DNA diagnostics: goals and challenges

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The exponential increase in the discovery of human disease genes over the past 10 years has transformed DNA diagnostics from a minor research-based activity to a major professional operation. Mutation testing and linkage analysis are now used to provide prenatal or postnatal diagnosis for a wide range of monogenic disorders, but robust automated procedures for scanning disease genes for mutations are not yet available. The discovery of genes which confer susceptibility to common disorders is likely to create demand for high throughput testing for specific mutations or clinically relevant polymorphisms. Widespread genetic testing must be supported by adequate genetic counselling and by education of healthcare professionals in order to ensure the appropriate application of this information for the benefit of patients and their families.

The provision of DNA diagnostics for genetic disorders is a youthful occupation which is little more than a decade old. What began as a research activity in a few laboratories is now a fully fledged professional activity with its own national organisations, training and qualifications, which provides thousands of genetic tests every day. This transformation was made possible by the extremely rapid pace of disease gene discovery, and by the development of techniques for the detection of specific DNA sequences. First among these was Southern blotting, and later the diagnostic field was transformed by the polymerase chain reaction (PCR) which permits amplification of specific DNA sequences from very small quantities of genomic DNA (see Weatherall1 for a review of methodology). This review considers what can and is being done in DNA diagnostics, what may be done in the future, and what principles should underpin our use of genetic information.

Human disease genes: a growth industry

Ten years ago, only a handful of genes which caused genetic disorders in humans had been identified. Today, at least 12 000 different mutations have been detected in more than 600 different genes, and this number is
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... growing rapidly\textsuperscript{2}. Most of these are associated with Mendelian disorders such as cystic fibrosis, in which a single, rare gene is mutated in a family and confers a very high risk of developing the disease. Although the frequency of each of these disease genes is low in most populations, the cumulative frequency of several thousand such genes adds up to a significant healthcare burden, quite apart from individual tragedy for the affected families. We are also beginning to see other kinds of genes being added to the list, genes which are common in the general population and which confer a moderate degree of genetic susceptibility to common disorders such as diabetes and asthma. Some of these genes have been localised to specific chromosomal regions by typing very large numbers of families with polymorphic DNA markers and demonstrating excess marker sharing in affected siblings\textsuperscript{3}, and others have been identified by association studies of candidate genes. Homozygosity for the E4 allele of the APOE gene, for example, has been shown to confer increased risk of, and reduced age of onset in Alzheimer’s disease\textsuperscript{4}. Although the number of such genes which have actually been identified is still small, there is a strong expectation that the number will grow very rapidly in the next 5–10 years.

**Mutation detection**

Once the disease gene has been identified, a direct diagnostic test requires knowledge of the specific mutation in a particular family. This may not be as easy as it sounds: the cystic fibrosis (CF) gene, for example, has more than 600 different mutations, many of which have been found in only one or a few families, and these mutations are scattered throughout the gene. It may, therefore, be necessary to scan the entire coding sequence of the relevant gene to identify the single nucleotide which is altered. Obviously this can be done by sequencing the gene, but even with the help of automated DNA sequencers this is labour-intensive and expensive, particularly if the gene in question happens to be large. Many disease genes have coding sequences which are 5000–6000 base pairs (bp) in length. A further complication is that most genes are highly interrupted, with the coding sequence often divided into as many as 40–50 exons. These must either be amplified individually from genomic DNA, or the mRNA can be reverse transcribed and amplified by PCR in one or a few large fragments for subsequent analysis. A variety of mutation scanning methods have been developed\textsuperscript{5}, such as chemical cleavage, in which a heteroduplex DNA molecule formed between the mutant and a wild-type DNA is chemically modified and cleaved as a result of distortion of the double
Fig. 1 Mutation scanning of exon 11 of the BRCA1 gene by chemical cleavage analysis in three patients. The PCR product from each patient has been labelled with a different fluorescent dye, allowing analysis of all three patients on one lane of a fluorescent DNA analyser. In the sample from patient 1 the full length PCR product of 1519 bp has been cleaved into 2 fragments of 843 and 676 bp – DNA sequencing of the region of mismatch revealed a deletion of a C nucleotide at position 2360 of the coding sequence of the BRCA1 gene. Three common polymorphisms were detected in patient 2, and no mutations were found in patient 3.

helix at the position of the sequence mismatch, and the cleaved fragments are then detected and sized by gel electrophoresis. The mutation must be characterised by sequencing the region of cleavage. Several different fragments can be analysed simultaneously if they are labelled with fluorescent dyes of different colours and separated on a fluorescent DNA analyser, thus permitting scanning of as much as 4000 bp for a mutation in one lane of the gel with high sensitivity. The use of this technique to detect a mutation in the BRCA1 gene, which causes predisposition to breast and ovarian cancer, is shown in Figure 1.

