Chapter 4

Clinical applications

Introduction

4.1 This chapter reviews potential clinical applications of genetic research into mental disorders. These include improvements in:

- classification and diagnosis;
- risk assessment for genetic counselling;
- drug treatments;
- preventive medicine; and
- possibly in the more distant future, gene therapy.

4.2 In the case of disorders largely determined by alterations in single genes, genetic information is already being used for classification and diagnosis, genetic counselling and preventive medicine. The pitfalls in these relatively straightforward situations illustrate the many potential difficulties that lie ahead in translating genetic research findings relevant to the more complex mental disorders into useful clinical applications. As such applications have not yet been developed for these mental disorders, the analysis in this chapter is based on two sources of information; first, extrapolations from single gene disorders such as Huntington's disease, second, experience gained in multifactorial disorders for which some of the susceptibility genes have been identified, such as Alzheimer's disease and the non-psychiatric examples of diabetes and familial hypercholesterolaemia.

Classification and diagnosis

4.3 An important distinction between psychiatry and most other branches of medicine is that, although psychiatric diagnoses made by different practitioners show a high level of agreement, little is yet known about any underlying physical changes. Consequently, laboratory tests to confirm or refute diagnoses are generally unavailable. It is possible, therefore, that some psychiatric diagnoses include distinct disorders with different causes. This variation may be due to the interaction of different genes, to the interaction of genes with specific environmental factors, or to the existence of separate disorders in which the same symptoms occur, but genetic predisposition plays little or no role.

4.4 Developments in our understanding of genetics may allow psychiatrists to define subtypes of mental disorders with different underlying causes (paragraph 3.8). Such developments are more likely to result in modification rather than the complete revision of systems of psychiatric classification, but may be very important for understanding the causal mechanisms of disorders.

4.5 The discovery of genes with different mutations has had profound implications for the diagnosis of many single gene disorders. For example, the characterisation of a particular type of mutation called expanded triplet repeats in diseases of the nervous system such as Huntington's disease (Box 3.2) and Friedreich's ataxia has important implications for diagnosis and prognosis. This may occur either in the context of a person who is already ill, for whom a genetic test may confirm or refute a particular diagnosis; or it may predict the later development of an illness in an apparently healthy person or fetus (presymptomatic or prenatal test). However, even single gene disorders are affected by other genetic and environmental effects, so that, for example, age-of-onset and severity in such diseases may be quite variable (paragraph 3.5). It may sometimes

be difficult to establish whether a particular alteration in a gene is pathological or not and, even in single gene disorders, different mutations may have different qualitative and quantitative effects on disease severity.[1] So it is never possible to predict the complete clinical picture from knowledge of mutations in a single gene.

4.6 For disorders with more complex causes susceptibility genes play a role but are neither necessary nor sufficient to cause the disease. This limits the usefulness of genetic tests in either a diagnostic or a predictive context. In familial hypercholesterolaemia (FH), for example, diagnosis by the presence of a specific gene variant is of no better predictive value than a cholesterol assay. Moreover, the development of heart disease is strongly influenced by many factors in addition to FH, including environmental factors (diet and smoking) and other disorders such as obesity, diabetes and hypertension, making prediction of disease risk by genetic testing for FH impracticable for most individuals in the population.

4.7 An example relevant to psychiatry is late onset Alzheimer's disease (Box 3.3). The finding that a gene variant called the apoE4 allele is more common in patients with Alzheimer's disease than healthy controls has shed new light on the biochemical basis of the disease, but the effect of the gene variant accounts for only 15% of susceptibility to the disease. About 50% of all affected patients do not possess an apoE4 allele. Recent studies have concluded that, while apoE4 testing may be important for research, it is not appropriate either for diagnosis or for prediction in members of the population as a whole,[2] although debate on this issue continues.[3] Given the findings from genetic linkage studies (paragraph 3.21) it is likely that few, if any, susceptibility genes associated with mental disorders will make a larger contribution to susceptibility than apoE4 does for Alzheimer's disease. If this turns out to be correct, the usefulness of these loci for either diagnostic or predictive genetic testing will be limited. A positive ratio of benefits to risks of any potential test would need to be demonstrated and replicated in a research setting before routine clinical implementation could be recommended.

4.8 It is perhaps more likely that the identification of susceptibility genes could lead to a better understanding of disorders and hence the development of useful diagnostic tests. Type 1 diabetes (the form of the disorder that occurs early in life and is treated with insulin) is an example. Although a number of susceptibility genes have been identified, notably the HLA and insulin genes, the genetic tests have low predictive power. But by measuring an intermediate clinical feature, the presence in the blood of autoantibodies, healthy siblings of diabetics can be identified who have a greater than 90% risk of developing diabetes within ten years.

