DNA diagnostics

Gezondheidsraad
Health Council of the Netherlands President

To the Minister of Health, Welfare and Sport
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Subject	: Presentation of report
Your reference	: ZZT/TOPAZ/944037
Our reference	: U 5478/94/ig/mr/491-Y3
Enclosures	: 1
Date	: 28 April 1998

On 28 October 1994, the Health Council received your request for a report on clinical genetics. The Committee on DNA Diagnostics, formed specifically for this purpose, has drawn up a report on a section of this issue. Having consulted the Standing Committee on Medicine, the Standing Committee on Medical Ethics and Health Law and the Standing Committee on Genetics, I am pleased to present the result of the Committee's deliberations in the form of the enclosed report.

This report illuminates the current state of knowledge with regard to DNA diagnostics and provides a prognosis for the coming years, as well as examining the areas which offer the possibility of dramatic breakthroughs. While the significance of these developments cannot be overestimated, we should remain alert to the real danger of overhasty, ill-considered or unnecessary application.

The Committee is wise to argue in favour of controlled development. To make a distinction between two categories of DNA diagnostics on the basis of complexity may seem contrived, given the conclusion that virtually all present cases should be regarded as complex. With the expected sharp rise in the number of cases, however, this distinction is expected to gain in significance.

The arguments for continuing the concentration of complex forms of germline diagnostics are self-evident. The role of the university hospital in this respect is key in the light of the need for embedding DNA diagnostics in clinical practice. I share the Committee's view that the diagnostics of somatic mutations and chromosome abnormalities are not inherently different from other diagnostic procedures. I support the Committee's proposal that the incentive regulation (Section 8 of the Special Medical Services Act) be applied to complex forms of this procedure, both in order to facilitate the withdrawal of bone marrow chromosomal examinations from Section 2 of the Special Medical Services Act and to promote a system of self-regulation. Further conditions should be worked out in greater detail.

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Your questions addressed the entire field of clinical genetic examinations. In the Netherlands, this incorporates a cohesive package of genetic counselling, the family investigation which forms its basis, and laboratory work and prenatal diagnostics included in Section 18 of the Hospitals Act (now Section 2 of the Specifial Medical Services Act). My predecessor considered it worthwhile to single out postnatal diagnostics from the other aspects of your request and to limit the response, for the present, to your questions on this topic with the help of a committee whose expertise reflects the relatively rapid developments in this specific area. In addition, the National Health Insurance Funds Council began its own evaluation of 'clinical genetic examinations and genetic counselling' at the same time, within the framework of the policy evaluation of Section 18 provisions which you had requested. This process is due to be completed soon: the report of the study carried out for this purpose by the Institute for Medical Technology Assessment (ITMA) has been finalized and the Health Insurance Funds Council expects to complete its evaluation by the end of May.

In its report, the Committee adheres to the cohesive nature of the present functions of the Clinical Genetics Centres but, in the light of the above, has not considered the question of whether these centres should continue their existence as independent organizations or be integrated into university hospitals. In my opinion, the Committee's conclusions and recommendations provide a clear basis for policy with regard to both options.

On the basis of the information contained in this report and in the reports referred to above, I would ask you to consider the extent to which you still lack information which you consider necessary for updating the planning decree on clinical genetic examinations and genetic counselling and to identify any questions you might wish to put to the Health Council in this respect.

I would like to conclude by stating that we have always enjoyed a high level of expertise in the Netherlands where the field of clinical genetics is concerned and have therefore served as an example to many other countries in this respect. It is vital that these standards be maintained and used for the benefit of more and more people with genetic risks.

(signed)
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Health Council of the Netherlands: Committee on DNA diagnostics

To:

The Minister of Health, Welfare and Sport

No. 1998/11E, Rijswijk, the Netherlands, 28 April 1998

Preferred citation:
Health Council of the Netherlands: Committee on DNA diagnostics. DNA diagnostics.
Rijswijk: Health Council of the Netherlands, 1998; publication no. 1998/11E.

ISBN: 90-5549-249-3

Contents

Executive summary

This advisory report, published at the request of the Minister of Health, Welfare and Sport, contains information on the current level of knowledge of postnatal DNA diagnostics and it contains recommendations on organization and regulations.

The nature and current extent of DNA diagnostics

In this advisory report, DNA diagnostics refers to the study of changes and variants in endogenous DNA that are associated with the occurrence, risk, and progression of particular clinical pictures, or with the reaction to certain medical treatments.

Monogenic diseases

More than 4,000, largely rare, hereditary diseases are known to be caused by a change (mutation) in the DNA code of a single gene. Such monogenic diseases display a Mendelian heredity pattern. That is to say, reproduction involves a high risk of bearing a child with the hereditary disease (25% for a recessive mutation in both parents and 50% for a dominant mutation in one parent). The first such genes and mutations were described in the mid eighties and DNA technology made it possible to directly display mutations in the cell material of patients and healthy carriers. This type of DNA diagnostics was placed under the responsibility of the Clinical Genetics Centres (CGCs) right from the start. These are independent organizations for heredity advice, the underlying family investigation and laboratory research (at the biochemical,

chromosomal and DNA level) and prenatal diagnostics. The centres' activities are covered by a single package of legislation under Section 18 of the Hospital Provision Act (known by its Dutch initials, WZV) which is currently Section 2 of the Special Medical Services Act (known by its Dutch initials, WBMV). During the last decade, the number of DNA diagnoses for monogenic diseases has increased ten-fold to around 12000 in 1997. This concerns around 130 different and usually rare diseases. The diagnostic tasks are divided nationally between the CGCs.

Monogenic diseases often become apparent at or shortly after birth, but sometimes later in life. DNA diagnostics can provide definite information, even in an as yet healthy person (presymptomatic diagnostics). One example of this is Huntington's chorea. In other cases, it is possible to demonstrate the carrier state in a healthy person, i.e., someone who will not personally get the disease, however, the children of (two) carriers may get the disease. This applies, for example, in the case of cystic fibrosis.

Multifactorial diseases

Most diseases in which hereditary factors play a role are not monogenic but are determined multifactorially, i.e., their development usually involves several genes and also environmental factors (including nutrition, habits, such as smoking and alcohol consumption, as well as radiation and chemical environmental factors). Examples of these are hereditary types of cancer, certain cardiovascular diseases, susceptibility to thrombosis, diabetes, asthma, multiple sclerosis, and various neuropsychiatric diseases, including Alzheimer's disease. Most of these diseases develop in adults. An examination of genetic risk factors in (as yet) healthy people is known as predisposition testing. The relationship between (determining) a mutation and the onset of the disease is often less clear than in the case of monogenic diseases. Moreover, multifactorial diseases not only concern rare mutations, but also combinations of frequently occurring variations (polymorphisms).

The extra likelihood of disease occurring as a result of a mutation varies considerably. The likelihood sometimes remains small, even in people with the mutation. This applies to the factor V Leiden mutation, for example, which leads to a four to nine times greater likelihood of venous thrombosis in heterozygotes. Without other risk factors, the likelihood of disease symptoms occurring is less than 0.1 percent per year. The risk to homozygotes is higher, at around one percent per year. On the other hand, some (generally multifactorially determined) diseases involve genetic risk factors that are so powerful that some families may display an almost dominant Mendelian heredity pattern; the Committee refers to these as monogenic variants of multifactorial diseases. Examples of these include (BRCA) mutations, in which carriers have a 60 to 85 percent risk of developing breast or ovarian cancer, (HNPCC)

mutations with about an 80 percent risk of developing intestinal cancer, and (FH) mutations with an 80 percent risk of hypercholesterolemia and heart attack at an early age.

In the case of hereditary types of cancer, DNA diagnostics, the family investigation and the heredity advice takes place in joint ventures between the CGCs, university hospitals and the non-affiliated cancer centres. This involved a total of around 3000 people in 1996. Other organizations besides the CGCs are also becoming increasingly involved in DNA diagnostics. STOET, the foundation for hereditary tumour-screening, contributes to medical follow-up studies of risk-bearers, particularly in the field of intestinal cancer. Within the scope of an experimental population screening in 1996, STOEH, the foundation for hereditary hypercholesterolemia-screening, examined 1000 people, including a relatively large number of children, for mutations in the FH gene.

Besides that carried out by the CGC laboratories, DNA research is also carried out by the Central Laboratory of the Blood Transfusion Service (CLB) and a few haematological, immunological, pathological and clinical-chemical laboratories, either attached to university hospitals and non-affiliated cancer hospitals or otherwise. Sometimes this is in connection with patient care, and sometimes in connection with scientific research, the clinical significance of which has not yet been validated. The greater part of DNA diagnostics relating to monogenic diseases that takes place outside the CGCs is concerned with hereditary types of anaemia, cystic fibrosis and hereditary haemochromatosis. It appears that the statutory prohibition can be ignored or circumvented in this field. Genetic risk factors diagnosed outside the CGSs are mainly those for venous thrombosis and cardiovascular diseases. Research at the DNA level into the HLA-risk factors for Bechterew's disease and other rheumatic conditions is also carried out at various laboratories. An estimated total of 8000 diagnoses of germline mutations per year are made outside the CGCs.

Somatic mutations

The aforementioned cases concern germline mutations that can be transmitted to all the cells of offspring via the DNA of parental gonocytes. However, changes may also occur in the DNA of certain somatic cells which are therefore not heritable. Such somatic mutations play a role in the occurrence and progression of tumours. Sometimes the occurrence of a tumour involves a combination of a germline mutation and one or more somatic mutations. DNA testing for somatic mutations is a new form of diagnostics, which can provide important indications of the anticipated progression of the disease and the most suitable method of treatment.

The organization and development of somatic DNA diagnostics varies considerably, both inside and outside university hospital and oncological centres. In almost all cases, the financial resources provided for scientific research are used for these types of patient diagnostics. This concerns a total of 5000 tests per year.

There is no absolute distinction between monogenic and multifactorial diseases, or between germline mutations and somatic mutations. Nevertheless, the Committee considers it useful to employ these terms in this advisory report as separate categories, both in terms of content and for defining the required organization and statutory regulations.

Expected developments

Around 15,000 human genes were mapped in 1997, within the scope of the Human Genome Project. Around 1500 of these have been shown to be associated with a disease. At least one mutation associated with a disease was discovered for approximately 650 of these 'disease genes'. The expectation is that all human genes will have been mapped by the period 2003-2005, and that their functions will be clarified in due course.

In the case of monogenic diseases, the indications area for DNA diagnostics will expand, but mainly in relation to (extremely) rare diseases. This will lead to a certain degree of stabilization. The number of DNA studies concerned with hereditary types of cancer is expected to double within five years.

Laboratory research will undergo major developments. The first examples of DNA microchips have already been described, which enable tens of thousands of DNA specimens to be examined simultaneously. This is important for the DNA diagnostics of hereditary diseases, in which many hundreds of mutations may occur in a single gene, such as cystic fibrosis and hereditary types of breast cancer and intestinal cancer. It will also facilitate research into certain mutations among very large numbers of people. Moreover, it will be possible to detect combinations of specific DNA sequences in various genes, which offers possibilities for predisposition testing for multifactorially determined diseases.

During the next few years, increasing numbers of genetic factors will be identified which, especially in combination, result in an increased or even reduced likelihood of developing a particular disease. The Committee describes the most important clinical fields in which DNA diagnostics play a part or are at hand, such as in diabetes, cardiovascular diseases, clotting disorders and neuropsychiatric conditions, including bipolar disorders and Alzheimer's disease. The Committee is unable to make any

precise forecast about when the genetic research into these common diseases will be sufficiently advanced to enable its introduction into clinical care. Experts consulted in the pharmaceuticals and biotechnology industry do not expect any explosive breakthroughs within the next three to five years, but anticipate a significant increase in scale afterwards.

Other scientific developments may also have major quantitative consequences. It is anticipated that certain characteristics of DNA will be indicative of the response to medication and other methods of treatment. In the future, it should be possible for these forms of therapy to be more adapted to the specific characteristics of the individual. For example, a research group recently announced that one in six patients with atherosclerosis and heart problems shows no response to a particular cholesterol-reducing drug and that this is associated with homozygosis for a certain DNA variant. If it emerges that a 'pre- trial' would be worthwhile for this drug, it would involve tens of thousands of DNA analyses per year.

Furthermore, some methods of laboratory research will be replaced by DNA technology, and DNA testing is expected to play a role in the early detection of diseases on a larger scale.

In the longer term (5-10 years) the Committee expects DNA testing of germline mutations to be common in many areas of health care. Somatic DNA diagnostics will acquire a permanent place in cancer diagnostics. The Committee expects this field to double over the next five years and to continue increasing afterwards. This leads to a cautious estimate of a total of 50,000 diagnostic DNA analyses per year over five years.

Considerations when determining a genetic risk

Apart from the technical possibilities, many factors play a role in deciding whether a particular test should be applied, such as the predictive value, the extent of the risk, the severity of the condition, the treatment and prevention possibilities and the psychosocial aspects. As the number of genetic risk factors involved increases, the relationship between a single risk factor and the occurrence of disease symptoms will become less clear. It is already difficult to draw the right conclusions. A favourable DNA result means that the risk is lower than was feared, but is no guarantee that the clinical picture in question will not develop.

An individual's own experience with a disease has a major influence on the perception of the risk and on the choices that are made. The choices of people requesting advice are also influenced by education, age, living conditions, whether or not they have a healthy child, religious background, the opinion of people in their

immediate surroundings, and their future expectations, also with regard to their own resources.

Moreover, what people think they would do given the availability of DNA diagnostics (according to their responses in questionnaires), is often completely different from their behaviour when they actually have to make a choice. They generally make less use of DNA diagnostics than expected. It is therefore difficult to predict the future use of DNA diagnostics.

When is DNA testing appropriate?

DNA testing is important to health care for a number of reasons. It may be a central or contributory factor in making a correct diagnosis and it forms the basis for reliable heredity advice. Furthermore, elucidating the genetic components involved in the development of disease can lead to greater comprehension of the underlying disease processes. DNA testing can also offer new points of attack for treatment or prevention.

If a patient has various disease symptoms, then DNA testing may be of specific importance to that individual in terms of reaching a reliable diagnosis, a more accurate prognosis and the best method of treatment. If a germline mutation is discovered, it may also have consequences for the healthy members of the patient's family. DNA diagnostics may even have no consequences for the individual patient but may serve the interests of family members.

A major argument in favour of the predisposition testing of healthy individuals is the opportunity of preventing the development of disease symptoms or of favourably influencing the course of a disease. This could involve modifying lifestyle and behaviour, regular medical examination to detect the disease at an early stage, early drug treatment, or preventive surgical intervention. Often a combination of methods is involved. Examples of this are regular intestinal examinations for carriers of a mutation associated with cancer of the large intestine, as well as diet and the use of medication in the case of a genetic predisposition to diabetes or familial hypercholesterolemia, and preventive surgical removal of both breasts and ovaries in carriers of a BRCA mutation. Healthy carriers of such a mutation are faced with difficult decisions, which they must be allowed to take freely, after receiving proper information.

Although the idea of 'no treatment, no test' often prevails in public discussions, the reality is more subtle. The Committee realizes that medical treatment options are an important condition for predisposition testing, but believes, along with other bodies, such as the VSOP (the Dutch umbrella organization representing patients with hereditary and congenital diseases and their parents), that other considerations also play a role. For example, studies of possible carriers of the incurable Huntington's

chorea showed that the removal of uncertainty, the wish to be able to make more informed choices about offspring and, more generally, the possibility of being able to plan the rest of one's life better, were seen by a relatively small group as important reasons for requesting a DNA test.

DNA diagnostics for children (and others unable to give informed consent) are a special case. The Committee recommends that, wherever possible, this should be postponed until the person concerned is able to decide personally. In some instances, however, where early treatment may reduce the likelihood of disease symptoms, the interests of the child are served by early DNA diagnostics. Although the Medical Treatment Contracts Act (known by its Dutch initials, WGBO) contains stipulations about research on and the treatment of children, no answer is provided to the question of when a child ought to be informed about the existence of genetic information obtained earlier and sometimes even before birth.

Screening at the population level is subject to the government requirements laid down in the Population Screening Act (known by its Dutch initials, WBO). This issue is not discussed any further here, as the Health Council has already examined the possibilities and limitations of genetic screening in an earlier advisory report.

In the case of individual DNA diagnostics, arising directly from patient care, requirements should be set for the indication, advice, quality of the test and the medical facilities considered necessary as a result of the outcome of the DNA test (the pre-test and post-test trajectories). The Committee considers it inadvisable to introduce new methods for genetic risk factor DNA diagnostics straight from the laboratory into patient care. The Committee believes it is the responsibility of the clinical professional groups involved, taking account of recommendations from experts in the technical and psychosocial field, to determine whether the available knowledge about a new form of DNA diagnostics is sufficient to justify its introduction into patient care. The opinions of patient groups can also play a role in this. In developing a consensus about the indications, a clear distinction should be made between the interests of the patient and those of healthy family members.

Approaching the patient and family

The patient should be informed about all the relevant aspects of diagnostics and treatment, including the possible consequences for family members. However, this may aggravate matters and be difficult to cope with at a time when the person's illness and treatment demand all of his or her attention. The Committee recommends that wherever possible DNA diagnostics should be discussed and performed at a time when the patient and the care provider are in a suitable frame of mind to consider all the

aspects properly. In the event of a decision being taken to do so, the greatest of care should be exercised in approaching family members. The CGCs have gained a lot of experience in this over the years and family members are generally contacted through the index patient. However, the index patient is often in a vulnerable position and other methods of approach deserve consideration. As stated in other Health Council advisory reports, in the event of the index patient not being willing to cooperate, the care provider should only contact family members if there are major reasons for doing so.

Access to health care

The advantages of DNA diagnostics include the possibilities that exist for favourably influencing or preventing disease symptoms. This means that risk-bearers must have access to facilities that can offer them a better chance of health. Whereas it is obvious that patients who already have disease symptoms should be entitled to access to and payment of medical technology, drugs, (heredity) advice and guidance, it is a good deal less clear in the case of healthy people. The Committee believes that DNA diagnostics that could reveal a significant risk of developing a severe or potentially fatal condition should not be undertaken without first guaranteeing a responsible follow-up procedure. Organizations that provide DNA diagnostics of this type must undertake to provide this and be enabled to do so.

Social aspects

DNA diagnostics may also have social implications, such as early medicalization, the uncertain effect of genetic knowledge on behaviour, the forming of relationships and motivation, and problems with access to social services. The Committee urges further interpretation of the Dutch Medical Examinations Act at an early date. The effect of international developments will be felt in all kinds of areas. Likewise, information on DNA diagnostic tests and their availability is becoming a world-wide phenomenon, particularly via the Internet. A number of commercial companies abroad are offering DNA tests and even marketing do-it-yourself (DIY) kits. The Committee wonders whether it will be possible to prevent these developments taking place in the Netherlands in due course. For the foreseeable future at least, the Committee believes the present approach to DNA diagnostics in the Netherlands is preferable, because it attaches importance to careful referral, information and advice based on the test result.

Controlled development: recommendations for regulations

The Committee believes the current organization, regulations and financing of DNA diagnostics, which are almost solely concerned with the activities in the CGCs, are no longer sufficiently in line with anticipated developments. The Committee thinks it is necessary to create conditions for controlled development. This includes formulating general quality requirements, distinguishing complex types of DNA diagnostics which require an appropriate concentration policy, and indicating which types of complex DNA diagnostics require statutory regulations. In its recommendations, the Committee accords the non-affiliated cancer centres the same status as the university hospitals. It emphasizes that, in the case of hereditary mutations, DNA diagnostics cannot be seen as something separate from the pre-test and post-test trajectories: the referral, information and counselling of the patient and possibly family members.

The Committee's conclusion is that the majority of current DNA diagnostics are complex and ought to be concentrated in the academic centres.

Complex diagnostics concerned with germline mutations should be statutorily regulated on the basis of Section 2 of the Special Medical Services Act (WBMV). The most important reasons lie not only in the special requirements set by the pre-test and post-test trajectories with regard to informing and counselling a patient and healthy family members, but also in the requirements concerning registration, protection of privacy and data storage. The technology and interpretation of the results are to a large extent still very complex, certainly if many different mutations or several genes have to be examined. Moreover, the concentration of knowledge, material and patient care is advisable when the relationship between DNA mutations, clinical pictures and the effectiveness of intervention in research still has to be clarified.

The above does not affect the fact that some testing of germline mutations can already be classified as non-complex and need not therefore be statutorily regulated. This category is expected to expand considerably. Current examples include the diagnostics for the factor V Leiden mutation in thrombosis and the HLA-B27 characterization in patients with Bechterew's disease, which generally involve hardly any implications for family members. In the future, it will often be possible to consider diagnostics of more genetic risk factors and also DNA diagnostics related to therapy-response as non-complex.

In the diagnostics of somatic mutations, the aforementioned familial, psychosocial and ethical aspects do not play a role. In principle, the Committee views somatic DNA diagnostics as any other type of laboratory research. The technology is still developing rapidly, however, and should still largely be considered complex. For a small number of indications DNA diagnostics already determines the choice of treatment, which may

possibly involve resorting to extremely drastic forms of treatment with a direct effect on the chance of survival. Concentration is therefore necessary to guarantee the quality of care. Initiatives have been taken in the pathology and clinical chemistry professional groups to achieve such concentration through self-regulation. The situation is complex in haemato-oncology. Owing to the required laboratory expertise, chromosomal examinations of bone marrow cells form part of the work of the CGCs. However, somatic DNA diagnostics in this field, which was developed later, takes place outside the CGCs. Both chromosomal examinations and somatic DNA diagnostics have proven to be important for the treatment and prognosis of a number of relatively rare types of leukemia, especially if a bone marrow transplant and intensive chemotherapy are being considered. This concerns around 400 patients a year, for whom approximately 3000 DNA analyses are required. As part of the diagnostic examination is now governed by the current statutory regulations, adequate developments in self-regulation in the professional group concerned with haemato-oncology are not yet underway. Therefore, the diagnostics required for this group of patients could not be sufficiently guaranteed at the moment, if the statutory regulations were to be removed.