Once the causative mutation has been identified, a simple PCR assay can be devised to test for it in other family members. In the case of mutations of a single nucleotide, diagnosis is usually by use of a restriction enzyme which has an altered fragmentation pattern at the site of the mutation, or by use of specific PCR primers which will only amplify from the normal or from the mutant allele. Mutation detection in disorders which result from expanded triplet repeat sequences, such as Huntington's disease, is relatively straightforward since the region of the gene which undergoes expansion can be amplified by PCR, and the products sized by gel electrophoresis. PCR can also be used to detect the
large deletions which occur within the dystrophin gene in Duchenne muscular dystrophy, and, with the help of fluorescent DNA analysers, to detect carriers of gene deletions or duplications by quantitative gene dosage assays. However, the interpretation of what constitutes a causative mutation is not always straightforward. Clearly large deletions which remove part of the coding sequence of the gene or mutations which produce a stop codon resulting in premature termination of translation of the mRNA are likely to disrupt the function of the encoded protein, but missense mutations which alter a single amino acid residue may be genuine mutations or rare variants which have no effect on protein function. Such changes must fulfil criteria such as co-segregation with the disease in the family, absence in substantial number of ethnically matched controls, and must be predicted to have a significant effect on the structure of the protein in order to be regarded as pathogenic mutations.

**Linkage analysis with polymorphic markers**

The first step in the identification of a disease gene has often been a linkage study, wherein the chromosomal location of the gene is established by a genome scan. Many families with multiple cases of the disease are typed with polymorphic DNA markers from each of chromosomes 1–22 (in a condition with autosomal inheritance) or from the X chromosome in X-linked disorders, until a marker is found which co-segregates with the disease. Once tightly linked markers are found, not only can the gene be identified by so-called positional cloning, but the markers can be used for indirect diagnosis even before the gene in question has been cloned. Once the allele of the polymorphism which is linked to the disease gene in a particular family has been identified, it can be used to track the inheritance of the mutant gene in that family and predict, for example, the affection status of a fetus. The pace of genome mapping and sequencing has reduced the mean interval from establishing a linkage to the cloning of the disease gene dramatically (it took 10 years to clone the Huntington’s disease gene), thus reducing the need for this indirect form of diagnosis. However, the problems of mutation detection already mentioned have led to the continued use of linkage analysis in families in whom the causative mutation has not been identified. The choice of diagnostic method is sometimes dictated by resources, since if DNA samples from the relevant family members are available, it may be quicker (and cheaper) to type them with a few highly informative polymorphic markers than to scan their gene for the mutation. However, the problems associated with indirect diagnosis based on linkage analysis may render accurate diagnosis impossible.
These include the occurrence of new mutations, germinal mosaicism, meiotic recombination between the marker and the disease gene, and unavailability of samples from key family members.

**Diagnosis of monogenic disorders**

*Confirmation of clinical diagnosis*

The description of so many genes and their causative mutations has led to a change in the function of DNA diagnostics in recent years. Initially, mutation or linkage analysis was performed for families in whom an unequivocal clinical diagnosis had been made, in order to provide carrier testing or prenatal diagnosis. Increasingly, the function of DNA diagnostic laboratories is to test specific genes for mutations in order to confirm the clinical diagnosis or to provide the primary diagnosis. For example, a child with a chronic chest infection and a borderline sweat test might be confirmed as having cystic fibrosis by being shown to be homozygous for the common CF mutation; detection of a homozygous deletion in the gene for spinal muscular atrophy might lead to a decision to discontinue ventilation in an infant with a poor neuromuscular response; detection of a duplication of the PMP22 gene on chromosome 17 would confirm a diagnosis of hereditary motor/sensory neuropathy type 1A. Thus disease taxonomy is increasingly being defined at the molecular level. This presages a much greater role for genetic diagnosis in the future, as the number of genes and mutations associated with human disease continues to expand.