4.9 Genetic tests open up the possibility of prenatal diagnosis of the fetus and, assuming that a termination of pregnancy in such circumstances would come within the terms of section 1(1) (d) of the Abortion Act 1967,[4] termination of pregnancy. Prenatal diagnosis is offered in the UK for serious single gene and chromosomal disorders such as fragile X and Down's syndrome that are generally associated with mental retardation from birth and for which a cure appears unlikely.

1 Kahn P (1996) Coming to grips with genes and risk, **Science** 274:496–8; Humphries S, Galton D and Nicholls P (1997) Genetic testing for familial hypercholesterolaemia: practical and ethical issues, **Quarterly Journal of Medicine** 90:169–81.

2 American College of Medical Genetics/American Society of Human Genetics Working Group on ApoE and Alzheimer disease (1995) Statement on use of Apolipoprotein E testing for Alzheimer disease, **Journal of the American Medical Association** 274:1627–9; Lovestone S with UK Alzheimer's Disease Genetics Consortium (1995) The genetics of Alzheimer's disease, **International Journal of Geriatric Psychiatry** 10:1–7.

3 Post S *et al.* (1997) The clinical introduction of genetic testing for Alzheimer Disease, **Journal of the American Medical Association** 277:832–6.

4 See the discussion in Kennedy I and Grubb A (1994) **Medical Law: Text with Materials**, Second Edition, Butterworths, UK pp 877–8.

By contrast, the uptake of prenatal diagnosis for single gene disorders that predominantly affect adults, such as Huntington's disease, has been relatively low.[5] In other nervous system disorders such as neurofibromatosis the demand for prenatal diagnosis is even lower.[6] Pre-implantation genetic testing is now feasible for couples at risk for transmitting an identified single gene disorder to their children. To date, uptake has been limited by the technical difficulty, expense and low rate of completed pregnancy associated with the procedure. However, this option may become more popular if these technical hurdles are overcome.[7]

4.10 For mental disorders of complex aetiology any one susceptibility gene is very unlikely to be necessary or sufficient to cause a disease, making it difficult to predict its future occurrence and severity in a fetus or child with any certainty. Unlike Huntington's disease, many mental disorders already have reasonably effective treatments and there is every prospect that those treatments will improve further in future decades. Quite apart from the ethical and legal considerations discussed in Chapter 5, therefore, prenatal diagnosis for the common mental disorders is unlikely either to have sufficient predictive value to be indicated medically or to be demanded by families.

Genetic counselling

4.11 The Working Party adopted a broad definition of genetic counselling as "*the process by which patients or relatives at risk of a disorder that may be hereditary are advised of the consequences of the disorder, the probability of developing or transmitting it and of the ways in which this may be prevented, avoided or ameliorated*."[8] Adults may want to confirm the diagnosis of an existing disorder or to explore their own risk of developing a disorder and its likely severity. Genetic counselling in relation to children may have the same aims but it raises additional issues of consent if genetic testing is contemplated. In addition, adults may seek genetic information about themselves, their partners, their children or a fetus in order to help them make reproductive decisions.

4.12 In the UK, genetic counselling is a specialist service for individuals and families provided by clinical geneticists and other trained professionals in regional centres. At present, genetic counselling for complex mental disorders occurs fairly rarely. It has been said that families show a thirst for knowledge,[9] and it is generally thought that the demand for genetic information is likely to increase.[10]

4.13 Genetic counselling depends on two types of risk figures, *empiric* and *calculated*. *Empiric* risk figures are based on gathering data on the frequency of a disorder in a population. Thus the empiric risk of schizophrenia in the UK population is about 1%. Such figures 'average out' differences in actual risk between individuals. If the empiric risk figure is relatively low (less than 2%) this may often provide reassurance in a situation where people overestimate risks and assume the worst. However, the empiric risk figures for first-degree relatives of individuals

5 In one study of Huntington's disease, for example, only 7 out of 38 (18%) of couples eligible for a prenatal test decided to proceed. Optimism about the discovery of a cure was the predominant reason given for not considering prenatal testing (Adam S, Wiggins S, Whyte P, Bloch M, Shokeir M, Soltan H, Meschino W, Summers A, Suchowersky O, Welch J, Huggins M, Theilmann J and Hayden M (1993) Five year study of prenatal testing for Huntington's disease: demand, attitudes, and psychological assessment, **Journal of Medical Genetics** 30:549–56).