The Committee believes the (temporary) application of Section 8 of the Special Medical Services Act (WBMV) is advisable for both complex chromosomal and DNA diagnostics for somatic abnormalities in genetic material. Positively encouraging academic centres which commit themselves to agreements concerning indication and division of tasks can promote controlled development and self-regulation. This would facilitate the smooth withdrawal of bone marrow chromosomal examinations from the licence regime of Section 2.

In the event of the government not adopting this proposal, the Committee recommends that chromosomal examinations and somatic DNA diagnostics for rare types of leukemia should as yet continue to be covered by Section 2 of the Special Medical Services Act (WBMV), or made subject to it.

Recommendations for the organization

Developments in DNA diagnostics outside the CGCs are fragmented and in different phases, both in university hospitals and elsewhere. Partly because of this diversity, the Committee chooses an organizational form that provides leeway to enable the best possible coordination of the existing activities and which also offers the possibility of dynamics: a possible shift in duties and tasks when the time is right, the possibility of new developments, and the efficient use of resources and expertise. The Committee suggests setting up a network structure in university hospital centres in which all the departments and laboratories involved with statutorily regulated DNA diagnostics have to participate. This should guarantee the contribution of clinical specialists in the

interpretation of DNA diagnostics. The CGCs should also participate in any such network, at least in relation to their expertise in the field of DNA diagnostics, family investigation and heredity advice. The existing organization, tasks and financing of CGCs can be left unchanged. It should also be possible for these networks to enter into joint ventures with non-academic institutes, such as the Central Laboratory of the Blood Transfusion Service (CLB) and certain peripheral laboratories and departments that satisfy the quality requirements in a specific area of DNA diagnostics. The type of network could be determined locally, in line with the available expertise and areas for special attention. Within a network responsibilities for its functioning, quality policy and health care should be established and further arrangements can be made concerning the division of tasks, consultation, referral, etc. The laboratories in the network would participate in procedures within the scope of quality assurance and would have to conclude geared annual production agreements between themselves. For new developments or for rare DNA tests, a national division of tasks would be advisable.

The Committee suggests partially granting the licence for statutorily regulated 'heredity analysis and advice of a complex nature' to the CGCs (basically the present package) and partially to the university hospitals (basically the DNA diagnostics for multifactorial diseases, including the pre-test and post-test trajectories). The networks could also play a coordinating and motivating role in DNA diagnostics that is not statutorily regulated.

Other recommendations

Although a discussion of the financial aspects is not part of the Committee's task, it points out the necessity of making sufficient resources available, both to clear the backlogs and to create new possibilities. The required infrastructure for family investigation and heredity advice, including the training of the necessary specialists and paramedics will have to be strengthened. In general, genetic aspects must become a distinct part of medical training. General practitioners will have to be trained to deal with patients who have a hereditary risk of disease as well as with members of the patient's family, if necessary.

Scientific research into the psychological and social aspects of predisposition testing should be encouraged, as should medical follow-up studies of risk-bearers who have received or are receiving a given treatment.

The adequate provision of information to the public concerning all aspects of genetic testing is a prerequisite for a realistic weighing-up of the benefits and drawbacks.

In view of the rapid scientific and technological developments in genetics and DNA technology, as well as unpredictable social developments that may affect the use of the technology, the Committee recommends that the level of scientific knowledge and the quality of tests in health care be reviewed again approximately five years from now.

Chapter 1

Introduction

1.1 Background

More and more medical conditions are being identified whose occurrence or progression is influenced by genetic factors. Such factors are sometimes hereditary and specifically associated with a high incidence of a particular disease in a family. Other hereditary factors are associated with apparently isolated, so-called sporadic, cases of a given disease. However, non-hereditary anomalies of the genetic material in body cells also play a role in medical conditions, cancer in particular.

In the Netherlands, heredity analysis takes place mainly in the Clinical Genetics Centres (CGCs). Most analyses are concerned with rare hereditary conditions and congenital abnormalities. Laboratory diagnostics relating to metabolic products, proteins, chromosomes and DNA forms a coherent field of expertise with family research, heredity advice and prenatal diagnostics. Most tests relating to hereditary forms of cancer and to the non-hereditary chromosome abnormalities associated with leukemia are also performed at the CGCs. All these activities are subject to statutory regulation under Section 2 of the Special Medical Services Act (WBMV), for which purpose they are classed as ‘clinical genetic testing and heredity advice’ (WVC94).

Rapid theoretical and technical advances are being made in the field of DNA testing, largely as a result of progress with the Human Genome Project (HGP). Supported by governments and scientific research organizations in many different countries, the aim of the HGP is to identify all seventy to one hundred thousand human genes. The expectation is that this objective should be achieved in four to six years, but

many obstacles remain to be overcome (Koo98). Work on the next stage of the project — determining the function of each gene — is already underway.

DNA testing is important in relation to health care, for several reasons. It can be essential for, or make a significant contribution to correct diagnosis, and it forms the basis for good heredity advice. Furthermore, identification of the genetic components associated with diseases can improve understanding of the underlying processes. DNA testing can also provide new starting points for the development of treatments and preventive strategies.

The range of conditions for which DNA diagnostics is indicated is expanding rapidly. The technique can play a role in diagnostics, prevention and treatment for more and more patients and an increasing number of common diseases. This is already the case in fields such as oncology and haematology, as well as in relation to certain cardiovascular diseases.

One notable feature of research into the hereditary factors associated with disease is that it can benefit not only the sick, but also their healthy relatives. In this context, the circumstances under which testing is indicated must be carefully defined, weighing up the relative and individual risk against the risk to the population as a whole and the reliability of the technique. Psychological factors play a role as well: some people prefer and are able to cope with uncertainty and hope, while others like to know precisely what risks (if any) they run, so that they can prevent or delay the manifestation of disease and can plan their lives accordingly.

As the scope for presymptomatic DNA diagnostics and genetic risk assessment increases, the CGCs and clinical specialists as well as first-line health care professionals will find that DNA diagnostic tests — with all their implications — are indicated more and more often. It is therefore pertinent to ask whether the existing educational, organizational and financial provisions require modification. The wider social implications of DNA diagnostics also need to be considered well in advance.

1.2 Ministerial request for the report and composition of the Committee

On 28 October 1994, the Health Council was asked to prepare a report on clinical genetic testing (see Annex A). The wish was for the Council both to produce a general survey of the present range of clinical genetic testing and heredity advice services provided by the CGCs and to look closely at the field of DNA diagnostics. More particularly, the Council was to report on the scientific status of DNA diagnostics, likely future developments, potential social and ethical issues, the level of demand now and in the future, appropriate practical and organizational preconditions and quality

requirements, the desirability and need for concentration and the organizational and legal means by which any such concentration might be effected.

The report now before you is concerned exclusively with postnatal DNA diagnostics. This subject has been addressed in isolation for two reasons. First, because of the extreme rapidity and far-reaching nature of the developments in this field, the issues raised were felt to be sufficiently complex to warrant the preparation of a separate report. Second, when the Committee began its work, it learned that the National Health Insurance Fund Council had already commissioned an analysis of CGC activities in the context of a policy evaluation of so-called 'Section 18 facilities' on behalf of the Ministry of Health, Welfare and Sport (Dutch initials: VWS). The study, which was to be conducted by the Institute for Medical Technology Assessment (iMTA) at Erasmus University in Rotterdam, appeared to cover some of the ground which the Health Council had been asked to explore. Following consultation, therefore, it was decided that the Health Council should concentrate on postnatal DNA diagnostics. In preparing this report, the Council has assumed the existence of CGCs organized along the present lines, but has taken account of the possibility that organizational changes may be made in the future. If the Minister should consider it appropriate, the Health Council will turn its attention to the other topics referred to in the original brief once the National Health Insurance Fund Council has completed its policy evaluation.

In September 1995, the President of the Health Council set up a Committee to prepare the report (see Annex B). In relation to certain specialist topics, the Committee consulted various external experts. Although advice was thus obtained from non-members, the Committee naturally retained full autonomy and responsibility for the ultimate content of the report. The individuals consulted are also listed in Annex B.

1.3 Scope

The Committee confined its deliberations to DNA diagnostics involving endogenous DNA. Hence, the extensive field of microbiological diagnostics in connection with infectious disease was excluded from the scope of the Committee's work. In quantitative terms, a large area of activity was thus left unconsidered; experts in the field estimate that in future approximately 80 per cent of DNA tests on patients will be concerned with infectious diseases, particularly viral infections. However, such testing does not involve endogenous DNA and therefore has no direct connection with clinical genetics. As such, infectious disease testing does not invoke the psychological, social or ethical issues which characterize clinical genetics.

Furthermore, the Committee decided that neither the genetics of normal physical or psychological traits and habits, nor the scope for determining parenthood, was

relevant to its brief. Also outside the scope of the report is (the desirability of) genetic screening of (sections of) the population for specific medical conditions. In this context, the Committee would refer readers to the Health Council's report 'Genetic screening' (GR94) and to the procedures drawn up pursuant to the Population Screening Act (WBO).

The main focus of this report is postnatal DNA diagnostics in connection with common and generally multifactorial diseases, insofar as such techniques are currently in use or are expected to come into use within five years. In many cases, diagnostic techniques of this kind are relevant to the familial forms of the diseases in question. Detailed consideration is therefore given to the question of how the relatives of a person who has been found to have a genetic abnormality (an index patient) should be approached and counselled. The report also outlines anticipated longer-term developments, the exact timing of which is difficult to predict, but which nevertheless warrant organizational, financial and educational provisions.

1.4 Structure of the report

The report begins with brief definitions of a number of basic terms and an outline of the clinical fields to which DNA diagnostics is relevant (chapters 2 and 3). This section of the report closes with a short review of quantitative developments. The central theme of the following two chapters is the characteristics and implications of diagnostic techniques used to assess hereditary risk factors. Chapter 4 deals with the level of individual care, while chapter 5 reviews the social, ethical and legal issues. The final chapter of the report is concerned with the organizational and the regulatory provisions necessary for controlled development in this field.

Chapter 2

Terminology

In this report, the term DNA diagnostics refers to the study of changes in and variants of endogenous DNA which are associated with the occurrence, risk and progression of certain patterns of disease or with the reaction to certain medical treatments. Like chromosomal examination, DNA diagnostics is concerned with genetic material. Abnormalities in this material may be related to diseases in a wide variety of ways.

2.1 Genetic material

The genetic material of a cell is made up of DNA. DNA carries the hereditary information needed for construction of the proteins which are responsible for the development, regulation and cessation of all cell functions. This information, or code, is recorded in the sequence of four DNA bases (adenine, guanine, thymine and cytosine: AGTC).

A piece of DNA that carries the code for manufacture of a single protein is referred to as a gene. Most genes are made up of thousands or even hundreds of thousands of DNA bases linked together to form a functional unit. It is estimated that there are between seventy and a hundred thousand human genes, grouped largely in chromosomes. The nucleus of each body cell contains forty-six chromosomes in twenty-three pairs (including one pair of sex chromosomes); when a cell divides, these chromosomes are duplicated, then divided equally between the daughter cells. Reproductive cells, i.e. sperm and egg cells, each contain a single set of twenty-three chromosomes. Upon conception, these cells form a new cell with a double set of

chromosomes: one set from the mother and one from the father. A small amount of DNA is located outside the nucleus, in the mitochondria. This DNA is inherited exclusively from the mother.

The complement of DNA in a cell is known as the genome. Genes form only a small proportion (a few per cent) of a cell's genome. The function of the remaining DNA is as yet largely a mystery. A series of connected DNA bases, whether contained in a gene or not, is called a DNA sequence.

During the formation of reproductive cells, during normal cell division, and under the influence of external factors, changes often take place in the DNA of a cell. These changes can involve a single base or a larger piece of DNA, and may entail discontinuity, duplication or rearrangement. Changes in the DNA of reproductive cells lead to variations in the hereditary material of a population. Thus, many DNA polymorphisms (regular variations occurring in the population) have come into being. If a person inherits two different forms of a gene, one from the mother and one from the father, these are referred to as alleles of the gene in question.

Many of these variations have no adverse consequences, either because they have little or no effect on the properties of the protein produced, or because the body is able to compensate for any difference in protein function. Nevertheless, this general scheme of ongoing genetic variation forms the context within which the influence of a single gene or a change to a gene must be viewed. Under certain circumstances — when it coincides with environmental factors, for instance — a particular variation can be significant.

Some changes can lead to or are associated with disease. In this report, all such changes are referred to as mutations or genetic defects. An individual with a genetic defect involving a single allele of a gene is known as a heterozygote; someone with a defect affecting both alleles is a homozygote. If a mutation in a single allele is sufficient to cause a disease, the mutation is said to be dominant; a mutation which only causes a disease if present in both alleles is described as recessive. Genetic complexity is further increased by the fact that the nature of a mutation in a given pair of alleles is not always the same. Mutations in the sex chromosomes are associated with gender-related diseases.

The association between a mutation and a disease is not always complete. Sometimes the disease in question will not occur, or will manifest itself only later in life. The closeness with which a particular mutation is associated with a disease is referred to as the penetrance of the mutation.

2.2 Chromosomal examinations and DNA diagnostics

Genetic material can be examined at various levels. In chromosomal examinations, abnormalities affecting complete chromosomes or parts of chromosomes can be detected under the microscope. Such abnormalities nearly always involve dozens or even hundreds of genes. Congenital chromosome abnormalities consequently often cause complex conditions, many of which are fatal. However, chromosome abnormalities in particular body cells can also develop postnatally, as is the case in cancerous tissue.

In DNA diagnostics, on the other hand, various specialized molecular biological techniques are used, and the focus is nearly always on a single gene or a small number of genes or DNA sequences. To check the structure of a complete gene, thousands of DNA bases have to be analyzed. Consequently, using the methods currently available, only small genes can be fully analyzed. Where large genes are concerned, examination has to be limited, either by concentrating on the analysis of part of the gene, or by using a more superficial form of testing which can only give a general indication as to the presence of (an abnormality in) a particular sequence. The performance of DNA analyses requires great expertise. The reliability of the tests can be very high, but only if they are conducted with great care. Techniques do exist which bridge the gap between DNA diagnostics and chromosomal examinations.

Gene function can also be studied indirectly by looking at proteins. However, the identification of a functional abnormality does not conclusively prove the existence of an underlying genetic defect. Very recent research findings suggest that errors in the transfer of DNA code information (RNA editing) can cause protein abnormalities (Lee98). This intriguing possibility requires further research, however (Vog98). The protein defects associated with approximately 450 hereditary diseases have now been isolated.

In recent decades, around fifteen hundred diseases have been linked to specific genetic sequences and some seven hundred or so ‘disease genes’ have been identified. This has opened the way for direct (prenatal) diagnosis of hereditary conditions and reliable testing to determine whether a person is a carrier.

The potential significance of DNA diagnostics differs greatly depending on whether the associated abnormality is a (hereditary) germline mutation or a (non-hereditary) somatic mutation. The difference between these two types of mutation is considered in sections 2.3 and 2.4.

2.3 Germline mutations

A germline mutation is a mutation present in the DNA of all body cells, including those of the germ line (gonocytes). Mutations of this kind can occur at various junctures: they may originate in an ancestor, at the conception of the individual in question, or during his or her lifetime. Thereafter, however, they are hereditary. The presence of a germline mutation can lead to the frequent occurrence of a disease within a family; however, 'familial occurrence' can be partly or wholly attributable to other causes, such as exposure to similar environmental factors. Hereditary mutations can play a wide variety of roles in the occurrence and progression of disease. This is very important in terms of the implications that a hereditary mutation has for a given individual. For practical purposes, it is useful to divide the causal relationships between mutation and disease into a few broad groups. For DNA diagnostic purposes, it is also significant whether the subject is ill or in good health.

2.3.1 Monogenic diseases

A monogenic disease is a disease caused by a hereditary mutation in a particular gene, in the sense that the genetic defect in question (almost) always leads to the disease *and* that the disease does not occur where the defect is not present. In such cases, one can be reasonably sure that if the mutation is found to be present, the disease will occur, and that if the mutation is not present, the disease will not occur.

The inheritance of monogenic diseases is usually predictable, since it follows a Mendelian pattern. The situation with a few monogenic diseases is more complex, however, due to the nature of the genetic defect. So, for instance, the genetic defect can change from one generation to the next at the so-called 'trinucleotide repeats'. This phenomenon was first observed in fragile X syndrome (a form of mental disability) and is now known to play a part in various diseases, including Huntington's chorea.

More than four thousand hereditary diseases are now recognized, most of them rare (McK90). Where nearly a thousand of these diseases are concerned, chromosomal localization of the relevant gene has been achieved and in a few hundred cases the disease gene and the mutations affecting it have been described. With some of these diseases, such as sickle-cell anaemia, many patients have been found to have the same genetic mutation. In the case of familial hypercholesterolemia (FH) and other such conditions, however, two or three hundred different mutations in the disease gene have been identified, while more than seven hundred mutations in the cystic fibrosis gene are already known to exist.

The form in which a hereditary disease occurs is subject to variation and is partly determined by genetic factors other than the associated mutation and by environmental factors. Nevertheless, where monogenic conditions are concerned, the presence of the relevant mutation is almost always associated with the disease, although penetrance is not necessarily complete. Furthermore, the disease may not manifest itself until later in life (age-related penetrance). When a mutation is identified in an apparently healthy person, this is referred to as presymptomatic diagnosis. In such cases, the disease will nearly always manifest itself some years or decades later.

2.3.2 Genetic risk factors in multifactorial diseases

A multifactorial disease is caused by the complex interaction of various genetic and environmental factors. In recent years, research has found links between specific DNA sequences and an increasing number of these generally common diseases. Using this observation as a starting point, it is possible to identify the genes which play a part in the occurrence and/or development of the disease. Certain DNA sequences have also been found to have a protective effect.

If a mutation is known to increase the risk of a multifactorial disease, a genetic risk factor is said to exist. Where such a factor is found to be present, the individual in question is more likely to develop the relevant disease, but not certain to do so; penetrance is not complete.

Scientific research into genetic risk factors is in its infancy. The influence of such factors varies, partly as a result of interaction with often unknown environmental factors. Furthermore, the number of genes associated with a disease can vary considerably. Fourteen mutations are already known to be associated with type I diabetes, for instance, one of which has a protective effect. If the genetic risk is determined by a combination of several mutations or genetic variants, a genetic risk profile is said to exist. Naturally, the more genes and environmental factors are involved, the more complex the nature of the inheritance pattern.

For some diseases, one or more specific genetic risk factors have already been identified. Inheritance of a single mutation follows Mendel’s laws, but the occurrence of the condition associated with the mutation does not. Healthy individuals with the mutation have a predisposition: they are at greater risk of contracting the disease in question. The actual likelihood of contracting a given multifactorial disease, as calculated using DNA diagnostic methods, varies enormously. Although the carrier of a given mutation may in some cases be much more likely to contract the associated disease than a non-carrier, the risk is always less than — sometimes much less than — 100 per cent. So, for instance, a heterozygote with mutation in his or her so-called factor V gene is several times more likely to develop venous thrombosis than someone

without the mutation. However, the actual risk is less than 0.1 per cent per year. By contrast, other mutations can bring a much higher risk of disease: more than 80 per cent in certain cases.

2.3.3 *Monogenic variants of multifactorial diseases*

Various multifactorial conditions are known to have variants in which a particular mutation or genetic factor is so influential that certain families display an almost dominant Mendelian inheritance pattern. In families where several members suffer from a given disease which manifests itself at a relatively early age, the genetic risk can be nearly 100 per cent. Generally speaking, these virtually monogenic variants affect only 5 to 10 per cent of the total number of patients with the disease concerned. The situation with breast cancer illustrates this point. There is a 50 per cent chance that a woman carrying mutations in certain genes will develop breast cancer before the age of fifty. The chance increases to nearly 90 per cent for women who reach an advanced age. Where the genetic risk factor is not present, the chance of breast cancer is about 10 per cent. Thus, around 90 per cent of all cases of breast cancer are not associated with any known genetic factor. With these ‘monogenic variants’, the degree of variation in the clinical picture (age of onset of the condition and nature and seriousness of the symptoms) is generally greater than with ‘true’ monogenic diseases.

2.3.4 *Mitochondrial DNA abnormalities*

Cellular DNA is found not only in the nucleus, but also in small quantities in the mitochondria. Abnormalities in this circular mitochondrial DNA (mt-DNA) are responsible for a separate category of hereditary conditions. Every mitochondrion in a cell contains several copies of the individual’s mt-DNA, and there are dozens, or sometimes even hundreds, of mitochondria per cell. Mt-DNA abnormalities can only be passed on by the mother. Often, only some copies of the mt-DNA are abnormal and there are variations in the ratio between abnormal and normal mt-DNA per tissue, per patient. Consequently, individuals in a family with abnormal mt-DNA may display considerable differences in clinical phenomena such as developmental retardation, muscular weakness, deafness, diabetes, sight impairment and so on. Once an mt-DNA abnormality has been detected, the inheritance pattern can be reliably predicted, but a clinical prognosis for the carrier’s offspring is hard to make. No further consideration is given to abnormalities of this kind in this report; in the context of the Committee’s organizational findings (chapter 6) the investigation of such abnormalities may be considered a form of complex germ line diagnostics.

2.3.5 *Medication-related DNA diagnostics*

A DNA polymorphism or mutation can be associated not only with an increased risk of a disease being contracted or following a particular course, but also with a given response to a particular therapy. Scientific understanding of such associations is presently sketchy, but may be expected to increase very quickly. In this context, DNA diagnostics could provide a basis for individualized therapy, but would generally be of little or no clinical significance for healthy family members.

2.3.6 *DNA diagnostics for germline mutations in the patient*

In relation to the use of DNA diagnostics for the investigation of hereditary mutations, it is pertinent to ask: when may a person be regarded as a patient? The pertinence of this question lies in the fact that germline mutations occur in people who are (still) healthy. In the context of this report, the terms 'ill' and 'patient' are applied only to individuals who already have a medical condition or the clinical symptoms of a particular disease. All other people are deemed 'healthy', or, where applicable, carriers of a mutation or genetic defect. A patient whose condition is the basis for testing other members of the same family is referred to as an index patient.