*Carrier testing and presymptomatic diagnosis*

Carrier testing is now possible for a wide range of autosomal recessive disorders, but is generally only requested if there is a family history of the condition and if it is relatively common in the population in question. Examples are cystic fibrosis in Europeans and North Americans, and β-thalassaemia in certain Mediterranean populations. This requires knowledge either of the causative mutation in the family, or at least of those mutations which are common in the particular population. In the latter case, the carrier risk can be substantially reduced, but not eliminated, if the consultand does not have any of the common mutations. Carrier testing for X-linked recessive conditions such as Duchenne muscular dystrophy and haemophilia also requires knowledge of the mutation for an accurate diagnosis, although linkage analysis can be helpful if the mutation is unknown. Presymptomatic
diagnosis or predictive testing for a number of adult onset disorders is also now possible for patients who are at risk because of their family history and who may wish to know whether they carry the relevant mutation. This may be in order to plan life decisions such as whether to have children and, if so, whether to undergo prenatal diagnosis, or simply to eliminate the uncertainty. The disease may be incurable, such as Huntington's disease or early onset familial Alzheimer's disease. In other cases, useful preventative action may be taken, such as surgical removal of polyps for familial adenomatous polyposis. This form of genetic testing is more complex and challenging in terms of ethical considerations and patient care, and requires clearly defined protocols and careful genetic counselling.

Prenatal diagnosis

Prenatal diagnosis by DNA analysis of a chorionic villus sample (CVS) taken in the 11th to 12th week of pregnancy is now routine for a large number of monogenic disorders, provided that the mutation in the affected family member is known, or that linkage analysis can determine whether the fetus has inherited the allele of the polymorphism which is linked to the mutant gene. The fact that sufficient DNA can be extracted directly from the CVS, and that the diagnosis is generally (but not always) performed by PCR, means that a result can often be provided to the family within a few days, and a first trimester termination of the pregnancy can be carried out if necessary. The molecular work-up of the family should precede the pregnancy in order to establish whether an informative prenatal test is possible. Regrettably this is not always the case, since cogitation does not always precede procreation. The CVS should also be tested to exclude even a small amount of contamination with maternal cells, since the sensitivity of PCR may lead to a false negative or false positive diagnosis as a result of amplification of a mutant or wild-type maternal allele.

Pre-implantation diagnosis

The triad of technical developments of in vitro fertilisation (IVF), PCR and fluorescent in situ hybridisation (FISH) have created the possibility of carrying out pre-implantation genetic diagnosis (PGD). The fertilised embryo is biopsied at about the 8-cell stage, with one or two cells being removed for molecular or cytogenetic analysis. Since a single cell should contain the full genetic complement of the embryo, any specific sequence can in principle be amplified by PCR and analysed for the
relevant mutation. Similarly, FISH can be carried out to sex the embryo (in X-linked disorders), or to test for chromosomal abnormalities. The PGD process is time-consuming, expensive and limited by the success rates of the IVF procedure. However, there is a continuing demand for PGD from the significant minority of patients for whom termination of pregnancy is not acceptable. Molecular PGD is associated with a significant risk of diagnostic failure because of the perfect sensitivity required for PCR from a single cell, or of misdiagnosis as a result of PCR contamination from the high number of PCR cycles required to amplify a single molecule to detectable levels. Thus a PCR assay for a deletion of an exon of a particular gene, such as the dystrophin gene in Duchenne muscular dystrophy, could easily produce a false negative (i.e. normal) result in an affected embryo if any of the reagents were contaminated with either genomic DNA or a very small amount of the relevant PCR amplification product\textsuperscript{13}. The use of linked highly polymorphic microsatellite markers is helpful in this context, since they provide a rather specific DNA profile of the identity of the biopsied cell. In spite of these difficulties, successful PGDs have been performed by PCR, with one group reporting the birth of 5 unaffected children after PGD for cystic fibrosis\textsuperscript{14}. FISH currently appears to be a more reliable technique in a PGD setting, and will be used increasingly to detect chromosomal aneuploidy in cases of recurrent miscarriage of conventional pregnancies. Systematic monitoring of outcomes and error rates for PGD, and publication of these data, should be required at this rather experimental stage of the technique.