6 Ponder M, Murton F, Hallowell N, Statham H, Green J. and Richards M (1998), Genetic counselling and future reproductive intentions of people with neurofibromatosis type 1 (NF1), **Journal of Genetic Counselling**, in press.

7 Schulman J, Blake S, Handyside A and Nance W (1996), Preimplantation genetic testing for Huntington's disease and certain other dominantly inherited disorders, **Clinical Genetics** 49:57–8.

8 Harper P (1993) **Practical Genetic Counselling**, Fourth edition, Butterworth-Heinemann Ltd, Oxford,.

9 Office of Technology Assessment/Congress of the United States (1994) **Mental Disorders and Genetics: Bridging the Gap Between Research and Society**, OTA-BP-H-133, US Government Printing Office, Washington DC, p36.

10 McGuffin P (1994) Genetics, Chapter 4 in Paykel E and Jenkins R (eds) **Prevention in Psychiatry**, Gaskell Press, London.

affected by certain mental disorders of complex basis are often considerably higher. For example, the sibling and offspring risks for individuals affected by schizophrenia are around 10% (Appendix 1, Figure 1). The usefulness of empiric risk figures in genetic counselling for the occurrence of mental disorders in relatives has never been evaluated but making decisions based on such low risks is often very difficult.

4.14 *Calculated* risk figures are based on objective criteria, including knowledge of the specific mode of inheritance and/or the results of blood tests, X rays or genetic tests, to modify empiric risks. In some cases this will result in an increased or decreased individual risk figure. Arguably, the value of genetic counselling depends on the possibility of categorising an individual's risk on objective, rather than empiric criteria. To what extent, then, will genetic testing for complex mental disorders make it possible to provide individualised risk figures?

4.15 Individual risk figures that combine a knowledge of the family history with the results of single locus testing can be obtained by a type of mathematical reasoning called Bayesian theory.[11] It can be shown that this approach works fairly well in predicting risks for relatives of affected individuals even when the risk contributed by each susceptibility gene is comparatively small.[12] For example, the risk of developing schizophrenia if one has a first-degree relative (parent, brother or sister) already affected is about ten times the general population risk, or about 10%. Genetic research is beginning to identify potential susceptibility genes for schizophrenia and one of these is a variant in the serotonin receptor (5HT2a) gene which, one study has shown, occurs in about 70% of people with schizophrenia in the UK (Table 3.1). The variant also has a high frequency in healthy controls (about 55%) but the difference between the frequencies in people with schizophrenia and controls is statistically significant.[13] What would be the risk of developing schizophrenia for someone who already had a brother affected by schizophrenia and who tested positive for the serotonin receptor variant? The answer (using the Bayesian method) is 12.3%, in other words, only a little higher than the 10% empiric risk figure. Such an increase is unlikely to be clinically significant given evidence that reduction in uncertainty is one of the most common reasons given for undergoing a DNA test.[14]

4.16 Despite such examples, it has been claimed that gene identification will be very valuable in personalising risks, and that the increase in precision provided by the ability to calculate risks on an individual basis will be of enormous clinical benefit.[15] Evidence to support such claims, however, is lacking. There is currently very little provision, or demand for, genetic counselling in any of the common multifactorial disorders such as cardiac disease and diabetes, even where tests are available that would allow the calculation of individual risk. Indeed, no objective study of genetic counselling in these diseases has been undertaken. One possible reason for this is that, in the absence of effective therapeutic interventions for people found to be at high risk, such studies have not been considered either ethically acceptable or cost-effective. Studies are now being contemplated (for example, in diabetes), however, and their findings might have important implications for the management of mental disorders and for genetic counselling.[16]

11 This takes into account an individual's initial risk (the so-called prior probability) of disease and then allows a calculation of the modified risk once the result of a test is known (the posterior probability).

12 It is possible to take the empiric risk as the prior probability and use genetic marker data to calculate the posterior probability of becoming affected.

13 Williams J, Spurlock G, McGuffin P, Mallet J, Nöthen M, Gill M, Aschauer H, Nylander P, Macciardi F and Owen M (1996) Association between schizophrenia and T102C polymorphism of the 5-hydroxytryptamine type 2a-receptor gene. European Multicentre Association Study of Schizophrenia (EMASS) Group, **The Lancet** 347:9011, 1294–6.