Where a patient displays the symptoms of a monogenic disease, the purpose of DNA diagnostics is to suggest or confirm a diagnosis, or to provide a more precise diagnosis, with a view to facilitating treatment and/or heredity advice. Furthermore, once a particular mutation has been identified in a patient's DNA, other members of the same family can be checked for its presence. In cases of multifactorial disease, DNA diagnostics can also assist clinical diagnosis and provide valuable etiological and prognostic information. The availability of such information can influence decisions regarding treatment and follow-up. In principle, identification of a genetic risk factor opens the way for predisposition testing of family members. The circumstances under which such testing is advisable have yet to be defined. In the future, DNA tests may also be indicated with a view to predicting the patient's reaction to therapy.

2.3.7 *DNA diagnostics for healthy individuals: presymptomatic diagnostics, carrier testing and predisposition testing*

DNA diagnostics can provide information on the chance of a healthy individual contracting a disease in the future or passing a disease on to his or her offspring. Testing for the mutations associated with monogenic diseases is divided into two

fields: presymptomatic diagnostics, where dominant mutations are concerned (the carrier of a dominant mutation is certain to develop the associated disease in due course *and* liable to pass it on to his or her offspring), and carrier testing, where recessive mutations are concerned (the carrier of a recessive mutation will not develop the associated disease, but is liable to pass it on to his or her offspring). Testing whose purpose is to identify a genetic risk factor is referred to as predisposition testing: an individual with a genetic risk factor is more likely but not certain to develop the associated disease; the chance of illness in his or her offspring is generally more difficult to quantify.

When considering a DNA diagnostic test on a healthy individual, it is very important to know precisely what mutation one is looking for. If the individual in question is the relative of an index patient, then the mutation has already been identified. Furthermore, the significance of a risk factor can more readily be assessed if there is a family anamnesis for the relevant disease. All manner of complicating factors can exist, however. In some cases, although a family anamnesis may suggest that an individual is very likely to develop a particular disease, no living member of the family may have the disease, so there will be no index patient. Alternatively, there may be clinical indications of a genetic risk factor, but insufficient family members to produce a clear family anamnesis. In other cases, the risk of contracting a disease is significantly increased only where a combination of several mutations and sequences exists.

The development of DNA diagnostics gives an extra dimension to carrier testing. Recessive monogenic diseases or comparable conditions manifest themselves only in homozygotes; in principle, heterozygotes should not contract such diseases. However, it has been clear for some time that this general rule is not universally valid: slight symptoms are sometimes evident in healthy members of a family affected by such a disease. Now that DNA diagnostic techniques enable the identification of heterozygous carriers, the significance of a single recessive gene can be determined more precisely. It has already been established that heterozygous carriers of various conditions can also exhibit unexpected clinical symptoms. So, for example, a particular cause of infertility in men is more common in (heterozygous) carriers of a mutation in the gene associated with cystic fibrosis.

2.4 Somatic mutations

A somatic mutation is a mutation in one or more body cells (somatic cells), acquired after conception. Some such mutations enable the affected cell(s) to grow more rapidly than other cells, thus leading to benign or malignant tumours. Researchers now believe

that a cascade of different changes in the genetic material is responsible for the development and spread of malignancy. Thus, all forms of cancer are associated with abnormalities in the genetic material, sometimes at the chromosome level. Such abnormalities are present only in tumour cells and are not hereditary. Somatic mutations can therefore only be studied in material from the tumour.

Cells have a sophisticated system for tracing and repairing or otherwise neutralizing DNA damage. If this system should malfunction, the risk of cancer is increased; the genes responsible are therefore sometimes referred to as cancer genes. A malfunction of this kind can be caused by a germline mutation; even in such cases, however, a tumour will generally develop only if one or more somatic mutations also occur in the cells of the tissue or organ in question. The situation becomes even more complex if the process by which these somatic changes take place is itself determined (partly) by hereditary factors, or if the somatic mutation occurs in the sex glands.

The presence of a particular somatic mutation can serve as a criterion for the diagnosis of a particular form of cancer, or as an indicator for the likely course of the disease or reaction to treatment. Unlike germline mutations, somatic changes vary during the course of the associated diseases, making it necessary to perform diagnostic tests repeatedly if one is to monitor the genome abnormalities. The preliminary stages of certain cancers can be tracked and distinguished from benign proliferations in this way. If sufficiently sensitive detection methods are developed, it should in the future be possible to conduct such tests on body fluids containing the cells under consideration, such as urine or saliva. This possibility opens the way for the early detection of primary or recidivistic tumours without causing any great inconvenience or discomfort to the patient.

Methods of analysing DNA from body cells are also being developed which, instead of enabling the identification of particular mutations, would allow tumour cells to be identified from other characteristics of the DNA. The use of such methods could become an alternative to employing cytological or histological diagnostic techniques.

Somatic mutations may well also be involved in the ageing processes and in non-cancerous disease processes, such as abnormalities in embryonic development. Little is yet known about these fields, however.

Chapter 3

The clinical application of DNA diagnostics

This chapter contains a (non-exhaustive) survey of the main clinical fields in which DNA diagnostic techniques are presently used or likely to come into use in the next few years. On the basis of this survey, certain conclusions are drawn regarding the quantitative trends in the application of such techniques. The extent to which DNA diagnostics come into use will depend not only on technological developments, but also on the precision with which the indications are defined and the degree of social acceptance. These issues are discussed in later chapters.

It should be noted that there are large areas of medical science where, although hereditary factors are known to play a role, understanding of the associated DNA abnormalities has yet to reach the point where it can be put to practical use.

3.1 Clinical genetics

In 1989, clinical genetics as then practised was designated an exceptional procedure under Section 18 of the Hospital Provision Act (WZV), which has since been superseded by Section 2 of the Special Medical Services Act (WBMV). The activities thus brought within the scope of statutory regulation include heredity advice in complex situations, the family investigation upon which such advice is based, post- and prenatal chromosome, DNA and biochemical laboratory testing and prenatal ultrasonography aimed at the detection of foetal malformations. Seven CGCs are licensed to carry out such work. Until recently, DNA diagnostic techniques were used only in connection with serious monogenic diseases which manifest themselves in

childhood. In practice about 130 such conditions can be diagnosed, most of them rare. The licensed CGCs have coordinated their diagnostic activities so that both straightforward and difficult procedures are evenly distributed among the centres, while a complete range of services is available across the country as a whole. The most commonly conducted tests are for mutations of the cystic fibrosis (CF) gene and of the fragile X gene, which causes a form of mental retardation. Now that automated test kits are available to check on the presence of some of the most common mutations associated with cystic fibrosis, a few large clinical chemistry laboratories use DNA tests instead of the traditional 'sweat chloride' test, which is less sensitive, more laborious and less reproducible. The test is usually performed to exclude the possibility of cystic fibrosis in patients whose clinical symptoms are unclear. If a mutation is detected by the hospital laboratory, the case is referred to a CGC for confirmation of the diagnosis and follow-up action. The number of tests performed per patient diagnosed with CF is therefore increasing.

DNA testing for a few, mostly recessive, monogenic blood diseases is generally, or even as a matter of course, conducted outside the CGCs. The diseases in question are mainly hereditary forms of anaemia and haemochromatosis (see 3.6); in addition, diagnostic tests for one rare condition (pyruvate kinase deficiency) are carried out by a peripheral clinical chemical laboratory working in association with one of the CGCs, because the laboratory in question has relevant specialist expertise.

Increasingly, however, the CGCs are being called upon to perform tests in connection with conditions affecting adults, which are known to be associated with a causal genetic defect or to have an almost monogenic variant (Tib96). In recent years, for instance, there has been increasing demand for tests to detect hereditary mutations in various cancer genes (see 3.2). In some of the CGCs, such work already accounts for nearly a third of the total manpower allocated to DNA diagnostics and heredity advice. Together, the CGCs currently perform more than fourteen thousand DNA analyses a year.

Risk factors which bring a less obvious predisposition to disease are investigated both at the CGCs and elsewhere. As more and more genetic risk factors are found to be associated with common patterns of disease, interest in DNA diagnostics is increasing amongst clinicians in various disciplines. Furthermore, DNA testing is no longer intended purely to support heredity advice services or personal counselling, but also to assist decision-making regarding the most appropriate forms of treatment and follow-up. Various groups and organizations undertake DNA diagnostic activities on a small scale, without any CGC involvement. Such activities are sometimes explicitly for research purposes, but creeping movement towards inadequately proven introduction in patient care cannot be excluded.

This report is not concerned with the indications for DNA testing in the CGCs, as presently formulated. For financial management reasons, the indication ranges are agreed between the CGCs and the care insurers. The Committee believes that the CGCs and their laboratories can be regarded as centres of highly specialized expertise in DNA diagnostics, including the associated fields of guidance, counselling and family investigation. They serve as a breeding ground for the training of both laboratory technicians and clinical counsellors. Although in clinical genetics expertise in the field of DNA diagnostics was originally based on monogenic conditions, there is no reason why it should not serve as a foundation for further successful expansion into other disciplines and to other laboratories.

3.2 Oncology (1): hereditary mutations associated with solid tumours

3.2.1 Introduction

After clinical genetics, oncology is the area of medicine in which DNA diagnostics currently has the most numerous and far-reaching implications. In oncology, distinction is made between solid tumours (located in a tissue or organ) and haematological malignancies (malignant diseases of the blood or lymphatic system). For DNA diagnostics purposes, however, there is no essential difference between the two types of cancer.

Hereditary DNA abnormalities may influence a person's chances of developing cancer in numerous different ways. A few forms of cancer are almost monogenic in character. Such diseases are associated with what are known as 'major cancer genes'. In many cases, mutations in these genes — which are rapidly being unravelled — lead to cancer, often relatively (and even very) early in life. Where there is a substantially increased risk of developing specific combinations of tumours, a tumour syndrome is said to exist.

However, there are also forms in which a hereditary pattern is barely detectable, if at all. The often small number of children per family can be a factor in this context. Such forms of cancer may be attributable to common genetic abnormalities with low levels of penetrance. Furthermore, other genes can influence the effect of a predisposition gene. It is not inconceivable that genetic factors are much more significant in relation to an individual's susceptibility to cancer than might be supposed purely on the basis of what is known about clearly familial forms.

At present, hereditary tumours and tumour syndromes are identified on the basis of the clinical picture and family anamnesis. The criteria used concern the number of blood relations who have developed particular types of tumour and the closeness of their blood relationship to the individual in question. The inheritance pattern is

generally autosomally dominant; in other words, each child has a 50 per cent chance of inheriting the predisposition from the affected parent. Increasingly, those at risk can be confidently identified by DNA testing. The penetrance in the case of the syndromes recognized to date is generally high: in most cases, a carrier of the predisposition gene has an 80 per cent chance of developing the disease in question at some point in time. As more becomes known about the genes involved, the demand for DNA testing, risk assessment, counselling and advisory services from the CGCs is increasing rapidly.

Clinical interest in the genetic aspects of cancer is clearly growing. The identification of a germline mutation can have various advantages: determination of the most appropriate forms of treatment and follow-up, accurate prognosis and predictions regarding the likelihood of other conditions developing and the provision of heredity advice. At present however, it is not yet apparent just how beneficial DNA diagnostics may be for the patients themselves. Testing is generally indicated primarily with a view to preventing development of the disease in other members of the family and so that heredity advice can be provided. At various places around the country, there are special out-patients' clinics for hereditary cancer sufferers and their families, run partly by hospital oncology departments, categorical cancer centres and CGCs. Where bowel cancer and certain other cancers are concerned, the Foundation for the Detection of Hereditary Tumours (STOET) is involved in identifying people who may be at risk, so that they can be referred for testing in good time. Since 1985, STOET has been tracing families with particular hereditary forms of cancer and compiling a register of risk-bearing family members who take part in a surveillance programme aimed at the early detection and treatment of particular types of tumour.

At present, the registers compiled by STOET and the CGCs are not sufficiently well harmonized to provide a comprehensive national overview of the number of patients and risk-bearing family members. Furthermore, in some cases, STOET's activities go beyond the registration and surveillance of patients and overlap with those of the CGCs, particularly when it comes to approaching and testing healthy family members. Better demarcation between the relevant organizations is therefore desirable in the short term.

3.2.2 Hereditary forms of breast and ovarian cancer

It is estimated that 5 to 10 per cent of people who contract breast or ovarian cancer have a genetic predisposition. Given that nearly ten thousand new cases of breast cancer a year are diagnosed in the Netherlands, this would suggest that five hundred to a thousand of the women concerned are predisposed to the disease. Indicators of predisposition to breast cancer are early onset, manifestation in both breasts, familial occurrence and occurrence of the disease in combination with certain other cancers

within the family (cancer syndromes). In most of the families concerned, ovarian cancer also occurs, either separately or in combination with breast cancer. However, breast cancer can also occur in certain other, much less common tumour syndromes, including the Li-Fraumeni multiple tumour syndrome (see 3.2.6), as well as in heterozygous carriers of the Ataxia Telangiectasia (AT) gene. Ovarian cancer can form part of the HNPCC syndrome, the chief characteristic of which is a form of colorectal carcinoma (see 3.2.3).

In families with hereditary breast and ovarian cancer, most (more than 50 per cent) of cases involve mutations in the BRCA 1 or 2 gene. Research suggests that 60 to 85 per cent of women affected by this abnormality will develop breast cancer before the age of seventy, and half of them before the age of fifty (Cou97, Str97). Although the two genes bring different levels of increased risk, such women are also more likely to contract ovarian cancer or a second tumour in the breast. In some cases, men carrying BRCA 2 mutations can also develop breast cancer, while those with BRCA 1 mutations suffer higher than average rates of prostate cancer.

Mutations in the BRCA genes are not confined to such families, however. Research amongst breast cancer patients aged less than thirty-five has shown that about 10 per cent carry a mutation of the BRCA 1 gene (Lan96). Estimates of the frequency of the mutation in the Dutch population vary from one in two hundred to one in a thousand women (Meij96a). The nature and frequency of such mutations can vary from one region or population group to another. Studies indicate that 2 per cent of women (and men) of Ashkenazi Jewish origin carry a BRCA mutation (Odd96, Str95).

By the middle of 1997, a total of more than two hundred different mutations of the large BRCA genes had been discovered. Sixty to eighty of these mutations have been found in the Dutch population. It is not clear whether the various mutations bring similar levels of risk.

In the rarer tumour syndromes involving breast and ovarian cancer, the p53 gene plays an intriguing role. Germline mutations in this gene are responsible for many cases of the Li-Fraumeni multiple tumour syndrome (see 3.2.6). The risk of breast cancer is substantially increased but the frequency of the relevant germline mutation is so low that it accounts for only a very small proportion of hereditary breast cancers. However, the cells in nearly 60 per cent of all tumours do exhibit a somatic mutation in this gene.

In conjunction with the two oncological centres (the Dutch Cancer Institute and the Daniël den Hoed Clinic) and the oncology departments of certain university hospitals, all CGCs have been conducting DNA tests for breast cancer genes since 1994. The number of tests conducted is quite large: approximately fifteen hundred in 1996. Tests for BRCA mutations account for 10 to 15 per cent of all DNA diagnostic procedures performed at the centres. The complexity and labour-intensive nature of these tests is

such that 20 to 30 per cent of the centres' personnel capacity is devoted to them (Gal97a). By the middle of 1997, more than a thousand families in the Netherlands were known to have a hereditary risk of breast and ovarian cancer. More than 250 of these families carry a germline mutation in BRCA 1 or 2. Experience has shown that on average, for every diagnosed carrier, five or six healthy family members come forward for DNA testing. Where a family anamnesis suggests that a woman runs a very high risk of breast cancer, but there is no living index patient, a far larger number of family members is sometimes tested.

3.2.3 *Hereditary forms of colorectal cancer*

Some 10 to 15 per cent of patients with colorectal cancer come from families in which the disease is prevalent. In 1993, approximately six thousand new cases of colorectal cancer were diagnosed. Published estimates suggest that about 5 per cent of cases involve hereditary non-polyposis colorectal carcinomas (HNPCC), while around 1 per cent involve familial adenomatous polyposis (FAP). In the Netherlands, there are 150 to 750 new cases of HNPCC a year and ten new cases of FAP. At the start of 1996, more than 200 Dutch families were known to be affected by FAP (Vas96). At the beginning of 1997, STOET anticipated registering another sixty new families with hereditary colorectal cancer in the year ahead, fifty-two of them affected by HNPCC and eight by FAP.

Familial adenomatous polyposis is characterized by hundreds of polyps in the large intestine and rectum, which develop before the age of twenty. Without treatment, the condition almost always leads to the appearance of one or more malignant tumours. The disease also involves abnormalities of the skin, the duodenum and other parts of the body. The disease is generally caused by a mutation in the so-called APC gene. More than seven hundred different mutations of this gene have been identified in colorectal cancer sufferers. In most families affected by the disease, testing can confirm whether an individual has a predisposition to the disease. In about 30 per cent of patients, however, the disease is attributable to a new germline mutation and there is consequently no family history of the condition (Vas96).

With hereditary non-polyposis colorectal carcinoma, the clinical picture is very different. An abnormality develops in a specific location and probably becomes malignant very quickly. It is much harder to detect a tumour of this kind by clinical examination. Some forms of the disease are associated with increased incidence of stomach and uterine cancer. At least four different so-called DNA repair genes play a role in HNPCC. In half of the families affected by the condition, DNA diagnostic

techniques can give a reasonably accurate indication as to whether an individual is predisposed to the disease (Taa96a).

3.2.4 *Hereditary forms of prostate cancer*

Strong indications point towards the existence of a hereditary form of prostate cancer, which is responsible for about 9 per cent of all cases of the disease and more than 40 per cent of the rare cases involving individuals aged less than fifty-five (Kie96). Presumably hereditary prostate cancer is attributable to a rare mutation with high level penetrance, but no such genetic defect has yet been identified.

3.2.5 *Multiple endocrine neoplasia (MEN syndromes)*

Multiple endocrine neoplasia is a tumour syndrome which manifests itself as neoplasms in the thyroid, adrenal and parathyroid glands. With the exception of those in the thyroid, these tumours are not always malignant. Without supervision and treatment, patients live to an average age of forty-eight. In the Netherlands, the condition has been found in between 300 and 350 people in about thirty families (Bee96). There are two forms of the MEN syndrome. The MEN II syndrome is caused by germline mutations in the ret gene. DNA testing for the mutation — possible since 1993 — has now more or less replaced other diagnostic techniques. Somatic mutations in the same gene are associated with sporadically occurring endocrine tumours.

The MEN I syndrome has recently been linked to a genetic defect in the so-called MN-I gene. DNA testing for this condition is therefore now possible as well.

3.2.6 *Li-Fraumeni syndrome*

This tumour syndrome is characterized by a very high frequency of a wide range of different tumours within a family, as well as by the occurrence of several tumours in individual patients. The most characteristic feature of the syndrome is the development of a sarcoma early in life. Other forms of cancer associated with Li-Fraumeni syndrome are breast cancer, brain tumours, leukemias, tumours of the adrenal glands and, in some families, tumours of the reproductive cells, melanomas, prostate cancer and cancer of the pancreas. This rare syndrome is only known to affect twenty to thirty families in the Netherlands. Its cause is a germline mutation in the p53 gene. Detection of the responsible mutation is possible in about half of the families affected (Men95). Carriers of the gene may have a heightened sensitivity to X-rays, which can have consequences for treatment *and* for any screening methods.

3.2.7 *Retinoblastoma*

The retinoblastoma is the most common kind of eye tumour found in children. Thirty to 40 per cent of retinoblastomas have a hereditary basis. The retinoblastoma was the first hereditary tumour for which heightened risk was identifiable by testing (Jan90). Unlike solitary sporadic tumours, hereditary tumours tend to occur in both eyes or in the form of multiple tumours in the same eye. The disease only affects people who carry both a germline mutation and a somatic mutation in the Rb gene. Thus, the penetrance of the Rb gene is not complete; not every carrier of the abnormal gene develops a retinoblastoma. Most people with the germline mutation have no family history of the condition; it therefore appears that they have acquired a new germline mutation. In 1993, sixty-four cases of retinoblastoma were recorded in the Netherlands.

3.2.8 *Dysplastic naevus syndrome (DNS/FAMMM)*

DNS/FAMMM (familial atypical multiple-mole melanoma syndrome) is characterized by the occurrence of atypical naevi (moles) and melanomas. It accounts for approximately 5 per cent of all skin melanomas: about 235 cases a year. More than half of the affected families have been found to carry mutations in the p16 gene. The well-documented association between fair skin types and skin cancer is determined largely by mutations in the melanocyte-stimulating hormone receptor gene.

3.2.9 *Other syndromes*

A number of other hereditary tumours and tumour syndromes exist, in addition to those described above. These include Peutz-Jeghers syndrome and juvenile hereditary kidney tumours. Stomach cancer also displays familial clusters (Taa96b). Hereditary forms of ovarian and uterine cancer usually occur in the context of the tumour syndromes referred to.

3.2.10 *Quantitative evaluation*

At present, approximately 2,650 DNA tests a year are conducted on patients and their family members in connection with hereditary forms of cancer. The Committee expects this number to rise steadily, to the point where twice as many tests are conducted five years from now. Given the complexity of the procedures and the need

to support and, where applicable, to follow up individuals who are at risk, a doubling of the number of tests has far-reaching implications in terms of capacity.

3.3 Oncology (2): somatic mutations associated with solid tumours

In connection with solid tumours, somatic DNA diagnostic techniques are generally used to supplement morphological diagnostic examination of cell or tissue samples. Some applications of these DNA testing techniques already make a real contribution to diagnostics. Many others are just graduating from experimental to practical use. Given the oncological significance of somatic mutations, a number of potential applications may have far-reaching implications, both for clinical diagnosis and treatment and for the early detection of primary or recidivist tumours. The activities currently undertaken in various clinical diagnostic laboratories are:

- tumour diagnostics and classification
- the detection of circulating or residual tumour cells (so-called minimal residual disease)
- the early detection of tumours and
- differentiation between metastases and additional primary tumours.