Population screening

Most DNA diagnosis is provided for individuals and families with a history of a particular genetic disorder, but there has been considerable debate and research regarding the introduction of population screening for the most common disease genes in certain populations. There are several models for this, including screening for common β-globin gene mutations, which has led to a reduction in the incidence of β-thalassaemia in Southern Europe (reviewed by Modell\textsuperscript{15}), and antenatal screening for cystic fibrosis\textsuperscript{16}, which has been associated with a 65% reduction in the incidence of CF in the city of Edinburgh\textsuperscript{17}. The logic of attempting to reduce the incidence of life-threatening, incurable disorders is strong, but there are numerous practical challenges involved. These include decisions as to the appropriate age and circumstances under which to screen, the cost of screening for sufficient mutations to reduce the carrier risk greatly, the cost of provision of adequate genetic counselling for those who test positive, and concerns...
about the insurance consequences for carriers. The technical difficulties in screening for multiple mutations will probably be resolved with the advent of new DNA technology (see below), but each screening proposal will have to be carefully assessed in terms of logistics, cost, and ethical concerns.

**Genetic diagnosis of common, complex disorders**

Most common disorders such as diabetes and cancer are regarded as non-genetic, in the sense that there is often only one case of the disease in a family, and even if there is more than one case, no clear pattern of Mendelian inheritance can be observed. However, epidemiological studies of risks to relatives and of disease concordance in monozygotic versus dizygotic twins have shown that genes exist which confer moderate disease susceptibility on the individual, but that the presence of several such genes, in addition to an environmental trigger, is probably required to produce the disorder. Even for common diseases, there are sometimes a subset of cases which are associated with mutations in rare single genes of high penetrance. For example, mutations in the *BRCA1* gene confer a high risk of breast and ovarian cancer, and in the Presenilin-1 gene of Alzheimer’s disease. However, these mutations can generally be recognised by the early onset of the disease and the presence of a strong family history. They are, therefore, considered to be monogenic disorders, and are dealt with using diagnostic and counselling procedures already developed for disorders such as Huntington’s disease. However, the majority of cases of those common diseases for which there is epidemiological evidence of a genetic component, such as diabetes and asthma, will probably turn out to be associated with mutations in multiple genes, and these genes will be relatively common in the general population. One example of this is the apolipoprotein gene, the ApoE4 allele of which is associated with an increased risk of Alzheimer’s disease (reviewed by Pericak-Vance and Haines). The expectation is that many more such genes will soon be identified, and that this knowledge will be applied to disease diagnosis and classification, to stratification of drug therapy, and to disease prevention, since a predetermined genetic susceptibility could lead to an altered life style which reduces the environmental component of risk. Such information is likely to create an enormous demand for genetic testing in the future, which will be a new paradigm for DNA diagnostics in terms of the scale of sample throughput, the implications for those who test positive, and the method by which the information is conveyed to the patient.
The technical challenge

The major challenge which diagnostic laboratories face at present is to find the causative mutation in the relevant gene in each family referred for diagnosis. Although some disease genes have a simple mutational profile, with most cases being accounted for by one or a few mutations, for many the profile is complex. There is also the problem of genetic heterogeneity, in which mutations in more than one gene produce the same disease. In hereditary non-polyposis colorectal cancer, for example, the mutations are more or less evenly distributed between the MLH1

Fig. 2 Mutation screening of the CF gene using the chip. The chip in the upper panel has been hybridised with fluorescently labelled DNA from a sample homozygous for normal sequence, whereas the chip in the middle panel was hybridised with DNA homozygous for the R553X mutation. The lower panel is from a heterozygote, with both the normal and the mutant probes lighting up. (This figure was printed as part of Figure 3 in Cronin MT, Fucini RV, Kim SM, Masino RS, Wespi RM, Miyada CG. Cystic fibrosis mutation detection by hybridisation to light-generated DNA probe arrays. Hum Mutat 1996; 7: 244–55 and is reproduced here by kind permission of John Wiley and Sons Ltd, the copyright holder.)
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and MSH2 genes, both of which must, therefore, be screened to find the mutation in the patient. The mutation scanning methods developed thus far are labour-intensive and require considerable technical skill. There is a great need for a robust, sensitive and automated method which would allow the mutation in any gene of interest to be found in one or two days. The answer may lie in the microchip: not the electronic chip of the computer, but a chip upon which are bound tens of thousands of short oligonucleotide probes in ordered arrays of high density. Fluorescently-labelled target DNA (from the patient) is then hybridised to the chip, and will bind to complementary DNA sequences on it. Scanning of the chip with a confocal fluorescent microscope produces an image which provides information as to the nucleotide sequence of the target. There are two types of configuration for this approach. The simpler of these, termed a mutation array, involves the synthesis of two parallel probe sets for a given disease gene, one of which is complementary to many wild-type gene sequences and the other to the corresponding sequences of many known mutations. The use of this approach to detect a mutation in the cystic fibrosis gene is shown in Figure 2. The other, more complex, configuration is a ‘tiling array’ in which the entire sequence of the gene, or a part of the gene, is reconstructed as sets of overlapping probes which contain all possible variations of the nucleotide sequence. In principle, the use of tiling arrays allows the entire coding sequence of a disease gene to be scanned for all possible mutations in a single experiment. The method is, therefore, an immensely sophisticated form of allele-specific hybridisation, which was developed by Wallace. The equipment required for this approach comes with the modest price tag of about US$ 200 000, and chips for only a few genes are available as yet. Also, the sensitivity and accuracy of the method will have to be assessed in extensive diagnostic trials. However, the approach is exciting, is based on solid theoretical principles, and has already been applied to limited mutation scanning of the CF and BRCA1 genes.

