be welcomed in this respect.

Autosomal recessive carrier screening (cystic fibrosis, sickle cell disease, thalassaemia and Tay-Sachs disease)

In the case of autosomal recessive disorders, both parents must be carriers before there is a risk of affected offspring. The most appropriate group at whom to target screening is those with a family story of the disorder. By starting cascades of carrier testing in families with an affected individual and by testing relatives and partners of all those who test positive, one is reaching the group most likely to wish to know their carrier status, most likely to be relieved by reassuring results and to modify their family planning, including use of prenatal diagnosis,³ when carrier couples are detected. There is also a far greater chance of detecting these carrier couples compared to general unfocused screening programmes since the relative is much more likely to be a carrier. The North-Western Regional Health Authority has recently introduced cascade carrier screening for cystic fibrosis for those with a family story.

In a disorder like cystic fibrosis where there are a number of different mutations of the responsible genes, the relevant ones known to be in the particular family need to be known as well as the common mutations in the population under consideration. Thus genotyping of affected individuals is a prerequisite for proper cascade screening and knowledge of mutation frequencies in the test population is needed in calculating the carrier odds of those who test negative. This is because cystic fibrosis testing does not detect *all* carriers. Currently in the UK 92% of carriers can be detected or 88% by testing for the four commonest mutations.⁴

The ethnic background may be important. Cystic fibrosis tests in Ashkenazi Jews need to include particularly a test for W1282X, a mutation which accounts for 60% in this group and is very rare otherwise.

It is true that couples with a family story may only come forward for testing when pregnancies are under way; this may reduce the time available to determine the exact mutations which require testing and remove the option of very early prenatal tests. Our duty lies in ensuring that these relatives were aware of the availability of earlier tests.

Should one test children? Ideally not. However, one may serendipitously discover carriers among children, for instance after newborn screening for the disease state in sickle cell disease or cystic fibrosis, or after a full blood count in a child reveals a sickle cell or thalassaemia carrier. In those cases both parents should be tested and family relatives as part of a cascade. On some occasions one might discover that *both* parents are carriers.

Public awareness of these autosomal recessive disorders is on the increase and while we currently concentrate our carrier screening efforts on those with a family history, pressure for carrier screening in the absence of a family story may build up from certain sections of the public, sometimes with pregnancy as the event which stimulates a request. In future such screening may prove commonplace. At present one would generally wish to accede to a request for screening for any of these autosomal recessive disorders from an informed individual.

Semi-anonymous carrier screening arranged by religious leaders has had some success in young religious Jews. Carrier tests for Tay-Sachs are performed, with results held in confidence by the organizing rabbi with the permission of the tested individuals. Marriages then deliberately avoid carrier marrying carrier. Thus the dilemma of prenatal diagnosis and termination of affected pregnancies is avoided, with this approach deemed far preferable. Arranged marriage is commonplace in the Muslim community and it is possible that it would show interest in this approach in respect of thalassaemia.

Fragile X

Recent advances in DNA technology make screening for fragile X female carriers or transmitting females feasible, while the same tests applied to mildly mentally handicapped girls would have the capacity of diagnosing many who are at large risk of producing severely mentally handicapped offspring, male and female.⁵ How to apply the capacity to test once again requires very careful thought. Offering to test the relatives of known

affected people is once again the least controversial approach. The mother would invariably test positive. However, it may be her father or mother who is or was the transmitting (that is, mentally normal) male or female, and relatives on his or her side should be made aware of the offer of tests. Difficulties exist in application of prenatal tests for fragile X. When an affected male with evidence of a marked triplet expansion has been identified there is no doubt that there would be full expression of this severely disabling disorder. Females with similar expansion may have much milder mental handicap and could integrate quite normally into the less able part of society.

Testing of girls with mild learning disorder for fragile X seems superficially attractive, for they will be at risk of having severely handicapped offspring. Such girls when young women are not likely to request testing themselves. Does it not become the safer option to offer such tests of their daughters to parents who could then play a protecting role by preparing the daughter for the possibility of prenatal tests in each pregnancy? Would their marriageability be prejudiced by their being

identified as having fragile X as children? This would be a pity.

As with the autosomal recessives, when public awareness of the frequency of transmitting females of fragile X increases, there are likely to be requests for testing from mentally normal people with no family story. It is doubtful that general screening will be introduced, unless there were some way of curing the fetus or young child. When cures are available the whole philosophy of screening alters as a more wholesome dimension emerges.

There are a number of bodies attempting to increase public knowledge of genetic disorders; notable amongst these is GIG – Genetic Interest Group – which organizes a number of valuable interface meetings between the public and professionals. Such organizations, as well as regional genetic centres, act as important repositories of accurate information. General practices, community clinics and antenatal clinics should all carry information about common genetic disorders. Community services have the opportunity to include this as part of health promotion programmes in health shops on the high street.

References

1. Petrou, M., Bruiatelli, M., Ward, R.H.T. & Mosell, B. Factors affecting the uptake of prenatal diagnosis for sickle cell disease. *J Med Genet* 1992, **29**: 820–823.
2. Consensus Statement. *King's Fund Forum: Screening for Genetic Disease*. King's Fund, London, 1987.
3. Super, M., Schwarz, M.J. & Malone, G.M. Carrier screening for cystic fibrosis. *Lancet* 1992.
4. Super, M. The gene defect in cystic fibrosis and clinical applications of the knowledge. *J R Soc Med* 1992, **85** (Suppl 19): 6–8.
5. Pergolizzi, R.G., Erster, S.H., Goonewardina, P. & Brown, W.T. Detection of full fragile X mutation. *Lancet* 1993, **339**: 271–272.