3.3.1 Tumour diagnostics and classification

DNA diagnostics can play an important role in the differentiation between neoplasms and reactive processes, and between benign and malignant tumours, as well as in the classification of tumours. The use of DNA diagnostic techniques in connection with solid tumours is still largely experimental.

Precise classification of a known tumour can assist prognosis and provide information about the likely efficacy of possible treatments. Molecular subtyping of tumours has numerous potential applications with clinical implications. The procedures already in use include tests for lung cancer (activating K-ras mutations), neuroblastoma (n-myc amplification), breast cancer (c-erbB-2 amplification), pheochromocytoma/medullary thyroid carcinoma (ret point mutations), childhood Ewing sarcoma (t(11;22)-translocation) and liposarcoma (t(12;16)-translocation).

If it becomes possible to distinguish more confidently between benign and malignant tumours in cases of doubt, this would have enormous potential significance. One gene which might be used for this purpose is the p53 gene, which is abnormal in about 60 per cent of tumours. The discovery of very early tumours which cannot be declared either benign or (potentially) malignant is particularly common in screening programmes for breast and cervical cancer.

3.3.2 *Detection of circulating or residual tumour cells*

Following therapy, it is possible to check for tumour cells circulating in the blood or left behind at the site of the growth, with a view to ascertaining how successful treatment has been. DNA diagnostic techniques used for patients with solid tumours focus on tumour-specific translocations and on somatic mutations in the p53 gene and other so-called cancer genes.

3.3.3 *Early detection of tumours*

A great deal of research is being conducted into the possibility of detecting tumours at an early stage, by using DNA diagnostic techniques to isolate tumour cells from readily obtainable bodily fluids or excretions, such as blood, urine, faeces and saliva. Researchers are concentrating on genes which exhibit mutations early in the development of cancer. The abnormalities concerned include ras point mutations (which are associated with colorectal tumours when found in the faeces and bladder cancer when found in the urine), microsatellite instability in the blood (which is associated with the presence of a malignant tumour 'somewhere' in the body) and telomerase activity (which is associated with malign cellular degeneration). The tests for these abnormalities are not yet in clinical use.

It now appears that there may be a relationship between the precursors of malign degeneration discovered in cervical smear tests and infection by tumorigenic forms of the HPV virus. If this proves to be the case, it creates the possibility of carrying out tests for these viruses on screened samples found to contain abnormal cells. Tests of this kind, bridge the gap between virological molecular diagnostics and DNA diagnostics.

3.3.4 *Differentiation between metastases and additional primary tumours*

When a patient is found to have a second tumour, it is possible to determine whether this tumour is a metastasis of his or her first tumour or a second primary tumour by testing for tumour-specific DNA abnormalities. The general availability of such tests would have clear consequences for treatment. The techniques involved are so-called X chromosome inactivation testing and microsatellite analysis.

3.3.5 *Quantitative evaluation*

At present, somatic DNA diagnostic testing is indicated in connection with a few solid tumours, such as certain muscular and fatty-tissue tumours found in adults (soft-tissue sarcomas) and a few malign tumours in children. Testing for the examination of resection margins following surgery and for abnormalities which could be the precursors of malignant growth has, until now, been indicated to a lesser extent. Although the indication range can be expected to change over the next five years, it is not possible to predict with any degree of certainty the volume of molecular diagnostic testing that the clinical diagnostic laboratories will have to handle five years from now. If it is to be indicated for a given condition, a diagnostic test must influence clinical policy, not be unreasonably expensive, be performed sufficiently often, lend itself to reliable interpretation and not be redundant. It is very difficult to say whether the tests described will meet these criteria. For instance, it is not yet entirely clear whether the detection by DNA testing of a sporadic carcinoma cell in a lymph gland of a woman with breast cancer, when other diagnostic methods have failed to detect signs of cancer, would be significant in relation to prognosis or treatment. Also, there can be such a strong correlation between molecular prognostic factors and stage, histological type and differentiation level, that such factors do not provide any extra information and must therefore be regarded as redundant. Consensus must be sought regarding the circumstances under which testing is indicated, partly because the extent of the indication range determines the diagnostic ‘profit’ and, to a degree, the cost-benefit ratio.

The following figures have been extracted from the Dutch National Cancer Registry (Vis96):

Table 1 The incidence of certain tumours.

tumour type	number of new cases per year
soft-tissue tumours	660
malign childhood tumours (Ewing, neuroblastoma, etc.)	1,000
mammary carcinoma	9,700
lung carcinoma	8,700
colorectal carcinoma	6,000
prostate carcinoma	5,000
cervical carcinoma	700

A total of approximately sixty thousand new malign tumours is detected each year. The Committee estimates that, in the course of regular patient care, about three hundred DNA tests for somatic mutations are currently performed annually in connection with solid tumours of the kinds referred to above. However, as soon as it appears that a clinically relevant decision depends on the result of a DNA test and that the required information cannot be obtained in any other way, the test in question will become indicated for patients in the relevant group. In this way, as advances are made in clinical research, the indication range gradually broadens, resulting in more tests being conducted, sometimes thousands more. Furthermore, technological breakthroughs, such as the imminent introduction of chip technology for testing purposes, can even lead to rapid increases over and above this number. If at some time it should be deemed appropriate to screen for early signs of colorectal carcinoma or cervical carcinoma by testing for p53 or p16 mutations in the faeces or for HPV infections in cervical smear samples, this would involve tens of thousands or even hundreds of thousands of additional tests a year.

3.4 Oncology (3): combined somatic and germline mutations associated with solid tumours

It is known that some somatic mutations occur more frequently where certain germline mutations are also present. It may therefore be instructive to test a patient for germline mutations even though there are no other indications that he or she has a hereditary predisposition. If both a somatic and a germinal mutation are found, this can have implications for the treatment and support of the patient; naturally, the discovery of a germinal mutation also has consequences for healthy members of the patient's family.

The best example would be a patient with an apparently isolated pheochromocytoma of the adrenal gland. The normal treatment would be to surgically remove the adrenal gland, together with the tumour. Sometimes, a somatic mutation in the ret gene is discovered. If the mutation is also found in the germ line, both adrenal glands should be removed, since the patient evidently suffers from MEN syndrome and the likelihood is that a tumour will develop in the other gland too. What is more, the thyroid gland should be checked for cancer as well. Similarly, the results of a microsatellite analysis of a sample from a young patient suffering from bowel cancer despite the absence of any family history of the disease might indicate that the patient should be tested for germline mutations in the genes associated with hereditary forms of bowel cancer.

3.5 Haemato-oncology: chromosome abnormalities and somatic mutations associated with blood and lymph gland cancer

The clinical relevance of chromosomal examinations (cytogenetics) and DNA diagnostics has been convincingly demonstrated in various areas of haemato-oncology. In almost all cases, the tests concern acquired, non-hereditary abnormalities in the genetic material.

Until 1980, the techniques used in the diagnosis of haematological malignancies consisted almost entirely of dying cells and tissues in various ways, then examining them under an (electron) microscope. Since then, things have changed dramatically, due to cytogenetic testing, to the examination of immunological characteristics using antibodies (immunopheno-classification) and especially to the introduction of monoclonal antibodies. Between 1985 and 1990, molecular genetics began to make its presence felt in the research and diagnostic areas of haemato-oncology. The techniques employed involved both the detection of 'clonality' (whereby a group of cells all originate from a single mother cell) and the identification of tumour-specific changes in cancer and tumour suppressor genes. Polymerase chain reaction (PCR) and fluorescence in-situ hybridization (FISH) have proved particularly useful because of their speed and relative simplicity. Furthermore, the extremely high sensitivity and specificity of PCR have made it possible to test for very small numbers of residual cells (minimal residual disease, MRD).

Blood and lymph cancers can be divided into two broad groups: myeloproliferative and lymphoproliferative diseases.

3.5.1 Myeloproliferative diseases

Myeloproliferative diseases include the acute and chronic myeloid leukemias and the myelodysplastic syndrome ('pre-leukemia'). Five hundred or so new cases of these diseases are diagnosed annually. More than 60 per cent of patients with acute myeloid leukemia or myelodysplasia and more than 90 per cent of patients with chronic myeloid leukemia exhibit characteristic chromosomal abnormalities which can be detected using conventional cytogenetic methods. Due to the rapid development and application of molecular biological techniques, even quite subtle cytogenetic abnormalities can now be detected with confidence. Particular abnormalities in genetic material have been found to correlate with morphologically distinctive types of leukemia, their clinical pictures, certain reactions to therapy and disease-free survival. Information regarding these abnormalities is used to select the most appropriate forms

of treatment. For example, patients with acute myeloid leukemia who are found to have a particular genome modification are now given a special vitamin A derivative treatment, while those who exhibit certain cytogenetic and molecular characteristics which correlate with good recovery prospects receive less intensive treatment and are not put through bone marrow transplantation. As things stand, the analyses can only be performed on a small scale, despite the fact that they are clearly beneficial. Translocations can sometimes be missed using ordinary cytogenetic diagnostic techniques, while molecular diagnostic techniques constitute a more sensitive means of detecting certain abnormalities and therefore have direct therapeutic benefits. In cases of chronic myeloid leukemia, detection of the so-called Philadelphia chromosome and follow-up chromosomal and DNA tests are very important for selection of the most appropriate treatment and for prognosis. (The Committee has, however, observed that repeat tests are being discouraged; insurers will only pay for one repeat test, even if more tests are considered desirable with a view to monitoring the course of the disease and adapting treatment accordingly.)

People with so-called cytopenias (conditions characterized by a shortage of blood cells) suffer from a malfunction in the production of one or more blood cell types in the bone marrow. This malfunction can be caused by non-malignant conditions (partial or complete bone marrow failure, as in aplastic anaemia) or by malignant bone marrow diseases (such as leukemia). It can be difficult to distinguish between the early stages of leukemia and a benign disease, with physicians often having to rely on clonality testing, as mentioned already in connection with solid tumours.

3.5.2 Lymphoproliferative diseases

Lymphoproliferative diseases include a wide range of benign and malignant conditions; among the malignant conditions are lymphatic leukemias, malign lymph gland conditions and Kahler's disease.

Lymph cells, which are important to the body's immune system, can be divided into B and T lymphocytes. Reactive, benign, lymphoproliferative conditions are characterized by self-limiting polyclonal multiplication of B or T lymphocytes without gene mutations. Malign conditions generally involve unchecked growth or accumulation of monoclonal cells and one or more mutations of certain cancer genes. With B lymphocytes (and the derived malignancies), the nature of the clonality is almost always discernable at the protein level; in a proliferation of T lymphocytes, however, clonality can only be examined at the DNA level. Furthermore, it is almost impossible to trace changes in cancer genes other than at the DNA (or RNA) level.

With about eighty new cases diagnosed a year, acute lymphatic leukemia is the most common (lymphoproliferative) malignancy in children. In adults, non-Hodgkin's lymphomas and chronic lymphatic leukemia are more common. Non-Hodgkin's lymphoma is one of the ten most common malignancies in the Netherlands, with an incidence of approximately three thousand cases a year. Furthermore, epidemiological studies indicate an increase in the prevalence of the condition, which can only partly be attributed to population ageing and the presence of AIDS sufferers (who are more susceptible to the disease). With conditions in this group, precise diagnosis depends on differences in histology, phenotype and genetic changes. At least 85 per cent of non-Hodgkin's lymphomas are based on B lymphocytes and the rest on T lymphocytes. Therapy varies according to the classification of the condition and may involve a wait-and-see policy, radiotherapy, symptomatic treatment or fundamentally curative but sometimes very aggressive chemotherapy or bone marrow transplantation. Chromosome and DNA testing is carried out both in CGC laboratories and in the clinical diagnostic laboratories of certain hospitals.

3.5.3 *Quantitative evaluation*

It is estimated that 4,800 haemato-oncological DNA analyses are annually performed; of these, seven hundred concern rare leukemias. However, it seems likely that the clinical requirement is approximately 9,200 tests a year (see Tables 2 and 3). The discrepancy is due partly to the fact that, in many cases, repeat tests are indicated but cannot be conducted under the present system. Of the total number of tests required, about one third concern rare leukemias and two thirds non-Hodgkin's lymphomas.

Table 2 Diagnostics: one-off determination of clonality for the purpose of differentiating between benign and malignant growths.

	estimated annual test requirement
B lymphocyte non-Hodgkin's lymphoma: about 10% of all cases	300
T lymphocyte non-Hodgkin's lymphoma: 25% of all cases	125
acute myeloid leukemia, myelodysplasia, aplastic anaemia	50
total (this table only)	475

Table 3 Primary diagnostic tests for specific DNA abnormalities in malignancies, conducted partly as a basis for follow-up purposes or therapy evaluation.

	number of patients	estimated number of repeat tests required per patient	estimated number of tests required per year
Non-Hodgkin's lymphoma (NHL):		3	
t(14;18) - 30% of NHL cases	900		2,700
3q27 - 30% of giant-cell NHL cases	600		1,800
t(11;14) - 10% of NHL cases	300		900
t(8;14)t(2;8)/t(8;22)	25		75
acute lymphatic leukemia (approx. 30%) t(4;11), Ph[1] etc.	50	8	400
chronic myeloid leukemia (100%) Ph[1] t(9;22)	100	8	800
acute myeloid leukemia (approx. 40%) t(8;21); inv(16); 11q23; t(15;17) etc.	200	10	2,000
total (this table only)			8,675
total (including Table 2)			*9,150*

3.6 Haematology: non-malignant blood diseases

In recent years, the genetic abnormalities associated with a number of hereditary haematological conditions have been determined at the DNA level. These abnormalities can lead to phenomena such as a tendency to bleed, susceptibility to thrombosis, anaemia, blood platelet deficiency, white corpuscle deficiency and immune deficiency. The associated conditions are often recessive monogenic diseases. Until recently, diagnostics was based on protein analyses, generally conducted in haematological laboratories or the Blood Transfusion Service's central laboratory (CLB). Partly for this reason, DNA tests in this field are to a great extent conducted outside the CGCs.

DNA diagnostics can provide more detailed and more reliable diagnostic information, often complementing data from other sources. In cases where the functional tests are not sufficiently informative, DNA testing is vital. Most of the conditions concerned involve extremely diverse defects and sometimes hundreds of

mutations. This has far-reaching consequences for the testing methods used. A few more simple abnormalities are also found, however, such as the point factor V-Leiden mutation associated with increased susceptibility to thrombosis, the point mutation associated with sickle-cell anaemia, and the so-called inversion exhibited by about 40 per cent of patients with serious haemophilia A.

In most cases, no data is available on the frequency with which these abnormal genes occur in the population. The available prevalence figures are based largely on clinical experience. However, there are considerable variations in clinical presentation. So, for instance, estimates on the prevalence of Von Willebrand's disease (a common form of hereditary tendency to bleed) vary between 125 and eight thousand cases per million members of the population. These estimates are based on clinical data and protein test results, respectively. Another example is protein C deficiency. Clinical data suggests that one person in sixteen thousand is a heterozygote with the associated abnormality, but protein tests on healthy volunteers put the figure at one in 250.

Meanwhile, researchers are constantly discovering more about the genetic basis of immune deficiencies and susceptibility to infection.

3.6.1 Hereditary tendency to bleed (haemophilia)

Tendency to bleed is determined and analyzed at coagulation laboratories. In conditions caused by a recessive mutation, DNA testing is not really advantageous for the diagnosis of (homozygous) patients. DNA tests are nevertheless often conducted with a view to determining whether relatives carry the associated abnormality, to support heredity advice and to determine whether unborn babies are affected. Carriers themselves face barely any clinical consequences, except in hazardous situations involving, for example, trauma or medical intervention.

A number of autosomal dominant bleeding tendency conditions also exist, the main one being Von Willebrand's disease. Under certain circumstances, DNA diagnostics could be useful in relation to these conditions, provided that at least the specific mutation affecting the family were known. To date, however, this has almost never been the case.

3.6.2 Venous thrombosis

The origins of venous thrombosis are multifactorial, and there are various forms of hereditary predisposition. However, the most common form of the condition proves to be associated with a single easily detectable mutation, the so-called factor V Leiden mutation. This mutation is found in around 5 per cent of the population and in 18 per cent of patients with increased susceptibility to thrombosis. In families affected by

increased susceptibility to thrombosis, about half of the affected individuals have the mutation. The extent to which the risk is heightened depends on the presence of other risk factors (Blo95, Dah96, Des96, Rid95, Man96, Sol96). A heterozygous woman carrying a factor V mutation is between four and nine times as likely to contract thrombosis than a 'normal' woman (for whom the annual chance of developing the condition is about one in ten thousand). This level of increased risk is comparable with that experienced by women using the contraceptive pill and during pregnancy. Where additional risk factors (including smoking and other hereditary risk factors such as a predisposition towards hyperhomocysteinemia) are involved, an individual can be between fifteen and fifty times as likely to suffer from thrombosis (Blo95, Man96). For homozygotes, the risk is between fifty and a hundred times as great, with the result that about 1 per cent of such individuals contract the condition in any given year. Another fairly frequent genetic variation, in the prothrombin gene, is found in 2 to 3 per cent of the population and in about 7 per cent of patients with familial susceptibility to thrombosis. This abnormality triples the risk of venous thrombosis.

In this field, the potential significance of DNA testing for patient care derives in the first place from the scope for precise diagnosis when other tests are inconclusive (e.g. where the patient is receiving certain forms of medication). Further research is necessary before conclusions can be drawn regarding the value of DNA testing in relation to clinical policy formulation in cases where thrombosis has already been diagnosed or where preventive measures are being considered for the protection of individuals who are at increased risk (Sar98). On the basis of a rough inventory, the Committee estimates that approximately five thousand tests a year are currently conducted: about four thousand in peripheral laboratories and one thousand in university laboratories. In some places, index patients' relatives are given the opportunity to take a test with a view to determining whether they are carriers; actively approaching such individuals does, however, not appear to be appropriate (Mid98). It is anticipated that the number of tests performed will increase in the years ahead.

3.6.3 Hereditary forms of anaemia

Anaemia is a very common condition, usually caused by lack of iron. Where iron supplements fail to correct the condition, the patient may be suffering from a hereditary form of anaemia. These anaemias are a group of recessive monogenic diseases, including sickle-cell anaemia and the thalassemias. Such conditions were rare in the Netherlands until recently, but immigration of people from Mediterranean countries, Africa and Asia has led to a higher concentration of carriers in the Dutch population. There are currently estimated to be 140,000 heterozygous carriers in the Netherlands. Diagnostic testing using chromatographic techniques can be carried out

in clinical chemistry laboratories. Serious consequences arise only if a man and a woman who are both heterozygotes plan or start a family. It is believed that a few dozen homozygous children will be born each year. These individuals will require lifelong intensive treatment and have a life expectancy of no more than forty or fifty years (Gio98, Reg95). As a result, there will be about five hundred seriously affected patients who depend entirely on blood transfusions. DNA testing is the only way of detecting alpha thalassemia, but in cases of sickle-cell anaemia and beta thalassemia, it is used as a supplement or alternative to other methods.

Sickle-cell anaemia is caused by a single easily identified point mutation, but beta thalassemia is associated with numerous different mutations. In connection with these conditions, the CLB carries out about two thousand DNA tests a year on behalf of hospitals and laboratories all over the country. According to the information available to the Committee, about six peripheral laboratories in the Netherlands currently perform approximately 250 DNA tests for alpha thalassemia. Little is known about clinical follow-up activities, in particular the provision of information and the testing of partners. DNA diagnostics has only limited preventive significance, since very few of the patients and carriers or risk-couples are referred to CGCs for heredity advice.

The CGC laboratory at the Anthropogenetic Institute in Leiden acts as a reference laboratory and therefore receives about three hundred requests for testing a year.

In various countries with high concentrations of carriers (one in every seven to ten individuals), the number of homozygous patients has been very substantially reduced by large-scale screening programmes to identify carriers, who are then given heredity advice and access to prenatal diagnostic testing. In some regions, the disease has almost been eradicated.

3.6.4 Hereditary haemochromatosis

Haemochromatosis is a condition which affects the iron metabolism in the blood. It is characterized by the accumulation of iron in the cells of various tissues, leading to problems such as joint pain, the impairment of liver and heart function, chronic fatigue, loss of libido, diabetes mellitus and skin pigmentations. If detected in good time, preferably before clinical phenomena appear, the condition can be treated successfully by the controlled drainage of blood. In 1996 it was demonstrated that a recessive mutation in the HFE gene was responsible for more than 80 per cent of cases of this disease (Fed96). Since then, several other mutations have been linked with the condition (Ris97, Swi97). In the population at large, one person in ten may be a carrier, while amongst people of North European origin, one individual in every two to four hundred is likely to be a homozygote (Bar96). However, a diagnosis has been made in only a minority of cases. Given the importance of early treatment, DNA testing could

be beneficial to affected individuals in the short term. Nevertheless, the circumstances under which testing is indicated need to be carefully considered, partly because the clinical picture presented by patients can vary considerably. The significance of being a heterozygous carrier has yet to be determined with certainty, but seems unlikely to be particularly great in most cases (Swi97). The relevant test is performed at the CGCs and at various other centres, including the CLB. Relatively few tests are presently conducted (the Committee estimates a hundred or so), but the number is sure to rise.

3.7 Cardiovascular diseases

Although there are a few relatively rare familial-hereditary cardiovascular conditions, in connection with which DNA testing could play a role (Meij96b), the clinical significance of such diagnostic activities over the next five years is unlikely to be very great in relation to the size of this field of medicine. There are several reasons for this. Genetic determinants are important mainly in cases of cardiovascular disease involving individuals aged less than sixty-five, and such cases make up a relatively small proportion of the total: six thousand of the fifty thousand annual fatalities from cardiovascular disease involve under-sixty-fives (although, naturally, the total number of people in that age group with such a condition is higher. Small-scale use of DNA testing for young patients could be appropriate, but large-scale general testing would only be justified if the quality of life for older patients could thus be positively influenced by preventive action or early treatment.