The other major challenge facing DNA diagnostic laboratories will be to develop high throughput methods for the detection of susceptibility genes for the common disorders. Thus far, the challenge has been diversity, with many different kinds of tests being done on small numbers of samples. For many laboratories, the highest throughput has been for the Fragile X syndrome, with up to perhaps 100 samples being tested in any one laboratory per month. If genetic tests for conditions such as diabetes and asthma seem likely to provide useful information for the diagnosis of susceptibility or choice of therapy, the demand will be on a scale without precedent in diagnostic laboratories, and will require much more automation than has been necessary hitherto. These tests are likely to involve distinguishing between two alleles which differ by a single base change, and several such tests may be necessary to
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define the susceptibility profile of a patient. At least one highly automated method is already available for this purpose, known as the TaqMan assay. This involves synthesis of two different oligonucleotide probes, each of which is complementary to one of the two alleles. Each probe is labelled at its 5' end with a different fluorescent dye (the reporter), and both probes are tagged with a 'quencher' molecule which masks the signal from the reporter. During the PCR the probes bind to their complementary sequences on the products of the PCR reaction, and the reporter dye is then removed from the probe by the 5'-exonuclease activity of the *Taq* DNA polymerase enzyme. This release of the reporter from the proximity of the quencher results in a progressive increase in fluorescence throughout the PCR reaction, and the relative intensity of the two dyes is read at the end of the reaction by a scanner. The associated software converts these signals to a genotype for the two alleles (AA, AB or BB). The PCR reactions are set up in 96-well plates, and once this has been done the only further action required from laboratory staff is to insert the plate into the scanner. In this way, thousands of samples can be typed in a single day. The limitation of TaqMan is that only one sequence variant or polymorphism can be typed in the assay; further technical developments will be required for the simultaneous analysis of multiple variants.

Delivery of diagnostics to the patient

The identification of the genes for most of the common monogenic disorders created an almost instant demand by clinical geneticists for the provision of DNA diagnostic services. This provision evolved rapidly from a research-based operation by the laboratories involved in mapping and cloning the genes, into a professional routine diagnostic service with an ethic based on patient care and quality control rather than on the acquisition of original data. Thus a new profession was created, with its own set of goals and challenges. Three broad principles are apparent in the delivery of this service to the patient.

Benefit to the patient or family

The primary consideration in the decision on whether to establish DNA testing, either for mutations in a particular gene or for a polymorphic allele which confers an increased risk for a disorder, must be whether the test will be of benefit to the patient or their family. This may seem obvious, but it is a principle which is easy to forget in the excitement of an intellectual recognition of the research potential of screening, for
example, breast cancer patients for mutations in the \textit{BRCA1} gene. In this instance, the detection of a mutation will confer a risk of a contralateral breast tumour, and of ovarian cancer. This should prompt questions about what practical support can be offered to such patients in terms of long-term screening for additional tumours, and possible prophylactic measures such as tamoxifen therapy or mastectomy. There will also be important consequences for the patient's offspring, who may require genetic counselling and testing for the mutation. In the context of susceptibility genes for common disorders, there seems little point in testing an asymptomatic individual for the ApoE4 allele, for example, until we have reached the point where the knowledge that he or she is at increased risk of developing Alzheimer's disease is of some use in prevention or early treatment of the condition. Thus the goal must be to provide the patient or family with information which they can use for constructive decision making, rather than to augment the publications list of the investigator.