14 Marteau T and Croyle R (1998) Psychological responses to genetic testing, **British Medical Journal** 316:693–6.

15 Rutter M and Plomin R (1997) Opportunities for psychiatry from genetic findings, **British Journal of Psychiatry** 171:209–19.

16 British Diabetic Association (1996) Ethical issues in research into prevention of insulin-dependent diabetes mellitus (IDDM), **Diabetic Medicine** 13:399–400.

4.17 In type I diabetes, a number of preventive strategies are theoretically feasible for healthy siblings of diabetics who are identified by autoantibody measurement as at risk of developing diabetes. Placebo-controlled trials are under way to determine whether these strategies delay or prevent the onset of diabetes.[17] Here, prediction and prevention (or at least, its possibility) are being offered hand-in-hand in a research setting. Such studies allow the evaluation of the psychological effects of risk alteration and genetic counselling for common multifactorial diseases.

4.18 The value of genetic counselling in the common multifactorial mental disorders will depend on two principal criteria: the ability to calculate individual risks and the ability to identify preventive measures to reduce risk in individuals at high risk.[18] It is difficult to predict the extent to which these criteria will be met but, given the difficulty of identifying convincing susceptibility genes over the past ten years, it seems likely that only a small proportion of individual risk will be predictable even when multiple susceptibility genes can be tested. The 15% contribution that apoE4 makes to variance in risk for late onset Alzheimer's disease is probably the maximum contribution we can expect for individual susceptibility genes for most mental disorders; a more typical figure would be the 4% variance in novelty-seeking behaviour apparently explained by the DRD4 genotype (paragraphs 3.13–3.14).

4.19 The lack of usefulness of apoE4 testing for genetic counselling has already been highlighted (paragraph 4.7). The value of testing for most mental disorders will be still weaker if the genetic susceptibilities are lower. Even if sufficient susceptibility genes were identified to explain say, 30% of the variation in risk between different people in a population, without an understanding of the interactions between the genes, and between genes and environment, it would still be difficult to predict accurately the risk for an individual (paragraph 4.21).

4.20 To summarise, genetic testing in complex mental disorders is unlikely to improve on the empiric risk figures (paragraph 4.13) by more than a modest extent. Nevertheless, it is important to study genetic and environmental susceptibilities and their correlation and interaction, since this may shed further light on causal mechanisms and suggest novel therapeutic or preventive strategies. Empiric risk figures for recurrence of mental disorders in relatives already exist, yet their value in genetic counselling has never been evaluated. Similarly, no data are available on the value of genetic testing and counselling for common diseases (heart disease, diabetes) in which susceptibility genes have already been identified.[19] In mental disorders, direct investigation using brain imaging of how brain mechanisms are disrupted may yet be more convincing and have greater clinical implications than genetic approaches.[20]

4.21 If developments in genetics continue at the present rate, however, some possibilities that currently seem unrealistic, such as testing simultaneously for large numbers of susceptibility genes and examining combined risks, may become feasible. One obstacle to the potential usefulness of genetic tests for multifactorial disease is that we do not know how many susceptibility genes are involved nor how they combine and interact. For example, we do not know whether carrying several 'high risk' variants in different genes has a simple additive effect or whether the situation is more complicated.[21] Estimating the predicted risk where two predisposing genes are thought to be involved is not possible using the Bayesian method (paragraph 4.15) because the interactions between the genes are not known. Empirical research will be needed, examining the effects of

17 Alberti K (1993) Preventing insulin dependent diabetes mellitus, **British Medical Journal** 307:1435–6; Palmer J (1994) What is the best way to predict IDDM? **The Lancet** 343:1377–8.

18 Rutter M and Plomin R (1997) Opportunities for psychiatry from genetic findings, **British Journal of Psychiatry** 171:209–19.

19 Boerwinkle has pointed out the difficulties of attempting to derive estimates of genetic risk on the basis of retrospective or cross-sectional studies, and has emphasised the need for prospective studies to address these questions (Boerwinkle E (1996) A contemporary research paradigm for the genetic analysis of a common chronic disease, **Finnish Medical Society DUODECIM, Annals of Medicine** 28:451–7).

20 A point made by Professor Guy Goodwin, University of Oxford, Department of Psychiatry, in advice to the Working Party.

21 In other words, the effect of variant *a* and variant *b* may be *a* x *b* rather than *a* + *b*.

the genes of interest in large samples. Again, it must be emphasised that, even if all the susceptibility genes involved and their interactions were known, there are limits to the predictive certainty. Even if a pair of relatives are alike at all of the relevant genes and the first member of the pair develops schizophrenia, the second will not necessarily become affected too. We know this because the concordance rate for identical twins (who are 'natural clones' sharing 100% of their genes) is just under 50% indicating that non-genetic influences are also important (Appendix 1, Figure 2).