In cardiovascular medicine, the emphasis is now on intervention in response to the emergence of symptoms and on the provision of information on the ‘classic’ risk factors: gender, age, smoking, family anamnesis, blood pressure and glucose and cholesterol levels in the blood. Collectively, these factors have considerable predictive value, with the result that DNA diagnostics has little additional advantage to offer for the time being. Until recently, the effectiveness of established forms of intervention was also a disincentive for genetic research. The recent discovery that the effectiveness of cholesterol-reducing medication may be related to certain gene polymorphisms (Kui98) may have far-reaching consequences for the number of tests carried out in future, but further research is required before conclusions may be drawn regarding the clinical significance of DNA testing in this context (Ros98).

Predisposition towards cardiovascular disease is determined by numerous different genes and depends, moreover, on complex interaction with environmental factors. Consequently, the predictive value of tests based on a small number of genetic determinants is likely to be limited. Paradoxically, although familial occurrence (and therefore genetic predisposition) is regarded as a clear risk factor, little significance

can be attached to specific genetic factors for the time being. Nevertheless, certain new, partly hereditary specific risk factors appear to have been identified. Certain authors report, for example, that increased risk of arterial and venous thrombosis and of cerebral-vascular accident (stroke) is associated with raised homocysteine levels in the blood (Fer95, Per95, Ver96); other researchers have been unable to confirm this finding, however (Jon98).

3.7.1 Familial hypercholesterolemia (FH)

Hereditary forms of hypercholesterolemia and other abnormalities in the body's lipid metabolism systems warrant special attention. Familial hypercholesterolemia (FH) is caused by mutations in the LDL receptor gene, which result in LDL cholesterol levels two or three times higher than normal. However, the different variants are associated with considerable variations in the degree to which cholesterol levels are raised. The disease nevertheless follows a consistent familial pattern, so that the risk associated with the presence of a genetic defect is fairly predictable. In some families, a particular mutation can cause marked increases in mortality from cardiovascular disease relatively early in life.

Approximately one member of the Dutch population in five hundred carries an FH gene defect. So far, about sixty mutations have been found in the Netherlands. Nationally, more than 50 per cent of FH patients appear to be affected by one of these mutations (STO95), although a combination of mutations is sometimes found (Wal97). Variations in the seriousness of the clinical picture are probably attributable only partly to differences in the nature of the mutations; other genetic factors and environmental factors, including smoking, appear to play a greater role (Van96). FH patients represent only a fraction of the total number of hypercholesterolemia and hyperlipidemia sufferers. Consensus regarding the potential benefit of using DNA diagnostic techniques as opposed to other blood tests has yet to be reached.

The Foundation for the Detection of Hereditary Hypercholesterolemia (STOEH) operates a large-scale programme of family investigation, which includes DNA testing, to trace people with the disease. In 1996, STOEH carried out more than a thousand tests, many of them on minors. Over the next few years, the foundation hopes to annually screen about four thousand people. The pros and cons of such an approach and the implications for early treatment are the subjects of lively scientific debate (Van96). The Minister has indicated that she believes activities of the kind undertaken by STOEH require licensing under the Population Screening Act (WBO). Like the work carried out by STOET (see 3.2.1), STOEH's activities overlap with those of the CGCs.

3.7.2 Familial dysbetalipoproteinemia (FD)

Familial dysbetalipoproteinemia, which affects about one in three thousand people, is caused by recessive mutations in the APOE gene. Three common forms of this gene are recognized: E2, E3, and E4. Most patients are homozygous carriers of E2 mutations, but only one in twenty homozygotes exhibits clinical or biochemical symptoms. A small number of rare dominant E variants also exist. The APOE gene is also associated with Alzheimer's disease, which creates a particular problem in relation to any counselling that may be necessary. APOE is relatively easy to identify, but the significance of its presence is very difficult to interpret. It is believed that about six laboratories (including two university laboratories) in the Netherlands currently carry out APOE tests, and that each hospital commissions between ten and 125 tests a year. One peripheral hospital conducts five hundred tests a year as part of a research project.

Other hereditary abnormalities in lipid metabolism also result in a marked increase in the likelihood of cardiac infarction. Not enough is yet known about the genetic basis of these abnormalities, however. The most frequent form (familial combined hyperlipidemia, or FGH) probably involves several genes.

3.8 Endocrine and metabolic diseases

This group of diseases includes numerous, often rare, congenital metabolic conditions, for which diagnostic tests are conducted in the CGCs, mainly using protein analysis techniques. With a number of these conditions, DNA tests assist in the identification of carriers. Preliminary biochemical testing is carried out in a few clinical chemistry laboratories. New-born babies are screened for phenylketonuria (PKU) and congenital hypothyroidism (CHT) through the national heel-pric testing scheme. The genetic defects associated with a few conditions are now known; these include a recessive mutation responsible for hereditary homocystinuria. Homozygotes have serious symptoms of mental retardation, eye and skeletal abnormalities and frequent thrombosis. There are also indications that heterozygotes may be at greater risk of contracting thrombosis in certain circumstances (Man96).

A few monogenic endocrine diseases exist, most of which are very rare. However, there is one very common endocrine condition with genetic aspects: diabetes mellitus.

3.8.1 *Diabetes mellitus*

Diabetes mellitus, which involves a malfunction in the body's sugar metabolism, has an important genetic component. The Foundation for Future Health Scenarios estimates that by 2005 there will be between 150,000 to 175,000 diabetics in the Netherlands, but some researchers have forecast that the number may be three times as high (Cro95). Around 20 per cent of patients suffer from an insulin-dependent form of the disease (IDDM or type I), while the remainder have a non-insulin-dependent form (NIDDM or type II, also referred to as late-onset diabetes). Research has indicated that diabetes results from complex interactions between various genetic and environmental factors (Tac95).

NIDDM appears with more than average frequency in certain families, but the pattern of inheritance is complex. Twelve genetic risk factors and one protective factor have been identified (Tod96). In a subgroup containing 1 or 2 per cent of sufferers, symptoms appear unusually early in life, typically before the patient is twenty-five. This form of the disease (maturity onset diabetes of the young, or MODY) follows a Mendelian inheritance pattern (Tac95). In different families, the occurrence of MODY has so far been linked with three gene mutations, but not all cases of MODY can yet be explained on the basis of these abnormalities. A link has been found between one of these mutations and 'ordinary' IDDM (Pol96, Tod97). This discovery could form the starting point for acquiring a better understanding of the pathogenesis of multifactorial diabetes (Gal97b).

3.9 Neuropsychiatric diseases

3.9.1 *Huntington's chorea*

Huntington's chorea is a well-known monogenic, dominant hereditary neurodegenerative condition. The genetic defect at its root involves the repetition of certain DNA sequences (a so-called trinucleotide repeat). The number of repeats can change when the defect is passed on from one generation to the next, with the disease only occurring if a certain threshold number is exceeded. At around the age of forty, people affected by the genetic defect begin to exhibit increasing involuntary movement, behavioural and personality changes and a deterioration in cognitive capacity. No treatment for the disease is yet known. In recent years, a presymptomatic diagnostic test has been available, with which people whose families are affected can be screened. Huntington's chorea is often used as a point of reference for researchers

and commentators interested in the psychological, ethical and social issues associated with predictive genetic testing.

3.9.2 *Schizophrenia and bipolar affective disorder*

Studies of families, adopted children and twins have shown that the causes of various multifactorial neuropsychiatric diseases include a strong hereditary component. Such is the case with schizophrenia and bipolar affective disorder (manic depression), for example. Both of these diseases are very common. In the Netherlands, it was recently established that four people in a thousand develop a so-called non-affective psychosis at some point in their lives (Bijl98). The prevalence of bipolar affective disorders is estimated to be 0.4 to 1.6 per cent, depending on the population studied. Although various DNA sequences have been localized (Fre96, Jam96), no genetic defect has been identified which can be used for diagnostic purposes. It seems likely that protective or genetic risk factors for bipolar affective disorder and schizophrenia will be identified within a few years. However, several more years of research will thereafter be needed to determine the clinical significance of these factors for treatment and prevention of these diseases.

3.9.3 *Alzheimer's disease*

Alzheimer's disease is responsible for 50 to 60 per cent of all cases of dementia. The condition is very common in old age: between 2 and 5 per cent of the population above the age of sixty-five and 15 to 25 per cent of people aged more than eighty-five suffer from a form of the disease.

There are a few rare, presenile forms of Alzheimer's disease, which display a monogenic inheritance pattern. To date, three genes have been identified, (dominant) mutations of which can cause presenile Alzheimer's disease. No DNA testing for these mutations yet takes place in the Netherlands.

Furthermore, mutations in certain genes are known to cause a predisposition towards the common form of the disease, which affects people in old age. Particular attention has focused on the APOE gene. The APOE4 variant appears to be an important risk factor in both senile and presenile Alzheimer's, in its familial and sporadic forms. This variant is found in approximately 15 per cent of people of European origin. Individuals with a homozygous E4 variant are 5 to 18 times as likely to develop Alzheimer's disease, and heterozygotes are also at greater risk (NIA96). Nevertheless, some homozygous E4 carriers reach advanced ages without any trace of dementia; furthermore, by no means all Alzheimer's sufferers carry an E4 variant.

The APOE gene is important in lipid metabolism (see also 3.7.2), a process which plays an etiological role both in Alzheimer's disease and in atherosclerosis: a condition which can in turn contribute to dementia syndromes. Quite a lot of research has been conducted into the relationship between the APOE gene and Alzheimer's disease, in the context of which it has been possible to make some preliminary clinical evaluations of the value of DNA diagnostics in this field. Some researchers have concluded that DNA testing has no place as yet in the routine diagnostic procedures used in connection with Alzheimer's disease (Goo96, Slo96). Others believe that DNA analysis can sometimes provide a useful addition to other methods of testing (Fri97, NIA96). There is no firm basis for carrying out predisposition research into APOE variants in the families of Alzheimer's sufferers or in larger groups (NIA96). As previously indicated, APOE tests are carried out in various Dutch laboratories in the context of research into lipid metabolism. A recent study discovered an RNA-level defect (i.e. a defect in the transfer of information from the DNA code to the protein) in people suffering from the most common form of Alzheimer's disease, although no sign of a mutation in the corresponding DNA could be found (Lee98).

3.9.4 Multiple sclerosis

In the Western world, multiple sclerosis (MS) is the most common cause of neurological invalidity. Among Caucasians, the disease affects one individual in a thousand. Studies of twins and the pedigrees of MS sufferers clearly point to a genetic component, apparently involving various genes. It would seem that a component of the HLA system — which has a role in auto-immune processes — is involved (see also 3.13), along with other predisposing genes (Bar97). Environmental factors also appear to play a part by influencing the consequences of genetic predisposition to a significant degree (Ros97). Understanding of the genetic background to MS does not yet have any clinical applications.

3.9.5 Migraine

Some 10 per cent of the population suffer from migraine. Most sufferers are aged between thirty and fifty and women are three times more likely to be affected than men. The causes of the disease are complex and involve genetic factors, in addition to hormonal and environmental factors. About 30 per cent of patients report that their migraine headaches are preceded by an 'aura', characterized by disturbed vision and speech or, in rare cases, by other neurological phenomena. A gene recently found to be associated with one rare familial form of migraine appears to play a role in the common form of migraine as well. This discovery may lead to modification of the

theory regarding the pathophysiology of migraine and could thus influence the development of new medications. However, there are as yet no implications for individual treatment or prevention (Oph97).

3.10 Sundry chronic diseases

Various other multifactorial chronic diseases exist; in some cases, hereditary factors are clearly at work, even though the etiology or pattern of inheritance has yet to be discerned. A few of these chronic diseases tend to affect people fairly early in life, one being asthma.

3.10.1 Asthma

Asthma is a chronic disease which can appear in childhood or later in life. The prevalence of the disease is thought to be rising by 5 per cent a year. However, there is little international agreement about delineation of the term, with the result that reported levels of prevalence vary from 4 to 32 per cent. The disease definitely has a hereditary component. Various genes have been investigated for links with asthma, but none seems to have any great influence on its own. A major role is played by environmental factors, which certainly include smoking and may include air pollution and foodstuffs. In the foreseeable future, the hereditary aspects of asthma are not expected to be highly significant in relation to its treatment or prevention (Ano97).

3.10.2 Chronic diseases of old age

The chronic diseases which emerge in old age are almost all multifactorial, although there are a few exceptions and monogenic variants. Important examples include type II diabetes, rheumatoid arthritis, osteoporosis, arthrosis, Bechterew's disease, atherosclerosis and hypertension. Although these diseases do occur earlier in life, most sufferers are older than sixty-five.

There are indications that some of these chronic diseases have a genetic basis and (auto)immunological processes appear to play a role in several of the conditions. In all cases, possible risk genes have been suggested and in some cases theories exist regarding the etiological significance of the gene. Generally speaking, DNA diagnostic techniques cannot yet contribute any significant amount of relevant additional information regarding any of these diseases; nor are they likely to do so in the next five years. There are certain exceptions to this general picture, however, which are dealt with below.

Knowledge regarding the significance for the progression of these conditions of various individual gene variants or combinations of variants may in the future make it possible to intervene in the disease processes at an early stage. It is likely that the relevant gene variants will prove quite common in the population, with the result that DNA diagnostics might be an option for everyone with such a disease, necessitating very large numbers of tests. The advantages of conducting such tests will have to be assessed very carefully, unless DNA testing should replace other diagnostic techniques.

3.11 HLA tissue classification in connection with auto-immune diseases

HLA antigens are found on almost all cells of the body and play an important role in the recognition and neutralization of foreign substances. Numerous classes, types and variants of HLA antigen exist, making millions of different combinations possible. On the basis of these combinations, highly individualized tissue classifications can be performed. HLA tissue classification can be very useful for matching transplant and, in certain cases, transfusion donors and patients. The procedure can also be used to predict whether pregnant women will produce antibodies against the tissue characteristics of a foetus. In such cases, the tissue classification is of no particular significance in its own right; it is simply a question of determining the compatibility of two individuals. The old serological testing method is gradually being replaced by molecular techniques, in which it is not the antigen itself that is sought, but the underlying genetic code. The Dutch Immunology Association estimates that more than forty thousand HLA classifications are carried out annually in the Netherlands, ten to fifteen thousand by means of DNA analysis (NVI97). The expectation is that DNA-level techniques will gradually displace other methods entirely.

A few tissue types are known to be associated with certain mainly auto-immunological conditions, such as diabetes and Bechterew’s disease. Theoretically, therefore, tissue classification could be of diagnostic significance in relation to these diseases. One well-known example is the HLA-B27 classification, which is regarded as an indicator of Bechterew’s disease. Where this condition is concerned, tissue classification can be important if other tests are inconclusive. In individuals with Bechterew’s disease or related conditions, the presence of HLA-B27 appears to influence the course of the disease to some extent. However, it has not been convincingly demonstrated that tissue classification brings any real advantage for the patient in terms of prognosis or treatment. The presence of HLA-B27 has almost no significance for healthy individuals. Estimates suggest that nearly a thousand tests a year are conducted for this purpose using DNA-level techniques.

3.12 Medication-related DNA diagnostics

DNA polymorphisms or mutations are sometimes associated with the response to a particular form of therapy. A great deal of research into such associations is being conducted by the pharmaceutical industry, in connection with both established and new medicinal products. The genetic factors influencing the efficacy of pravastatine in the treatment of hypercholesterolemia have been studied, for instance (Kui98). Furthermore, the metabolic breakdown of certain medicines (including antipsychotics and tricyclic antidepressives) can be influenced by hereditary factors to such an extent that the dosages ought to be adapted to the individual in order to optimize the effect and to avoid toxicity. In this context, it is mainly mutations in the so-called cytochrome P450 system that are influential (Wei96). Another relevant phenomenon is the abnormal reaction to anaesthetics (malignant hyperthermia) displayed by individuals with a particular mutation.

There is also evidence to suggest that a relationship may exist between certain mutations and an individual's sensitivity to radiation and radiotherapy; the research findings are not yet conclusive, however. Nevertheless, if the presence of a particular gene polymorphism or mutation is shown to have clinically relevant implications for treatment, there will be a marked rise in the demand for tests. The reason being that test data will enable clinicians to determine more precisely what treatments are indicated and thus both to provide more individualized therapy and to avoid giving a particular patient a form of therapy which is unlikely to be very effective (Mar97). The mutations in question are not likely to be of any direct diagnostic significance in connection with patients' healthy relatives. The Committee believes that tests of the kind described will become available and enter widespread use before long.

3.13 Quantitative developments

It is extremely difficult to estimate future developments in the volume of diagnostic DNA testing with any great degree of confidence. Although the growth in volume is currently gradual, breakthroughs are in the pipeline which may well cause sudden surges in demand. In various areas, significant progress can be expected in the next few years. At the research laboratories, universities and cancer centres, in the biotechnological and pharmaceutical industries, in the engineering and computer sectors and, critically in relation to clinical development, in clinical research laboratories, major advances appear imminent. Before long, all human genes will have been identified and their codes deciphered; the functions of many will also have been determined. Meanwhile, technical developments will make it possible to perform large

numbers of DNA analyses at once, in numerous different combinations. The relationship between these combinations and clinical phenomena will be analyzed by computerized data processing systems. However, the clinical relevance — the diagnostic, therapeutic and preventive benefit — of all output data will have to be assessed. The amount of time and the numbers of patients required for such assessment will depend to a considerable extent on the complexity of the issues to be addressed.

Ultimately, application in the field must be determined by well-considered definition of the circumstances under which testing is indicated. Where germline mutations are concerned, specific considerations will be needed to specify when the testing of healthy family members could be justified.

In the following paragraphs, current testing volumes are summarized and the quantitative developments anticipated by the Committee over the next few years are outlined.

Germline mutations

Monogenic diseases

- The CGCs presently perform approximately twelve thousand tests a year in connection with a wide variety of monogenic diseases; the volume of testing in this field will gradually increase.
- In other laboratories, about three thousand predominantly haematological tests are annually conducted; given the make-up of the population, this number is sure to rise, probably to about four thousand.

Monogenic variants of multifactorial diseases

- Hereditary forms of cancer currently account for about 2,650 tests a year on index patients and members of their families (fifteen hundred BRCA tests, six hundred HNPCC tests, fifty FAP tests and five hundred other tests). More monogenic variants are likely to be discovered. As soon as the gene responsible for a condition and sufficient mutations have been identified, the demand for testing will increase until most families have been screened. The demand for testing from patients' relatives differs from one disease to another; experience to date indicates that an average of five or six relatives take tests for every breast cancer index patient, but in families affected by MEN, the number is generally higher. The number of tests indicated in this context is likely to double over the next few years.
- Where certain monogenic variants of other conditions, such as Alzheimer's disease, diabetes, cardiovascular disease, migraine, etc., are concerned, DNA tests can be expected to come into use for individual patient care and for scanning

healthy family members; the Committee cautiously estimates that something like a thousand tests a year will be required within the period under consideration.
- Readers are referred to the passage on screening for an estimate of the volume of testing for familial hypercholesterolemia (FH).

Hereditary risk factors

- Testing for the factor V-Leiden mutation, recognized as a risk factor in relation to thrombosis, is currently running at about five thousand analyses a year; as the test becomes more widely available, this number will easily rise to ten thousand.
- In the next few years, it will also become possible to test for risk factors connected with cardiovascular disease, diabetes, cancer and other conditions, with a view to enhancing treatment and prognosis. Within five years or so, this might be expected to create enough demand to necessitate several thousand more tests a year; if strong associations are discovered between genetic factors and the efficacy of particular therapies, the volume of testing required will be even higher. Still greater numbers will be involved if there are preventive grounds for testing patients' relatives.
- If it should be judged appropriate to test numerous older patients suffering from chronic conditions for genetic risk factors, the system will have to cope with a very large group of people and possibly a sizeable number of gene variants. However, the Committee does not expect such a development in the next ten years, since, once the genetic defects have been identified, years of research into their clinical significance will be required. There is unlikely to be very much demand for checking healthy individuals for such factors, because the predictive value of the tests will generally be very low.

HLA classifications

- About a thousand diagnostic tests for Bechterew's disease are presently performed each year. Given that the HLA system plays a major role in various diseases and that serological testing techniques are being replaced by DNA-level techniques, a substantial increase can be expected in the number of tests on patients. Generally speaking, however, the significance for healthy family members will be small.

Medication-related DNA diagnostics

- More research data will be published in the near future. It seems probable that DNA diagnostics will be widely used to test for gene defects and variants which have medication-related implications, partly because of the pharmaceutical industry's interest in this area. The significance of medication-related tests for

patients' healthy relatives will vary, but is generally unlikely to be very great. Tens of thousands of tests a year may be required.

Overall, the number of DNA tests on patients (which may be significant for healthy family members) will rise steadily over the next few years; five years from now, double the present number of tests will be required. By contrast, the demand for testing for other purposes, such as HLA classification and medication-related DNA analysis (which can generally be expected to have little significance for healthy family members), could increase quite suddenly.

Somatic mutations

At present, an estimated 4,800 or so tests are conducted annually in the field of haemato-oncology. About seven hundred of these concern rare leukemias. However, the Committee believes that more like 9,200 tests a year are actually required, roughly a third of them for the said leukemias and two thirds for non-Hodgkin's lymphoma. The number of indications and tests in connection with other (solid) tumours is still quite small (probably about three hundred a year). This figure could rise suddenly, however, as soon as DNA test results acquire greater clinical relevance. Once this stage is reached, a large proportion of patients may be considered for DNA testing, in view of the seriousness of both the diseases and treatments in question. In this field too, repeat tests can be desirable during treatment and follow-up. Since special techniques have to be used to obtain tumour tissue for analysis, it will not be appropriate to perform repeat tests as frequently in connection with solid tumours as in connection with leukemia. Nevertheless, far more people develop solid tumours, so several thousand tests a year will probably be needed before long. Furthermore, the established laboratory testing techniques are likely to be replaced by very accurate DNA-level techniques in fields such as urine cytology.