\textit{Provision of a high quality laboratory service}

This is of course a requirement for all types of diagnostic services, but the added challenges in the context of DNA diagnostics are the very rapid pace of gene discovery, which creates instant (and justifiable) demand for a new test, and of PCR technology, which allows one to set up the new test within days of the latest issue of a journal arriving in the library or on the Internet. This laudable enthusiasm must be tempered with sufficient restraint to permit reflection on the value of the test to the patient (see above), and on a technical evaluation of the accuracy of whatever assays are being put in place. There are also much broader requirements for a professional laboratory service, which should include: (i) direction of the laboratory by staff with appropriate qualifications and experience; (ii) structured internal quality control for checking of raw data and reports; (iii) strong emphasis on adequate staff training; and (iv) participation in an external quality assessment scheme. These standards can be encouraged by national laboratory accreditation schemes, such as Clinical Pathology Accreditation UK (Ltd) in the UK. In the US, the Task Force on Genetic Testing has recommended the creation of a genetics specialty for proficiency testing\textsuperscript{24}. The development of good laboratory services is helped greatly by the establishment of strong national professional organisations, such as the Clinical Molecular Genetics Society in the UK, which organise best-practice workshops, and issue detailed guidelines on testing for specific diseases. Such organisations can also have an important role in ensuring adequate provision of a full range of services nationally, and as a source of information for the clinician on which services are available.
**Linkage to genetic counselling**

In the context of the monogenic disorders, where rare genes confer high risks of developing the disorder on family members and pregnancies, the provision of DNA diagnostics has generally been tightly linked to clinical genetics services which provide pre- and post-test counselling to families. This is of fundamental importance to service provision, in order to ensure that tests are only carried out if necessary and appropriate, that the often complex information on the implications of the test result are understood by the counsellor, and that this information is conveyed to the patient or family with clarity and with sympathy. A very effective model for the provision of genetic services is the integration of clinical and laboratory services within one department or centre, but if this is not possible, there should at least be a close and structured working relationship between the clinical and laboratory components of the service. Direct linkage to counselling and critical analysis of the need for a test are more difficult to achieve in countries in which many of the laboratory services are private institutions which are operated for profit\(^\text{24}\). In the UK, the Advisory Committee on Genetic Testing has issued a code of practice on the provision of genetic tests directly to the public\(^\text{25}\) which recommended that this should be limited to determination of carrier status for recessive disorders, and that suppliers should facilitate genetic counselling as part of the testing procedure.

What is less clear is how we will deal with genetic information which relates to susceptibility to common disorders. This information differs from the bulk of our clinical experience with monogenic disorders in at least two respects. First, there is the question of volume, since potentially very large numbers of patients will be tested, and the labour-intensive process of genetic counselling by trained counsellors will not be sustainable. Secondly, the genotype obtained from the test will generally not be of overwhelming significance to either the patient or their family, as is the case with many of the tests for monogenic disorders, such as a positive predictive test for Huntington’s disease. Rather, it will be one of several factors used by the physician to make the diagnosis and to decide on the course of treatment, and may confer quite modest risks of developing the same disease to the offspring of the patient. These differences have been used to argue that we can cut the link between genetic testing and counselling in the common disorders, and that risk factors based on DNA can be treated in the same way as other risk factors such as blood pressure or cholesterol concentration\(^\text{18}\). However, there are real dangers here which will have to be taken into account and provided for. First among these is ignorance of the principle that the test must provide the individual and the physician with useful information...
which will lead to more accurate diagnosis, disease prevention, or appropriate therapy – we already have sufficient evidence of reflex box-ticking by junior medical staff on test request forms to realise the potential difficulties here. Secondly, there will often be consequences for the offspring. If, for example, knowledge of ApoE4 status helped to define drug response in Alzheimer's disease, and the patient were found to be homozygous, the probability of homozygosity in his or her offspring would be increased and, therefore, also their risk of developing the condition at a much earlier age than the general population. Thus there will have to be a mechanism by which a consensus is reached about the situations in which the test should be applied, and a clear understanding of its implications. This information will then have to be communicated effectively to the appropriate medical speciality. A considerable degree of will power and organisation will be required in order to avoid the potentially dire consequences of haphazard and indiscriminate use of genetic information.

What began, little more than a decade ago, with an occasional prenatal diagnosis for sickle cell anaemia or thalassaemia is now a substantial profession which provides diagnostic information for hundreds of genetic disorders. It is poised for a major expansion into testing for DNA sequence variants, which will have important consequences for both diagnosis and treatment of common diseases. There are major technical challenges to be met, but perhaps more difficult will be the task of ensuring that the new information is applied appropriately for patient care.

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