Development of new and better targeted drug treatments

4.22 Although many pharmacological and behavioural treatments have been identified for mental disorders, their therapeutic efficacy for a given individual can be unpredictable. To a degree, drug development for psychiatric disorders has been a question of trial-and-error. There is great optimism that a better understanding of brain chemistry in mental disorders will lead both to new treatments and to treatments that are better tailored to individual requirements, with fewer side effects. Finding specific alterations in susceptibility genes for mental disorders may provide a better understanding of the biochemical pathways of disease. Knowledge of these pathways may suggest entirely new drug treatments.[22]

4.23 Work to reduce the side effects of drugs which already exist is rather further advanced. The gene variants that influence whether a person suffers from side effects may be concerned with the general metabolic handling of the drug and, as such, may be distinct from the susceptibility genes associated with mental or other disorders. For example, a gene that codes for a type of enzyme called p450 determines the efficiency with which certain drugs are metabolised by the liver.[23] In most cases, this variation will be present throughout the population, rather than being confined to individuals with the disease. Such information may enable doses of medicine to be tailored more accurately to the individual so that therapeutic levels are achieved, rather than the patient being under or over medicated.

4.24 The pharmaceutical industry has been investing very heavily in genomics over the past few years and is optimistic about developing drugs which are targeted to specific patients. "*In clinical efficacy trials, genomics provides an increasingly sensitive tool to devise a novel framework for specific diagnosis, selective therapy and prediction of non-responders.*" [24] However, it should be emphasised that optimism about 'pharmacogenomics' is largely based on supposition, rather than on what has already been achieved. So far, the real contribution of molecular genetics to the production of medicines has not come from new gene discovery. Rather it has come from using recombinant DNA technology to turn organisms such as bacteria into 'chemical factories' by introducing known human genes, for example the insulin gene, and harvesting the gene product.

22 For example, the detailed causation of cystic fibrosis remained obscure until the identification of mutations in the CFTR gene in 1989. Subsequent studies showed that the CFTR gene is responsible for a chloride channel, a protein on the membrane of cells, that is involved in controlling chloride levels. If the gene is abnormal this particularly affects some parts of the body, such as the linings of the lungs and the intestines. This finding in turn has spurred an explosion of work on the biochemical pathway within which this chloride channel lies and hence the identification of 'weak points' which might be targeted by novel drugs. (Delaney S and Wainwright B (1996) New pharmaceutical approaches to the treatment of cystic fibrosis, **Nature Medicine** 2:392–3). An additional point to emerge from this work is that different therapies would be appropriate for different cystic fibrosis mutations. Such a refined approach to development of new medicines would have been inconceivable in the pre-genomic era. Nevertheless, it must be emphasised that, nearly a decade after the discovery of the CFTR gene, these new potential therapies are still some way from being applied clinically.

23 Another example of a situation in which part of the variation in response to medication is attributable to genetic factors is apoE in the context of familial hypercholesterolaemia (FH). In a study of the efficacy of the lipid lowering drug probucol in FH patients, apoE genotypes significantly influenced how well patients responded, but had no influence on hypercholesterolaemia not attributable to FH. (Nestruck A, Bouthillier D, Sing C and Davignon J (1987) Apolipoprotein E polymorphism and plasma cholesterol response to probucol, **Metabolism** 36:743–7.)

24 Shaw G (Chairman) (1995) **Human Genetics: The Science and Its Consequences, House of Commons Science and Technology Committee Third Report, Session 1994–95, Volume II Memoranda received up to January 31st 1995**, 41-II, HMSO, London, p81 submitted as part of the response by SmithKline Beecham to the Working Party's consultation.