Screening

Depending on the disease under investigation, screening may involve testing either for germline mutations or for somatic mutations. However, it is in principle always possible to determine the number of tests required when setting up a screening programme.

In the context of the experimental population screening programme for familial hypercholesterolemia (FH), about a thousand DNA tests are being annually conducted.

A surge in the demand for testing (easily running to several thousand tests a year) may be expected if it should become possible to use DNA-level techniques to determine whether very early growths found in the course of screening activities were benign or (potentially) malign. Still more analyses would be sought if the DNA-level analysis of bodily fluids and excretions should prove a reliable independent method of detecting conditions such as prostate cancer.

Concluding remark

Many of the possible applications of DNA diagnostics remain some way off and it is hard to estimate just how quickly they may become available. Experts in the field expect that, as research is now in progress and technological developments begin to bear fruit, advances will become more rapid from 2002 onwards. A sudden technological breakthrough — in chip technology, for instance — could have a major impact in a short space of time. It is therefore very important to make advance plans to enable the system to cope with and manage such developments.

Table 4 Quantitative developments in DNA diagnostics (annual numbers of tests).

clinical field or condition	current volume	forecast for 2003
DNA diagnostics for germline mutations		
CGC range, excluding hereditary tumours	11,500	12,000
hereditary tumours	2,650	5,000
new ‘monogenic variants’	N/a	1,000
hereditary anaemias	3,000	4,000
hereditary haemochromatosis	100	500
venous thrombosis (factor V)	5,000	10,000
Bechterew’s disease (HLA)	1,000	2,000
new genetic risk factors	N/a	thousands
medication-related	N/a	(tens of) thousands
FH (population screening)	1,000	4,000
total	22,750	(far) more than 38,500
DNA diagnostics for somatic mutations		
rare leukemias	700	3,000
other haemato-oncological and solid malignancies	4,100	(far) more than 8,000

Chapter 4

Making decisions in a state of uncertainty: pre-test and post-test trajectories

DNA diagnostics is defined in this report as the study of changes in and variants of DNA which are associated with the occurrence, risk and progression of certain patterns of disease or with the reaction to certain medical treatments. In this context, distinction is made between hereditary and non-hereditary mutations. This chapter explores certain aspects of diagnostic DNA testing for hereditary mutations, which have implications for what the Committee refers to as the pre-test and post-test trajectories.

The pre-test trajectory encompasses definition of the circumstances under which DNA tests on patients are indicated, including various matters which might determine whether such testing is appropriate in a given case and the procedures for predisposition testing for healthy relatives, the provision of information to patients and/or relatives regarding the implications of testing and decision-making by patients and/or relatives.

The post-test trajectory covers the explanation and interpretation of DNA test results, the provision of advice regarding the options open the subject and, where necessary, psychological counselling, together with appropriate follow-up activities.

4.1 The association between mutations and the occurrence of disease

4.1.1 The numeric expression of risk

The risk that the carrier of a mutation runs of contracting a particular disease is often expressed numerically. Such figures need to be interpreted with care (see also GR95

and GR96a). Where monogenic diseases are concerned, the association between a mutation in a disease gene and the occurrence of the disease is theoretically 100 per cent; it is more a question of certainty than risk. Where multifactorial diseases are concerned, a particular mutation increases the risk of developing the associated disease. The practical implications of this can vary enormously. To understand these implications, one must grasp the distinctions between basic risk, relative risk and absolute risk.

The basic risk of a particular disease is the likelihood of an average individual developing the disease in question. The assessment of the basic risk takes into account both people who carry a given (genetic) risk factor and people who do not. If the basic risk is determined on the basis of the prevalence of the disease in an entire population (e.g. the Dutch population as a whole, typically categorized by age and gender), it is referred to as the population risk. In terms of population risk, the chance of acquiring a very rare disease is slightly more than zero, while a woman's chance of getting breast cancer is about 10 per cent and the chance of cardiovascular disease is higher still. In certain groups (including particular families) the basic risk may be higher, on the basis of the prevalence and, where hereditary conditions are concerned, the inheritance pattern within the group. So, for instance, some diseases are either more or less common in particular ethnic groups than in the population as a whole.

Relative risk is an expression of the ratio between the risk for someone with a particular characteristic (for our purposes, the presence of a genetic risk factor) and the risk for someone without that characteristic. Thus, the significance of the relative risk depends to a great extent on the level of risk experienced by individuals without the characteristic. If the basic risk is itself high, a doubling of that risk is very significant; if the basic risk is low, a person who is at twice as much risk is still unlikely to contract the disease in question.

The absolute risk is the overall chance of a specific individual actually developing a particular disease. So, for example, a woman in a high-risk family who carries a mutation in one of the BRCA genes is believed to have about an 85 per cent chance of getting breast cancer; in families affected by familial hypercholesterolemia, individuals run about an 80 per cent risk of acquiring the disease. However, the level of absolute risk associated with other hereditary risk factors is much lower. Women without the factor V Leiden mutation or any other risk-increasing factors have about one chance in ten thousand of developing thrombosis in any given year. Those who do have the mutation have an increased relative risk: they are six times as prone to thrombosis. Nevertheless, the absolute risk is no more than 0.06 per cent - a level comparable with that experienced during pregnancy, when using the contraceptive pill, or by smokers. Where there is a family history of the disease, the relative risk for an individual

exposed to a combination of risk factors can be more than fifty. The absolute risk for such a person is therefore 0.5 per cent: one chance in two hundred per year.

The association between a mutation and a particular pattern of disease is often first deduced from the observation that a particular genetic sequence or mutation is more common in a group of patients with the condition in question than in the population as a whole. Where some multifactorial diseases, such as insulin-dependent diabetes, are concerned, more than a dozen genetic risk factors have been identified in this way. The more risk factors a person is exposed to at once, the greater the chance of that individual developing the disease in question.

4.1.2 *Variations in clinical symptoms*

The clinical picture exhibited by patients with a particular mutation can vary considerably. There may be differences in the seriousness of the disease, or in the age at which it manifests itself, or in the nature and progression of the symptoms. Multifactorial diseases are generally more variable than monogenic diseases. Scientists believe that in some cases such variations are related to differences in the nature of the mutation in the relevant gene. However, even in families where the same mutation is prevalent, a role is played by environmental factors and variations in other genes which can influence the clinical presentation of the condition in question.

4.1.3 *The significance of test results*

The issues outlined above are relevant in terms of the significance of test results. The reliability of the test is very important as well, of course. In addition, the significance of a test result depends in part on the frequency of the characteristic to which it relates: the more rare the characteristic is, the greater the chance of an erroneous result. Another important factor is whether the majority of the mutations which can cause the disease have been identified, expressed as the percentage of cases of disease for which they are responsible. Hundreds of different mutations of certain genes are known to exist, so laboratory testing sometimes involves looking only for the most common mutations.

If the mutation sought in the test is *not* found, this is significant primarily in cases where the subject's family history suggests a level of basic risk well above the normal level *and* the particular mutation *has* been found in a member of the family who has the disease. Under such circumstances, the risk to the subject is clearly not as high as the calculated (feared) basic risk and may be considered 'normal'. The subject should not, however, conclude that he or she is 'in the clear' and that general preventive

measures such as self-examination and mammography (in the case of breast cancer) are no longer necessary. In cases where the basic risk appears to be only slightly above normal or where many of the mutations associated with the disease remain unidentified, failure to find a particular mutation does not mean very much.

If the mutation sought in the test *is* found, this generally has clear informative value, especially if the family history is known (Hol97). If little historical information is available (perhaps because of a low child-count or early mortality in the family, or because family members are not in contact) the informative value is diminished.

In this context, it is important to recognize the difference between the significance of predisposition testing on DNA and established tests aimed at the early detection of disease, such as the mammographic scanning or cervical smear testing. With early detection testing, a wider margin of error and uncertainty regarding the predictive value are sometimes accepted, since the findings can still be verified by other methods: the actual presence of the disease can be detected in a subsequent test. By contrast, DNA test results cannot be verified, yet important preventive decisions must be based upon them.

For this reason alone, strict criteria should be set regarding the reliability of predisposition testing. Furthermore, it should be recognized that the results of a DNA test do not indicate whether disease is present at the time of the test.

4.1.4 Identification of risk groups

To assess the value of DNA testing for a given genetic risk factor, it is important to recognize the groups within which there is a strong chance of finding a mutation and in relation to which the test results will have genuine informative value. The most important criteria concern the degree to which occurrence of the disease is familial, the age at which it tends to manifest itself in the family, information on the role of specific mutations in the occurrence of the disease and the clinical picture. Three broad groups can be defined on the basis of risk levels:

- Individuals in whose families there is a history of a particular disease consistent with a Mendelian inheritance pattern. For such people, the basic risk is nearly 50 per cent in the case of a dominant risk factor and nearly 25 per cent in the case of a recessive risk factor.
- Individuals in whose families a disease is clearly familial and strikes relatively early in life. To determine whether someone falls within this group, certain standards can be applied, such as the number of first and second-grade relatives with the disease, the age at which the disease tends to strike and the level of basic risk in the family. The clinical picture can sometimes indicate the existence of an important hereditary factor as well.

- Individuals who belong to a population within which a genetic risk factor is relatively common.

Physicians should determine whether testing is indicated in connection with a given disease partly on the basis of criteria relating to family history and the level of basic risk. For various kinds of cancer, rules have been drawn up regarding the minimum number of first and second-grade relatives who must have the disease before it is considered hereditary in that family. Generally speaking, DNA testing is not indicated if the basic risk is less than 30 per cent.

Even where the basic risk, as determined from the family history, is clearly above average, a DNA test on a healthy individual is worthwhile only if the family-specific mutation has been found in a blood relative with the associated disease.

Where multifactorial diseases with a hereditary component are concerned, it is very important that DNA tests are conducted in accordance with clearly defined criteria regarding the risk group. The non-performance of a DNA analysis can be preferable to the testing of inappropriately selected individuals, with all its potential ramifications.

4.2 Options for reducing the risk of disease

One of the main motives for carrying out a predisposition test is the possibility of obtaining information which can be used to influence either the likelihood of a disease occurring or the progression of a disease. Depending on the circumstances of the case, this can be done in various (combinations of) ways:

- Lifestyle and behavioural changes can be made to influence non-genetic risk factors.
- Regular medical examinations can be conducted with a view to detecting a disease early and intervening in good time.
- Preventive surgery can be performed to prevent development of the disease in a particular organ.
- Medicinal treatment can be given to inhibit or positively influence development of the disease.

Referral of an individual for DNA testing can also be based on considerations such as the subject's psychological well-being and the need to obtain information that can facilitate important decisions which, while they do not relate to the subject's personal health, can be influenced by the risk of disease (e.g. family planning decisions.

4.2.1 *Influencing non-genetic risk factors*

Multifactorial diseases involve the interaction of genetic and environmental factors. Consequently, even if a person is genetically predisposed to a disease, the risk of its occurrence can be reduced by influencing the environmental factors, which may include diet, smoking, working conditions, exposure to the sun or other radiation sources, exercise and so on. The potential benefits of such preventive action have been demonstrated by epidemiologic research. One study focused on the offspring of a family affected by a particular mutation in the FH gene, some of whom lived in South Africa and some in Canada. Those in Canada were found to have much lower cholesterol levels and to suffer less cardiovascular disease.

Sometimes, the guidelines on lifestyle, diet and so forth given to an individual on the basis of DNA test data may consist of generally valid advice. Nevertheless, because the advice is personal and linked to the fact that the individual or family is known to be at risk, there could be a better chance that it will be accepted. In other cases, the advice may be geared quite specifically to carriers of a particular mutation. The carrier of a mutation in the AT gene, for instance, might be advised to avoid X-rays as far as possible, while a woman with the factor V Leiden mutation and a family history of thrombosis might receive special advice regarding methods of birth control, taking factors such as her smoking habits into account. With certain mutations, the use of particular medicinal products or exposure to particular substances can be undesirable.

4.2.2 *Regular medical examinations to detect disease early*

Regular medical examinations for the purpose of detecting a particular disease as early as possible (surveillance programmes) involve the use of established diagnostic methods, such as blood analyses, imaging, instrument-assisted internal visual examinations and so on. Such programmes should be started in good time, sometimes in childhood, and ought in principle to be maintained for the rest of the subject's life. However, regular examination not only raises the possibility of medical complications, but can also be a psychological burden. Consequently, such programmes should follow a protocol if they are to be responsibly designed and effective.

Surveillance programmes of this kind are already in place for various hereditary forms of cancer, including breast and ovarian cancer, familial melanoma and bowel cancer. In the Netherlands, the following recommendations are made in respect of people whose chances of contracting bowel cancer are substantially higher than average:

colonoscopy every other year from the ages between twenty and twenty-five; gynaecological examination every year or every other year for women from families in which uterine cancer is also prevalent, possibly supplemented by ultrasonography from the age of thirty; screening for tumours of the stomach, urinary tract and ovaries if there is a family history of these cancers. To date, such programmes have been considered appropriate only for people (sometimes including children) whose family anamneses suggest they are at particularly high risk. DNA diagnostics could be particularly valuable in this context as a means of distinguishing individuals for whom such programmes are desirable from those who need not take part because they do not carry the relevant genetic risk factor.

4.2.3 *Preventive surgical intervention*

With some diseases, the option exists of surgically removing the tissue in which the disease can develop: the so-called 'target organ'. Until now, this option has only been applied to hereditary forms of cancer. Thus, preventive mastectomies or hysterectomies, or both, are sometimes performed on women from families affected by mutations in the BRCA genes. Similarly, sizeable parts of the large intestine may be removed to prevent bowel cancer, while people who acquire a MEN syndrome early in life can have their thyroids removed or, if a tumour develops in one adrenal gland, the healthy one may be taken out as well. Preventive surgery of this sort, although a serious measure, seems a logical precaution; its success in preventing the development of tumours has been reported in various publications. Nevertheless, the value of such intervention in terms of increased life expectancy or quality of life has yet to be determined (Hol97). For instance, when a mastectomy is performed, small amounts of breast tissue are almost always left behind, in which cancer can still develop (Tem91, Wap90). Women with a hereditary predisposition towards breast cancer probably have a higher than average chance of developing cancer in these residual tissues. One problem is that the longitudinal randomized studies needed for prospective research take a very long time, during which a potentially valuable option cannot be exercised. Sometimes, retrospective research can also provide a clear indication of the value of preventive surgery. This is the case, for instance, with the removal of (parts of) the large intestine from patients with familial polyposis (Vas96).

4.2.4 *Medicinal treatment*

On occasions, where an individual is at risk of contracting a given disease, but has yet to develop any symptoms, it can be desirable to prescribe medicinal products normally used to treat the feared condition. This course of action is referred to as 'treatment of

the genotype', as opposed to 'treatment of the phenotype' (the latter being treatment of a disease which is already in progress). This option is being studied in relation to familial hypercholesterolemia, hereditary diabetes and other conditions. The benefits are potentially considerable, but its actual value remains unclear. It is not yet apparent, for example, whether medicinal treatment has any effect where functional changes have yet to take place. Researchers are therefore seeking to identify early indicators of functional change in people who carry a mutation in a particular gene. A study of this kind is underway, for instance, in the context of the experimental familial hypercholesterolemia population screening project. Although potentially beneficial for (some) mutation carriers, such treatment would entail the disadvantages (including possible side-effects) of very long-term medicine use. Furthermore, people who in fact have little or nothing to gain could become medicalized. To date, the value of 'treating the genotype' has not been demonstrated for any multifactorial disease.

4.2.5 Other options

The value of predictive DNA diagnostics goes beyond its potential in relation to the prevention and treatment of disease. For many people, the removal of uncertainty regarding medical predisposition is the principal benefit. Frequently, people wish to know what risks they face before making important personal decisions in areas such as family planning, general forward planning and the formation of relationships. For these reasons, the relatives of index patients with Huntington's chorea are given the opportunity to take presymptomatic tests, even though there is no cure for the condition. Where multifactorial diseases are concerned, it is not yet clear how much influence predispositional information would have on family planning decisions. However, from the limited experience gained so far with testing for the mutations associated with hereditary forms of cancer, it is apparent that people do take such matters into account.

4.3 Making decisions regarding testing and treatment

A person who must decide whether to take a diagnostic DNA test is likely to feel hope, uncertainty and anxiety. Hence, decision-making is not purely rational; it is also a very emotional process. Significantly, objectively determined risk and perceived risk often differ considerably. There is a similar discrepancy between attitude and behaviour, i.e. between what people think they will do in a particular situation and what they actually do when such a situation arises. The ultimate role of emotional forces is apparently hard to predict. One consequence of this fact is that it is difficult to determine the potential demand for DNA diagnostics from surveys in which people are asked about

their views. Attitude surveys of this kind generally indicate that more people would want to take a DNA test than actually proves to be the case.

4.3.1 *Perceived risk*

A person's perception of the risk of contracting a given disease depends not only on the objective level of risk, but also on his or her experience of the disease within the family, the seriousness of the condition and other psychological factors. A 'bad' experience in the family can lead one couple considering children to perceive a 1 per cent risk as high, while another will regard a 50 per cent risk acceptable. Further research into the personal and situational factors associated with risk perception is urgently needed (Ler94).

4.3.2 *Making decisions in a state of uncertainty*

The existence of risk inevitably requires people to make decisions in a state of uncertainty. It was originally thought that if people from families affected by hereditary disease were given accurate information on the likelihood of adverse developments, they would be able to make sensible decisions. However, it has become clear that decision-making processes are very complex and heavily influenced by conscious and unconscious emotions. Most of the data on this subject comes from research into the psychological aspects of monogenic disease counselling, where the result of a DNA test theoretically indicates conclusively whether the subject will develop the disease in question. Predisposition testing in connection with multifactorial diseases provides less certainty. Furthermore, there is often greater variation in the clinical picture associated with multifactorial conditions, making it difficult to predict when a disease will strike and what the symptoms will be, if the subject *is* affected. There is no linear association between the objective level of risk, the perceived level of risk and an individual's inclination to take preventive action. Many people continue to smoke, for instance, despite the substantially increased risk of lung cancer and cardiovascular disease, while information about the possible harmful effects of certain foodstuffs or the contraceptive pill can generate considerable unease, even though the risks involved are relatively small.

When faced with uncertainty, physicians too sometimes allow their decisions to be guided by subjective considerations. This can interact with patient anxiety and compromise the objectivity of the advice provided. The Committee therefore feels it is very important that consensus is sought within the relevant clinical professions before DNA testing is introduced in a particular field.

4.3.3 *Who will take DNA tests?*

Little is known about the inclination of index patients' relatives to take DNA tests with a view to obtaining information about the risks they face. Nevertheless, influential factors are known to include having seen the effects of the relevant disease at first hand (Dud94) and considerations regarding the likely significance of the result for direct relations, in particular children and parents (Ler96). Good, objective information is very important in this context (see also 4.5.3). There are indications that an inclination to take a test is associated with certain educational, insurance and personality characteristics (Blo92, Cod94, Eve97, Ler96, Ste94). Not surprisingly, the seriousness of the condition and the availability of treatment also play a part.

In the Netherlands, 10 to 15 per cent of people identified as possible carriers of the mutation associated with Huntington's chorea currently opt to take a DNA test. This is considerably less than the 50 to 80 per cent who indicated that they would do so when surveys were conducted before the test became available. When asked in advance, 67 per cent of people from high-risk families were positive about prenatal diagnostics, but in practice hardly any of them actually opt for testing. In families affected by breast cancer, where an index patient has been found to have a BRCA 1 mutation, nearly 60 per cent of immediate relatives take a DNA test. A study of families affected by type I diabetes found that only half of the family members wanted to know the results of predisposition tests performed, where the actual chance of an unfavourable result was less than 10 per cent (Wag95). A British attitude survey amongst the relatives of Alzheimer's disease patients found 75 per cent inclined to take a predictive test, despite the seriousness of the condition and the fact that no treatment was available (Mag96). Dutch researchers studying families with two hereditary neurodegenerative conditions (one of which was hereditary presenile Alzheimer's dementia) established that 64 per cent apparently wished to undergo a predictive test at some point. However, when given the chance to do so, two thirds declined (Tib97a). In the Netherlands, no diagnostic DNA testing is carried out in families with the hereditary, presenile form of Alzheimer's disease.

New technological possibilities and changing social attitudes may be expected to influence the numbers of people inclined to take DNA tests. The Committee expects that such developments will increase the demand for testing.

4.3.4 *Decisions regarding optional courses of action*

It is also relevant to consider the decisions carriers tend to make and the consequences of these decisions for themselves and their relatives. Little well-documented research

has been conducted in this area, which is unfortunate, since such research could facilitate formulation of the conditions applicable to counselling and support services (Dud97).

A study of 136 women with at least one first-grade relative (child or parent) affected by breast cancer found that 10 per cent decided on mastectomy, 47 per cent considered this option but decided against it and 43 per cent had no interest in such a course of action (Ste95). In more than three hundred families from the Rotterdam area affected by familial breast cancer, 87 per cent of identified BRCA carriers consented to removal of the ovaries and 57 per cent to a double mastectomy.

Clearly, some far-reaching decisions are associated with hereditary cancers. At present, one can only guess how hard patients will find it to make decisions in circumstances where lower levels of risk, less serious conditions or less serious treatment options are involved, and what options they will be liable to choose. With various diseases, there is a hope that 'treatment' by the presymptomatic administration of medicinal products may be beneficial; longitudinal research is needed to determine whether this is actually the case, which should take account of the possible side-effects of long-term medication use.

4.4 Psychological and relational consequences of testing

4.4.1 Predisposition testing

People respond in very different ways to the results of predictive DNA tests - and often in ways that they had not expected themselves. An individual may ask for a test to end his or her uncertainty, only to find that an unfavourable result is hard to deal with because the hope which is always possible in uncertainty is lost. Naturally, the response to a favourable result differs from the response to an unfavourable result. Even so, there can be negative consequences for people who receive good news, as explained later. It must also be recognized that test results do not always bring complete certainty; an element of doubt often still exists. Responses are additionally coloured by the availability and implications of treatment. Another very important factor proves to be whether the subject has seen the disease at first hand.

Most of the research carried out in this field has focused on the psychological consequences of presymptomatic diagnostic testing for Huntington's chorea. The fear that unfavourable results might make many people suicidal is eased by the findings of a recent global research project (Tib97b). It is clear that the removal of uncertainty can be a relief and can allow people to arrive at considered decisions regarding the direction of their lives. Unexpectedly, it proved that a favourable result was by no means always a similar relief, but sometimes led to feelings of guilt, disrupted family

relations and difficulties forming a new perspective on life. Where several family members took tests, those who received favourable results still had to deal with the fact that close relatives received unfavourable results (Dud94).

Another study has shown that the exclusion of a gene defect certainly does not always bring peace of mind, especially if the patient is of a nervous disposition (McD96). Where multifactorial diseases are concerned, a limited amount of research has been conducted into the consequences of analysing breast cancer genes for evidence of predisposition. A favourable result can reduce worry and at least means that the subject does not have to (decide whether to) participate in an intensive and often serious follow-up programme or undergo preventive surgery. In cases where subjects reported feeling depressed prior to testing, this appeared to be eased by news of a favourable result. Amongst women who received unfavourable results, depression was neither eased nor aggravated (Ler96).

4.4.2 The position of the index patient

The index patient is often regarded as playing a key role: given the physician's professional duty of confidentiality, the index patient must consent to his or her relatives being contacted and is generally expected to notify them personally. This places the index patient in a very difficult position (Dud97, Vri97). The information he or she must pass on is complex and creates uncertainty for the recipients. In most cases, the information is not directly beneficial to the index patient, since he or she already has the disease. The recipients can react in various ways, but the index patient, as the bringer of bad news, is often in an awkward position. The Committee believes that all these matters need to be addressed when informing subjects about testing and that support for the index patient should concentrate on his or her personal interest, raising the familial aspects only with great care. It is not realistic to expect index patients to inform their relatives personally in all cases. The Committee would like to see research carried out to determine the pros and cons of various ways of approaching patients' relatives.

4.5 Pre-test and post-test trajectories

4.5.1 Circumstances under which testing is indicated for patients

A patient should be given a DNA test for a germline mutation only if there are clear indications that his or her condition may have a genetic basis. Such indications may come from the family anamnesis, the clinical picture (in particular the patient's age at

onset of the disease) or from the fact that the patient belongs to a population group in which a particular gene abnormality is unusually common.

There are two reasons for testing a patient for a germline mutation. The first is to arrive at a more precise diagnosis with a view to facilitating prognosis and treatment of the patient. If, for example, a patient proves to have a hereditary form of breast cancer, treatment and follow-up can be adapted accordingly. The second reason for testing is to identify the mutation associated with the patient's condition, so that his or her healthy relatives can be tested for predisposition to the same condition (see also 4.5.2). In a given case, both reasons may apply. It is important to recognize that, even if the primary reason for testing is to facilitate treatment of the patient, there may inevitably be implications for the patient's relatives. If it proves that the patient's condition has a genetic basis, this is significant for the relatives, who may consequently wish to consider predisposition testing. The physician in charge of a case must take these matters into consideration and must tell the patient where testing may lead.

Frequently, it is not yet clear whether testing could be beneficial in relation to prognosis and treatment of the patient. DNA testing is nevertheless considered in such cases, if it can open the way for the predisposition testing of family members. However, before a test is conducted on these grounds, steps should be taken to ascertain that the availability of predisposition testing is desirable. Only then should the option of a DNA test be discussed with the patient and his or her permission sought to conduct a test for the said purpose. In practice, it is often assumed that the patient's interest is consistent with the interests of other family members, but this is by no means always so. It is quite possible that the various parties have conflicting interests.

4.5.2 Circumstances under which testing is indicated for healthy individuals

The predisposition testing of healthy individuals may be considered in various situations. If an index patient is found to have a genetic condition, tests on his or her immediate relatives may be appropriate. Alternatively, a healthy individual may ask to take a test if a particular disease is very common in the family. The Committee believes that in cases of these kinds, DNA testing is a natural part or consequence of individual patient care. This is significant in relation to certain issues connected with the scope of the Population Screening Act (WBO; see also 5.2.3).

DNA testing may also be appropriate if it appears that a given gene abnormality has a major impact in certain medical situations. Under such circumstances, there can be a case for notifying and testing people in those situations. It has been argued, for instance, that (potential) users of the contraceptive pill should be tested for the factor V Leiden mutation. The accepted view is that the very small risk of thrombosis attributable to use of the pill is outweighed by the potential problems — including the

risk of thrombosis during pregnancy — associated with the unwanted pregnancies that would follow if less reliable contraception methods were used (Sol96, Van96).

Actively tracing healthy risk-carriers in families or other groups in which a mutation is relatively common can also be justified. The identification of beta thalassemia carriers in people of Mediterranean origin and BRCA gene mutation carriers in Ashkenazi Jewish groups would come under this heading. A large-scale project to trace carriers of FH gene mutations in families affected by familial hypercholesterolemia is already underway in the Netherlands. In other countries, certain efforts are made to track down people who carry the cystic fibrosis gene.

In all these cases, the aim is the predictive testing of healthy individuals. With regard to the desirability of predisposition testing, the Health Council recommended in its report on genetic screening that the strict criteria (see Annex C) applicable to population screening (including forms of family investigation for which licensing is obligatory) as defined in the WBO should also be applied to other predictive testing situations (GR94). However, the Committee argues that the application of such criteria to the testing of patients' immediate relatives as a natural consequence of individual patient care can have a different outcome as when it takes place within the context of a screening programme (GR96b). Not only does the testing of relatives address higher levels of real or perceived risk, but also a clinical specimen of the mutation affecting the family has been isolated from the index patient. Having an identified mutation makes the analyses easier and clarifies the significance of finding the mutation in a relative. Furthermore, members of the same family typically care for, are concerned about and feel a sense of responsibility towards one another. Information about the presence or absence of a shared susceptibility can be important to their interrelationships.

It would be very unfortunate if the line taken on the desirability of family investigation in connection with a particular mutation differed significantly from one physician to another, or from one case to another. The relevant professional groups should therefore endeavour to arrive at a consensus or develop guidelines for various medical conditions, so that the circumstances under which diagnostic DNA testing is indicated are clear. In this regard, adequate distinction should be made between the patient's interest and the relatives' interest. Formal requirements could be made regarding the formulation of guidelines. Given the extent to which personal experience of a disease influences the perception of risk, parents' and patients' representatives should be involved in drawing up the guidelines. Guidelines regarding predisposition testing should not become operational without consensus about the appropriate consequences in terms of medical treatment and further testing where various conditions are

concerned. The guidelines on testing in connection with hereditary forms of cancer drawn up by the American Society of Clinical Oncology (ASCO96, Col96, Olo97, Sko96) and in connection with familial forms of Alzheimer's disease (ACMG95, NIA96) serve as useful examples in this context.

4.5.3 *Information and counselling*

The decisions associated with DNA diagnostics sometimes have far-reaching consequences and the decision-making process involves numerous subjective considerations. It is therefore very important that (prospective) subjects are properly informed. Unfortunately, this is very time-consuming, since the information is complex and not readily understood by all. Furthermore, account must be taken of the discrepancy between actual risk and the risk carrier's perceived risk (see also 4.3.1). The information provided and the way it is communicated affect the decisions made by the (prospective) subject. Despite these facts, little research has been conducted into information and counselling methods (Mic97). Many protocols have been formulated by modifying the counselling protocol for presymptomatic testing for Huntington's chorea to suit other patterns of disease and local attitudes (taking account of matters such as the scope for treatment and the age at which the disease strikes).

The purpose of counselling is to ensure that subjects are properly informed about any hereditary conditions they may have, any predisposition towards such conditions they may have and the possible consequences, so that they can make considered decisions about all the associated matters. Counselling should ideally be neutral and non-directive; to satisfy the latter condition, the counsellor should demonstrate recognition of the fact that the subject is ultimately responsible for making a decision on the basis of the information provided (Bol97). The counsellor should help the subject to digest the information and think the matter through, providing advice if asked to do so. Unconditional respect for the subject's wishes is essential, even if the subject's ultimate decision or behaviour is not what the counsellor might have hoped (Mic97). Nevertheless, the desirability of a completely non-directive approach is questionable in relation to diseases which could be prevented or delayed by lifestyle changes or medical intervention (Ano98, Ott97, Wer90).

The Committee believes that information and counselling methods and their evaluation should be covered by the protocols on clinical research on predisposition testing. The Dutch umbrella organization representing patients with hereditary and congenital diseases and their parents (VSOP) is also strongly in favour of a systematic and thorough approach to informing (prospective) subjects about the significance and consequences of DNA diagnostics; as well as lobbying, the organization endeavours to make a practical contribution in this field.

Where monogenic diseases are concerned, the CGCs have developed a system in which index patients, clinical geneticists (as counsellors) and GPs (as the parties who make the referrals) work together to contact patients' relatives. Similar working methods could possibly be adopted elsewhere. However, other approaches also need to be developed, especially for the provision of information and advice. The CGCs do not have the capacity to maintain the existing approach if there is further extension to the range of circumstances under which testing is indicated. Furthermore, extensive knowledge of the relevant (non-clinical genetic) field is needed to inform (prospective) subjects about the significance of the information that testing may yield and about the treatment options.

Various alternative approaches might be considered. A clinical specialist with expertise in genetics could take responsibility for providing information and advice. It is not certain, however, that specialists with sufficient time and expertise could be found. Alternatively, clinical geneticists working for the CGCs or clinical hospital departments might take on the task; so might specially trained paramedics or 'genetic nurses' (Bee97). This possibility is currently being investigated in a project financed by the former Prevention Fund (Praeventiefonds).

In the future, GPs will more often be asked about the hereditary aspects of various diseases. Furthermore, GPs have a natural role in this field, in the provision of information and counselling, and perhaps in referral. It therefore follows that a good understanding of genetics will be essential for all physicians in general practice. The circumstances under which it is appropriate to contact patients' healthy relatives must also be agreed. Consequently, a great deal needs to be invested in providing appropriate in-service training for clinical specialists and GPs. To this end, various proposals have been published (ASCO97, ASHG95, Col97, Ste97).

4.5.4 Guaranteed availability of medical treatment options

As soon as it has been determined that medical treatment is appropriate and wanted by the patient, steps should be taken to ensure that the treatment in question is available. It would not be responsible to go through the whole DNA diagnostic process if this were not the case.

This may appear to be stating the obvious, but in practice there are problems in this area. Health care budgets do not cover preventive care for healthy individuals. The provision of such care would involve a substantial drain on the resources allocated to imaging, surgery, out-patient support and so forth, certainly as long as preventive work is concentrated in a small number of hospitals. If left to compete for resources against care for the ill, the follow-up of asymptomatic mutation carriers might suffer. One could argue that preventive treatment is ultimately cheaper than treating preventable

disease. Although this is a valid argument, it does not remove the fact that additional resources are required for the provision of preventive care of the kind referred to. For one thing, it is not known how long follow-up activities should be continued or just how successful they would be in preventing disease altogether. What is more, if a person lives longer, they are likely to require treatment for other conditions at some point. Thus, the 'profit' in terms of increased life expectancy and quality of life will in itself need to justify additional finance.

In the Committee's view, diagnostic DNA testing which may indicate that the subject runs a significant risk of a serious or potentially fatal condition should not be carried out unless proper post-test care can be guaranteed. Institutions performing DNA tests should be obliged to provide adequate post-test care and should be given the opportunity to do so.

Chapter 5

Social, ethical and legal issues

While the preceding chapters of this report have been devoted to the significance of DNA diagnostics for individual patients and, in some cases, their relatives, this chapter deals with the issues and options which developments in the field place before society at large, as well as with a number of ethical and legal questions. To this end, a series of issues is set out, which warrant closer examination and require decisions to be made. It is not possible to make a positive or negative judgement of DNA diagnostics in any general, absolute sense. A separate decision will have to be made regarding the desirability of introducing each new diagnostic test or genetic risk assessment technique. Where the decision is made to introduce a particular procedure, the freedom of the individual to decide whether to take advantage of that procedure must be guaranteed. If the individual decides to do so, care providers must endeavour to secure the benefits of testing and to minimize the disadvantages both during the pre-test trajectory and during the post-test trajectory.

5.1 Dealing with risks

5.1.1 General considerations

People are always exposed to risk. Risk is inherent in life itself and risks of varying degree are associated with the numerous environmental factors which can affect health or exert some other influence. In relation to many of these risks, it is not clear whether and, if so, to what extent, the government has a duty to protect the public.

The government has set (in principle, generally applicable) limits on the level of exposure to certain hazardous environmental factors, such as ionizing radiation, chemical substances, noise and other environmental pollutants. The health risks to the individual citizen associated with these factors is often very small, but, because the number of people liable to exposure can be large, the total harm such factors can cause (expressed, for example, in the number of additional cases of leukemia or respiratory disease) can be considerable. Similarly, the government seeks to reduce road accident risks by imposing speed limits, strictly controlling alcohol use, improving the safety of road systems and transport media, making helmet and seat belt use obligatory and so on. Despite these measures, there is always some degree of residual risk, which the citizen apparently accepts; under normal circumstances, few people decide against using their cars or bikes for fear of an accident. The advantages of mobility apparently outweigh the risks (the precise level of which few people really know). Similar situations exist where numerous other potentially hazardous incidental and day-to-day activities are concerned.

In health care, physicians constantly have to weigh up the advantages and disadvantages of carrying out medical procedures on an individual whether it involves diagnostic testing, therapeutic intervention or the prescription of medicinal products with known side-effects. Rightly, the government strictly regulates population screening, taking numerous factors into account. Where the screening of new-born babies is concerned, these factors include the simplicity and reliability of the test and the scope for effective treatment or preventive action in the event of a congenital abnormality or hereditary disease being detected. Provided that the relevant criteria are met, large- scale screening programmes are considered worthwhile, even if the risk they are designed to combat is very small. (The incidence of phenylketonuria, for example, is approximately one in twenty thousand, while the risk of congenital hypothyroidism is one in 3,500). Decisions regarding the value of screening programmes for selected population groups (e.g. cervical smear testing or mammography for women in a particular age group) are based not only on the sensitivity and specificity of the screening method, but also on the level of disease risk and the scope for intervening to improve life expectancy.

Given that a perceived health risk can differ considerably from the objectively determined risk and that considerable variation exists in terms of individual risk perception, it is pertinent to ask whether the government or the relevant professional bodies are really capable of defining a level of risk that is acceptable to individual citizens. The difficulties inherent in defining acceptable risk will be more acutely felt in the years ahead, as it becomes possible to determine individual levels of risk for more and more conditions.

5.1.2 *Genetic risks*

In recent decades, a great deal of research has been conducted in the Netherlands and elsewhere into the attitudes of people at increased genetic risk, particularly in relation to the way family planning decisions are made. This research has yielded some interesting information regarding the various factors which influence such individuals when deciding whether to have children. The likelihood of a child being disabled is certainly one of the things people take into account, but other matters such as first-hand knowledge of a disease or disability and the presence or absence of a healthy child prove to be more important determinants of risk perception and decision-making behaviour. The degree to which a given risk can be perceived in quite different ways by different individuals is also apparent from the demand for prenatal diagnostics from women who become pregnant relatively late in life. Between the ages of thirty-six and forty-five, a woman's chance of having a child with a chromosome abnormality, such as Down's syndrome, rises from about 1 per cent to more than 10 per cent. In North West European countries, 50 to 65 per cent of pregnant women over thirty-five accordingly opt to undergo amniocentesis or chorionic villi sampling. Of those who do not, some have religious or ethical objections to the termination of pregnancy; most, however, simply think that the adverse aspects of testing outweigh the risk.

Recently, data has also been compiled on adults' attitudes to genetic testing designed to determine their personal health risks. Only 10 to 15 per cent of people identified as possible carriers of the gene defects associated with monogenic untreatable conditions such as Huntington's chorea opt for testing. By contrast, where preventive treatment is an option (as is the case with hereditary breast and bowel cancers), about 60 per cent of index patients' immediate relatives do take tests. Another factor that influences people when considering whether to take a DNA test is how the risk faced by the carrier of a mutation compares with the absolute risk in the wider population. Objectively speaking, the rarer a condition is, the greater the number of genes associated with it and the more complex the pattern of interaction between genetic and environmental factors, the less significant the discovery of a mutation becomes. In addition to these objective considerations, there remains the uncertain question of the individual's perception of the increased risk associated with a particular abnormality.

Exploring the limits of DNA diagnostics is bound to become more pressing in the years ahead, especially as microchip technology makes it possible to analyse numerous DNA sequences in large numbers of individuals. In the Committee's view, this means that the debate on limiting genetic risk testing must focus on the nature and implications of the testing; attention must also be given to the desirability (or

otherwise) of prenatal testing for diseases which do not manifest themselves until adulthood, to the possibility of self-testing (see 5.4.2) and to the consequences of establishing that a person faces an abnormal level of genetic risk. The Committee believes that these issues should be explored in relation to each type of test by the relevant professional associations, in consultation with parents' and patients' organizations. However, where testing may be expected to have wider social implications, the debate should not be confined to these groups.

5.2 Approaching patients and patients' relatives

As indicated, decisions regarding the introduction of a genetic risk assessment test depend in part on the availability of treatment and the subjective perception of the increased risk associated with the relevant abnormality. If manifestation of the disease in question can be prevented, delayed or mitigated, many people would want to take a test, even if the increased risk associated with the abnormality is only slight.

The provision of information on the value and likely effects of therapeutic or preventive intervention is problematic insofar as reliable data is not available in many cases. In this context, the Committee sees a clear distinction between cases involving patients who are already ill, in which DNA testing can form part of the processes of diagnosis and treatment, and cases involving patients' healthy relatives, which are medical only insofar as the individuals may be at increased genetic risk.

5.2.1 The patient: information and consent regarding DNA testing

In its report 'Heredity: science and society' (GR89), the Health Council gave extensive consideration to the position of people who undergo heredity analysis. The Committee fully endorses the conclusions and recommendations contained in that report. For convenience, the most important points on the subject of information and consent made in the earlier report are summarized below, as they apply in circumstances involving the diagnostic DNA testing of a patient who is receiving specialist treatment.

The informed consent of the patient, obtained without any form of pressure or coercion, is an absolute precondition of testing. Patients should be informed as fully as possible about all matters which are relevant to them. Such matters include both medical issues "the purpose, nature, risks and consequences" of testing and social issues, such as possible difficulties in obtaining employment or insurance (see 5.3.3). When deciding whether to take a DNA test, a patient may wish to consider the familial implications of testing. Under the Medical Treatment Agreements Act (WGBO), patients have to be informed about such consequences in advance, even if only in a general way. The extent to which a patient who has just learned that he or she has a

medical condition can adequately digest and weigh up such information is open to question, however. Furthermore, the need to process the sometimes very complex information is an undesirable additional burden upon the patient. Where possible, therefore, the test should be carried out and discussed at a time when both the patient and the physician are able to give due attention to the various issues involved, in order to enable the patient to make a genuine informed decision.

The reason for DNA testing is not always to facilitate prognosis or the (further) treatment of the patient. It is often the case, for example, that information obtained using other diagnostic techniques already provides an adequate basis for the formulation of medical policy, but that the isolation of DNA mutations carried by the patient can yield information on the risks faced by his or her blood relatives. Hence, the patient is tested primarily or exclusively in the interest of his or her relatives. In such cases, it is important to ascertain in advance that, if the test result should prove positive, it is appropriate to offer the relatives in question predisposition testing. Furthermore, it should be made clear to the patient why his or her cooperation is requested, and what the consequences of a positive result could be. If the patient's consent is to be valid, familial issues must be one of the central topics of the information given to the patient prior to testing.

The subject of a DNA test is entitled to know its outcome, or to stipulate that he or she should not be informed of the result or a particular element of the result. The care provider is obliged to respect the subject's wishes in this regard. In cases where a person who voluntarily consents to diagnostic DNA testing indicates a wish not to be informed of certain matters, the motivation may often be a desire not to learn of additional or unexpected findings. In such cases, the care provider can occasionally be justified in informing the patient, contrary to his or her instructions, if the importance of respecting the patient's wishes 'is outweighed by the potential disadvantages of withholding the information for the patient or for others' (WGBO).

5.2.2 The handling of genetic data and cell material

All diagnostic DNA tests which are not concerned with the identification of somatic mutations in tumours will yield information on inheritable abnormalities. Genetic data provides information not only about the subject, but also about his or her blood relatives. Given the highly sensitive nature of such data, its retention and use should normally be subject to special safeguards. This point too was emphasized in 'Heredity: science and society'. As well as once more endorsing the points made in that report, the Committee would refer readers to the Guidelines on Heredity Analysis published by the Dutch Association for Health Law (VGR91).

Naturally, personal genetic data is covered by the physician's duty of confidentiality. Where family research is concerned, however, this duty can have complex implications, which are thoroughly considered in 'Heredity: science and society'. The basic principle to emerge is that the subject's relatives should not be informed about the results of a DNA test without the subject's consent. If the subject neither wishes to inform his or her relatives nor consents to them being informed by the physician or anyone acting on the physician's behalf, the relevant individuals may be informed only if the following criteria are met:

- every effort has been made to obtain the subject's consent
- the physician is professionally compromised by his knowledge of the test results
- there is no other way of resolving the problem
- failure to inform the subject's relative(s) would have serious adverse consequences for the individuals in question
- it is almost certain that serious adverse consequences for the subject's relative(s) could be avoided or diminished by informing them of the test results.