Improved preventive measures

4.25 There is ample evidence that genetic background is usually not sufficient to cause mental disorder, and that interaction with environmental factors may be crucial for disease to occur. The identification of susceptibility genes would enable this relationship to be studied in a more sophisticated fashion. This might enable the identification of specific environmental triggers that cause disease in genetically susceptible individuals. For example, boxers show wide variation in their susceptibility to neurological damage. Preliminary evidence suggests that boxers with the apoE4 allele are more likely to suffer neurological damage than those without.[25] Even if this result is confirmed, however, the Working Party would caution against any suggestion that apoE4 testing should be used to enable boxers to assess their risk of suffering neurological damage more precisely, not least because this might lead people without apoE4 alleles to underestimate the risks of what is always a highly dangerous activity. This example illustrates the complexity which arises when variants of susceptibility genes are both relatively common in the population and associated with more than one disease or characteristic (paragraph 5.20).[26]

4.26 Many preventive measures for medical conditions require positive intervention, such as changes in diet (phenylketonuria), vitamin supplementation (neural tube defects) or hormonal replacement (congenital hypothyroidism). The risk/benefit ratio of such measures needs to be evaluated very carefully. For example, two drugs in the Coronary Drug Project secondary prevention trial had to be discontinued before completion of the study because of excess mortality.[27] The risks of such interventions are even more pertinent if individuals are susceptible to a disorder, but there is no certainty that the condition will develop in the absence of treatment.

4.27 There is preliminary evidence that a common variation in the dopamine receptor DRD4 allele is weakly associated not only with variation in a behavioural dimension (novelty seeking), but also with a number of pathological states such as attention deficit hyperactivity disorder, drug dependence, and major depressive disorder (paragraphs 3.13–3.14). It has been argued that these findings may suggest specific preventive measures, for example, avoidance or behavioural therapy. However, any use of targeted environmental modification may be unrealistic given that the health care and social welfare system has not eliminated simple, basic inequalities of service delivery which themselves contribute substantially to ill-health. Moreover, avoiding environmental triggers is not always realistic, especially if a number of family members suffer from a mental disorder.

25 Jordan B, Relkin N, Ravdin L, Jacobs A, Bennett A and Gandy S (1997) Apolipoprotein E 4 associated with chronic traumatic brain injury in boxing, **Journal of the American Medical Association** 278:136–40.

26 Indeed, another study has suggested that, while smoking is a strong risk factor for Alzheimer's disease in individuals without the apoE4 allele, it has no effect in people with this allele (Ott A, Slooter A, Hofman A, van Harskamp F, Witteman J, Van Broeckhoven C, van Dujin C and Breteler M (1998) Smoking and risk of dementia and Alzheimer's disease in a population-based cohort study: The Rotterdam Study, **The Lancet**, 351:1840–3).

27 Levine G, Keaney J and Vita J (1995) Cholesterol reduction in cardiovascular disease, **New England Journal of Medicine** 332:512–21.

Gene therapy

4.28 Gene therapy has received wide publicity in recent years but its clinical efficacy remains highly speculative. A report by a US National Institutes of Health Working Party (reviewed by Touchette[28]) criticised the standard of current gene therapy protocols and emphasised that therapeutic efficacy had not been demonstrated for any disorder. The report highlighted the mismatch between the poor knowledge of basic mechanisms of gene regulation and the mechanisms by which diseases are caused, and the ambitious nature of the therapeutic measures being attempted. Until there is evidence that gene therapy for technically more straightforward metabolic or haematological disorders is effective, it should not be applied to mental disorders. This is likely to take at least a decade. Even once this has been achieved, additional problems in treating mental disorders, such as the difficulty of modifying neural tissue which is both highly inaccessible and composed of non-dividing cells, will need to be overcome.

Conclusions

4.29 Developments in genetics may allow psychiatrists to define subtypes of mental disorders with different causes but this is more likely to result in modification rather than complete revision of systems of psychiatric classification. Identification of genes involved in susceptibility to common mental disorders is unlikely to lead directly to the development of diagnostic tests but may do so indirectly by improving understanding of abnormal biochemical processes.

4.30 Because of their complex aetiology, it is unlikely that genetic tests will be of much use for the diagnosis of most common mental disorders. Hence it is even less likely that genetic testing for common mental disorders will be useful for general population screening for susceptibility to mental disorders. Further research will be required before it can be known whether genetic testing will prove useful in the genetic counselling of individuals who are known to be at high risk because of a family history of mental disorder.

4.31 An improved understanding of biochemical processes resulting from genetic research provides long-term potential for the development of more specific and effective drug treatments. There may be potential for preventive measures once genes conferring susceptibility to common mental disorders have been confidently identified. However, preventive strategies are likely to be less clear cut than those for single gene disorders.

4.32 The usefulness of gene therapy in single gene disorders has so far been disappointing. Although the application of gene therapy to common mental disorders at some point in the future cannot be discounted, it would not be appropriate to formulate an approach until general principles have been validated in the technically more straightforward single gene disorders.

28 Touchette N (1996) Gene therapy: Not ready for prime time, **Nature Medicine** 2:7–8.