Before heredity data may be recorded or retained wholly or partly for a purpose other than strictly to support the process of caring for the subject (e.g. to assist relatives in the future or for use in medical research), the subject must be informed and must give his or her consent. The retention and use of cell material obtained for DNA diagnostic purposes is subject to similar conditions. In this context, readers are referred to the Health Council's report 'Proper use of human tissue' (GR94). Subjects are entitled to withdraw their consent for the retention of such material; if a subject indicates his or her wish for the destruction of stored material, this request must in principle be respected. It is the physician's task to make it clear to the subject that the retention of cell material is potentially very important for the subject personally, for other people (e.g. relatives) and for medical research.

The principles set out above are valid wherever heredity analysis is performed and irrespective of the reasons for it. Hence, steps must be taken to ensure that DNA diagnostic procedures undertaken at centres other than CGCs are subject to the conditions described. The handling of genetic data and cell material within the CGCs is now subject to adequate controls. However, as DNA testing activities spread beyond the CGCs, attention needs to be given to the practical implementation at other centres of the principles outlined above. In this context, the Committee would refer readers to the Personal Data Bill (which, when enacted, will supersede the Data Protection Act). If the Bill becomes law, not only will the processing of personal genetic data be subject to controls, but the formulation of codes of conduct will also be encouraged. Such codes are certainly desirable in relation to the handling of genetic data.

5.2.3 *Approaching test subjects' relatives*

The issues connected with approaching test subjects' relatives are also addressed in the report 'Heredity: science and society' (see also 4.5.1 and 4.5.2). Generally speaking, a physician is under no legal obligation to inform the subject's relatives, but it could be suggested that a moral obligation does exist. It will sometimes clearly be in the blood relatives' interest to know that they may bear a genetic risk. This is particularly likely to be so where the risk is of a condition with serious consequences and where knowledge of the risk could open the way to one or more real treatment options. Given that more and more tests are likely to concern multifactorial conditions and to take place at centres other that CGCs, it is essential that clinical specialists and geneticists together draw up clear guidelines on the circumstances under which family members should be approached. Such guidelines would help care providers to weigh up the issues involved and would reduce the likelihood of serious discrepancies in the policies adopted by individual clinicians or institutions.

Special consideration needs to be given to the question of whether the predisposition testing of relatives constitutes population screening in the sense of the Population Screening Act (WBO). In its report on the scope of the WBO (GR96b), the Health Council's WBO Committee distinguishes between population screening and the family research conducted in CGCs. Family research, it is argued, is a natural consequence of individual health care and relates directly to the original request for medical assistance. What is more, testing is normally made available to the relatives via the person who requested medical assistance. In most cases, therefore, it is reasonable to suggest that family research is 'made available on request', whereas the WBO is concerned with unsolicited testing. The Committee endorses this distinction. However, as DNA diagnostics widens in its scope, family research will be conducted at centres other than CGCs. Nevertheless, testing may be deemed to be made available on a similar basis, provided that the same conditions are met. In the Committee's view, the critical consideration is not where the research is conducted, but whether it is made available as a consequence of an individual request for medical assistance, as opposed to in the context of a systematic attempt to actively trace as many blood relatives as possible ('collective' family research, GR96b). Tests made available on the latter basis would come under the heading of population screening as referred to in the WBO. It should be pointed out that the Committee's views on the scope of the WBO have no legal validity and that the matters outlined above should ideally be addressed in the planned evaluation of the Act.

5.2.4 *Children and other legally incompetent patients*

The position of legally incompetent individuals requires special attention. Minors and legally incompetent adults are, by definition, not competent to decide for themselves whether to undergo a DNA test. The question therefore arises, to what extent are their representatives entitled to consent on their behalf? And how should data from DNA tests on incompetent individuals be handled?

A child is not an extension of its parents and has a right to autonomy, certainly where research into genetic risk factors is concerned. Where children (and other incompetents) are concerned, medical intervention is generally considered justified if it serves the patient's interest to a sufficient extent. Intervention (in this context, DNA testing) does not necessarily have to be *exclusively* in the incompetent's interest to be justified on this basis; intervention which is in the interest of a number of people *including* the patient (e.g. the patient and members of his or her family) is also acceptable. Even if in principle a test is clearly in a minor's personal interest, its performance is only justified if it cannot reasonably be postponed until such a time as the individual is legally competent to make or at least participate in making a decision.

Under the Medical Treatment Agreements Act (WGBO), a person is competent to participate in making a decision at the age of twelve years and to make an independent decision at the age of sixteen years. It should not be forgotten that a minor also has a right *not* to know the outcome of a test. Consequently, diagnostic DNA tests for conditions which do not manifest themselves until later in life should generally not be performed until the subject reaches the age of independent consent.

A minor can benefit from prognostic testing, particularly where there is the possibility of the early detection of disease, leading to prevention or treatment. Even in cases where the object of the test is to detect risk factors over which little or no influence can be exercised, early diagnosis (of, for example, conditions which can appear in early youth) can be beneficial if the prompt recognition of a problem can provide the basis for appropriate care. Nevertheless, whenever the advantages of testing for a minor are less clear, insofar as no adequate means of preventing or treating the condition are available, caution should be exercised. In cases of this kind, protection of the minor is an integral part of good care, which care providers are obliged to give under various statutes, including the WGBO. Professional consensus and guidelines on the acceptability of predictive research in various circumstances, bearing in mind the potential benefits for the subject, are even more important in relation to minors than in relation to incompetent adults.

If the DNA testing of an incompetent patient is considered acceptable, the informed consent of the patient's representative will be required. The WGBO

identifies the parties who may act as patients' representatives. Where a minor is concerned, the parents normally fulfil this role. As indicated above, where a child twelve or more years old is concerned, the child should also consent.

Finally, the testing of incompetent subjects raises special questions about the retention and use of data and cell material obtained for DNA diagnostic purposes. For example, should it be compulsory to inform a sixteen-year-old regarding the existence of genetic data obtained from DNA tests performed before he or she reached the age of independent consent? Under such circumstances, should the young person have the right to inspect the data, or to insist on its destruction, or to remain ignorant (permanently or temporarily) of its import? Insufficient attention has so far been given to questions such as these. Given the developments taking place in and the expansion of diagnostic DNA testing, this situation should be rectified promptly.

5.2.5 *Value and effect of post-test options*

Because the identification of genetic risk factors has only recently become possible and is therefore in an early phase of development, little is yet known about what motivates people to pursue particular post-test options or about the effectiveness of such options.

On the basis of inheritance pattern data and family anamneses, it has for some time been possible to identify people liable to contract certain hereditary cancers of the large intestine and to offer them regular colonoscopy. Recent identification of a number of the gene mutations associated with the disease has facilitated more precise selection of patients' healthy relatives. Although the follow-up programme entails early medicalization and although regular colonoscopy is a physical and psychological burden, the demonstrable benefits of early diagnosis and surgery, in terms of increased life expectancy, make it easier for the risk carrier to decide what course of action to take.

Preventive mastectomy and ovariectomy for carriers of BRCA 1 or 2 mutations is probably beneficial, but this has yet to be convincingly demonstrated. Nevertheless, more than half of the risk carriers identified at some Dutch centres opt for a double mastectomy and 87 per cent for an ovariectomy once their families are complete. In other centres, the percentages are lower, while in some other countries, a vigorous debate is still in progress regarding the desirability of carrier testing and surgery of the kind described.

It is not clear how willing people would be to modify their behaviour or lifestyles on the basis of their genetic risk patterns (if, for instance, test data indicated that they were at genetically increased risk of diabetes or cardiovascular disease). General

public information campaigns designed to persuade people to adopt more healthy lifestyles have not tended to be particularly successful. Individualized advice to the same effect based upon known genetic risk might, however, produce a better response.

Genetic testing will lead to the identification not only of individuals who are at increased risk, but also of people whose genetic make-up makes them less than averagely susceptible to a particular condition. The possibility cannot be excluded that such people would be inclined to complacency when it came to participating in screening programmes or in their attitude towards hazards such as smoking, drinking, overeating, etc.

Opinion is divided as to whether predisposition testing is justified if the associated post-test options do not offer the prospect of improved health. Some commentators are against testing under such circumstances, while others believe people have the right to information regarding the disease risks they face and should be given the opportunity to plan their families and their lives accordingly. These considerations, it is argued, are sufficient justification for testing for genetic risk factors, even if the disease is untreatable. In practice, few people take the opportunity to undergo presymptomatic diagnostic DNA tests for (monogenic) diseases such as Huntington's chorea. Several genetic risk factors are known to play a role in certain multifactorial conditions, such as Alzheimer's disease; to date, the medical professions have not come out in favour of testing for these risk factors, partly because there is no prospect of prevention or treatment, and partly because the test results are not sufficiently decisive regarding the subsequent development of dementia. The Committee too would wish to see restraint exercised in relation to DNA testing for such conditions.

The Committee believes it is very important that people are well informed about genetic risk factors, about their interaction with environmental factors and about the potential benefits and limitations of intervention for those known to be at risk. On the one hand, every opportunity to prevent, limit or delay the manifestation of disease should be taken; on the other hand, people should not be compelled to accept medical intervention and should be allowed to determine their own lifestyles. Nevertheless, the Committee expects that the widening scope for identifying genetic risk factors will lead to the lives of more and more healthy, young adults becoming increasingly medicalized. This process will become even more firmly established if professional medical advice or intervention is deemed appropriate for people with no demonstrable functional abnormalities, complaints or symptoms, on the basis of their genetic risk profiles.

5.3 Social consequences

5.3.1 Background and expectations

Through the human genome project and other initiatives, all human genes will be localized and their functions determined in the near future. Through parallel developments, more will be learned about gene interaction and about the clinical expression of gene mutations in relation to specific sequences in normal genes. Furthermore, new computer models and epidemiological studies will shed light on the way genetic make-up, environmental and behavioural factors interact, the latter being themselves genetically determined as well as socially determined. In an increasing number of cases, it will soon be theoretically possible to draw up an individual's genetic profile, showing the gene sequences which increase and decrease risk. It will become apparent that each person is, to a greater or lesser extent, genetically susceptible to certain conditions, which are also influenced by environmental factors. However, the smaller the impact of an individual mutation and the greater the degree of interaction with other genes and environmental factors, the less significant a genetic profile will be. Paradoxically, therefore, as the volume of available molecular data grows, so the scope for using such data to define a single set of risk- reducing guidelines and policies may diminish. Before this point is reached, however, the genetic defects associated with certain monogenic hereditary diseases and some common multifactorial conditions will be identified (see chapter 3).

There is a danger that carriers with a particular risk profile will not only become medicalized (see previous subsection) but also experience social disadvantages. These may stem from relational problems or a disinclination to study or work induced by a preoccupation with anticipated health problems. Such individuals may become fatalistic or excessively deterministic because 'nothing can be done, anyway'. An obsessive attitude towards behavioural and lifestyle changes could become an impediment to normal personal development, as could feelings of guilt towards immediate relatives and children (see chapter 4).

It is important to consider the extent to which the citizens of the future will retain any real freedom to decide whether to be tested for hereditary risk factors. Social pressures may make it very difficult to decline to modify one's behaviour or lifestyle so as to offset a particular hereditary predisposition. It is also possible that people with an 'unfavourable' hereditary predisposition might be denied automatic access to important social provisions or that increasing commercialization might have an adverse impact.

The Committee would point out that most of the (clinical) medical research conducted to date has focused on the hereditary factors associated with diseases and disabilities. In the long term, however, scientific understanding of the hereditary factors determining normal physical and mental characteristics is likely to increase (Gal97c). Articles have already been published linking certain DNA sequences with male homosexuality, impulsive-aggressive behaviour and novelty seeking. Such matters are not strictly within the Committee's remit and this area of science is in any case in its infancy; nevertheless, the possibility of DNA testing being used in areas such as these must ultimately be addressed.

Given the nature of the public and political reaction to developments such as the genetic modification of animals and foodstuffs, or, more recently, the cloning of mammals, the Committee believes that considerable thought must be given to early, balanced public information campaigns on scientific developments in the field of genetics and their potential social significance and applications. As our knowledge of genetic risk factors and their significance in interaction with the environment increases, genetic information will more readily be seen as commonplace, as one of the many kinds of data to which we have access. Wherever there is real scope for reducing the likelihood of disease for an individual or his or her offspring, adequate information and assistance should be made available. Good information material should discourage people from worrying unnecessarily or feeling powerless in relation to their own health, but should not deny the existence of real problems. The importance of ensuring information quality is strengthened by the manifold, diverse and global sources of information such as the Internet.

5.3.2 Access to care

Between the point at which a genetic risk factor is discovered in a scientific research laboratory and the point at which predisposition testing and follow-up are introduced to regular health care, there are several junctures at which decisions have to be made. First, it should be clear that meaningful conclusions can be drawn from the identification of a gene abnormality. The reason for this is that, if the clinical significance of a particular mutation is not yet apparent, testing for that mutation is not appropriate from the point of view of patient care, however desirable it may be for scientific purposes. Steps therefore need to be taken to ensure that tests are not introduced to general health care directly from the laboratory, without their clinical significance first being determined. Once the medical indication range has been carefully defined on the basis of what is known at the time, the government and insurers have to decide whether the cost of the test should be covered by health

insurance, bearing in mind that availability of the test must be linked to availability of follow-up, support and medical care designed to minimize risk.

Various issues need to be taken into account when considering whether the test should be made available. Is the test to be conducted on a patient or on a healthy person? Is the test a natural consequence of providing an index patient with medical assistance or is it considered in response to an independently initiated request? Do options exist for the reduction of risk?

If a diagnostic DNA test is clearly beneficial in terms of patient care, the Committee believes that the access and insurance arrangements should be no different from those which apply to other diagnostic procedures. Nevertheless, special care is required in relation to certain points because of the significance that the results of such tests can have for the patient's relatives. Where the benefit of a test in terms of patient care is less clear, but the importance of the results for patients' relatives is potentially considerable, tests on patients should come under the same heading as predisposition testing when it comes to decisions regarding availability, indications and insurance coverage.

Where the predisposition testing of patients' healthy relatives is concerned, distinction should be made between cases in which relatives are informed by an index patient (in consultation with a physician) about the possible significance and implications for them of a gene abnormality found in the patient, and cases in which a healthy individual independently asks for a predisposition test on the basis of his or her family history.

The predisposition testing of healthy individuals is medically and socially important mainly in circumstances where it is possible to substantially reduce the risk of a disease manifesting itself. A great deal of research is still necessary in this field, including longitudinal and long-term studies. Hence, a dilemma exists: on the one hand a cautious approach to the introduction of diagnostic tests with serious implications and unproven benefits is advisable; on the other hand, waiting for conclusive research results would mean withholding potentially valuable procedures for years to come. This dilemma can be resolved by initially linking predisposition testing to scientific evaluation projects wherever possible. For the time being, a test should be considered worthwhile if it appears likely that the options open to known carriers of the relevant genetic defect are more beneficial than general preventive measures.

Access to predisposition testing and to post-test care should be linked; if predisposition testing is indicated in a given case, appropriate follow-up, support and medical options should be open to the individual concerned, if warranted by the result and the level of risk. This is already the case in relation to testing for hereditary cancers of the breast and large intestine.

Where no scope exists for reducing the likelihood of disease manifestation in carriers of the relevant gene abnormality or their offspring, predisposition testing has no medical justification. However, given the very selective use so far made of testing for pressing psychological reasons, it is debatable whether there is any reason to withhold psychologically motivated testing.

The Committee believes that in the future, the government's role will have to be carefully examined. In situations such as those described above, should the state regulate the provision of DNA testing, or allow the forces of supply and demand free rein, irrespective of the availability of preventive measures or effective treatment methods? In this context, the development of 'DIY testing' should be taken into consideration as well (see 5.4.2).

5.3.3 *Access to social provisions*

The question of the influence which ongoing developments in genetic testing and screening might have on access to social provisions has already been thoroughly explored in two earlier Health Council reports. The emphasis in these reports was primarily on access to the labour market and to private life insurance, personal employment disability insurance and pension policies. Where private insurance (as opposed to social insurance) is concerned, cover is not compulsory and the insurer is not obliged to accept any given proposer. Private insurance contracts are not governed by the solidarity principle (whereby the strong pay for the weak), but by the equivalence principle (whereby the premium reflects the insured risk). Insurers in the Netherlands and abroad are concerned about the threat to the insurance system associated with inequitable access to information and self-selection. For their part, parents' organizations, patients' organizations and care providers emphasize the need to protect individual privacy and the danger that people may be deterred from seeking medically important heredity analysis because of a fear of losing access to private insurance and other social provisions.

In 'Heredity: science and society' (GR89), the Health Council advised against allowing employers or insurers to make genetic testing a condition of employment or insurance. The Council also indicated that employers' monitoring programmes were only acceptable if participation was voluntary or, in exceptional circumstances, necessary to safeguard the health of the employee in question or a third party. With regard to the use of data from previous tests, the Council recommended qualifying the obligation which an individual has, to declare relevant information when proposing an insurance policy, so that the declaration of earlier heredity analysis results would not be necessary in cases where the sum insured was below a certain limit. Similar recommendations were made in the report entitled 'Genetic screening' (GR94), which

also highlighted the fact that the insurers had, in line with the Council's 1989 report, declared a moratorium on heredity analysis. The report nevertheless came out in favour of statutory regulation, both in the field of genetic testing and in the field of pre-employment medicals.

In April 1997, the government introduced statutory control in the form of the Medical Examinations Act, which regulates medical testing in connection with the closure of contracts of employment or the forms of insurance referred to above. The main international (primarily European) aspects of these issues were extensively investigated and discussed when the legislation was being drafted. The Act prohibits research that would infringe unreasonably upon the privacy of the subject; this includes at least research conducted for the specific purpose of obtaining information about (the likelihood of) the occurrence of a serious, untreatable disease. Pre-employment medicals are allowed only where the nature of the employment is such that the employer must make special requirements regarding the medical fitness of the employee. In the field of insurance, the Act not only prohibits research into serious, untreatable diseases but also restricts the insurer's right to ask questions about serious conditions unless the sum insured exceeds a prescribed 'enquiry limit' (NLG 300,000). The Medical Examinations Act requires the interested parties to undertake additional regulatory activities themselves. The forms of self-regulation subsequently introduced, such as the insurers' indefinite moratorium introduced in 1995, represent the first steps in this direction. The Committee regards the Medical Examinations Act as an important milestone, not only in the protection of privacy and the aversion of unacceptable forms of social inequality, but also in assuring unfettered access to heredity analysis. Nevertheless, the development and spread of DNA testing referred to in this report is such that the issue of heredity analysis and access to social provisions remains topical. Consequently, it is important to ensure that the Medical Examinations Act does in practice prevent undesirable forms of selection on the basis of genetic information. To this end, the Committee would like to see the relevant parties expedite introduction of the self-regulatory systems called for in the Act.

The Committee is reluctant to make predictions regarding long-term developments in this field. Some commentators have highlighted the relativity of the predictive value of risk factors associated with common multifactorial conditions and see little reason for the insurers to classify risk in a more technologically sophisticated manner. Others have suggested that in the long term, as many risk factors as possible will be identified and that the public will become so familiar with individual risks and the scope for prevention and treatment, that greater openness can be introduced at the point of access to social provisions. The notion that these processes will ultimately lead to the

abandonment of distinctions based on risk categories is considered to be of dubious validity by the Committee.

5.4 The role of commercial organizations

In relation to the role of commercial organizations, it is appropriate to distinguish between developments in the field of diagnostic tests and in the field of treatment methods.

5.4.1 Diagnostic tests

The situation in Europe differs from that in the United States, insofar as commercial organizations do not have a significant role in general laboratory testing in connection with the diagnosis of disease. In the Netherlands, such testing takes place almost entirely in a number of clinical diagnostic laboratories, which are linked to one or more hospitals or serve general practitioners. Certain special analyses are performed in laboratories attached to independent institutions, such as the Blood Transfusion Service's central laboratory (CLB), the Dutch Cancer Institute and the National Institute of Public Health, and the Environment (RIVM) in Bilthoven.

Diagnostic DNA analysis is presently concentrated largely in the laboratories of the seven regional clinical genetics foundations, which have close ties with the university hospitals and medical faculties. In oncology, tests for germline mutations are also conducted by the Dutch Cancer Institute/Antoni van Leeuwenhoek Hospital (NKI/AvL), while some tests in other fields are performed at the CLB in Amsterdam and a few large peripheral clinical chemistry laboratories.

Even in the Netherlands, however, commercial organizations do play an indirect role in DNA diagnostics, since they supply almost all the necessary restriction enzymes, polymerases and other substances, as well as the analytical equipment, which before long will include microchip apparatus (with which samples from hundreds of individuals can be tested for numerous mutations at the same time, or tens of thousands of samples can be checked for a single mutation). Complete test kits are available for some relatively common gene mutations, promoting the decentralization of DNA diagnostics.

According to foreign business experts, the development of new diagnostic methods is not one of the pharmaceutical industry's main objectives. The focus for the time being remains principally on tests for common mutations associated with monogenic hereditary diseases, such as cystic fibrosis and fragile X syndrome. The widespread use of such tests is apparently unlikely until at least 2002 or so, because of the time required to integrate existing components to form convenient and functionally reliable

analytical kits, to complete clinical trials (one to two years) and to obtain a licence from the American Food and Drug Administration (FDA) or an equivalent authority. Nevertheless, in the United States there are a few smaller companies who will perform certain DNA analyses on a commercial basis. The analyses in question include testing suspected carriers of hereditary breast cancer for the BRCA 1 and BRCA 2 mutations; this involves sequencing entire genes. Although certain American companies involved in such work have plans to open offices in Europe, the Committee believes that, for several years to come, it will be preferable for the Netherlands to retain its current approach to laboratory diagnostics. This issue is considered more closely in chapter 6. Critically, close cooperation must be ensured between the laboratory and the parties responsible for the pre-test and post-test trajectories. The need to secure coordination would be all the more pressing if commercial laboratories were able to offer their services direct to the public. The fact that such a development is already being considered in some countries is apparent from the code of practice recently published by the UK Department of Health's Advisory Committee on Genetic Testing (ACGT97). The code covers genetic testing both for monogenic diseases and for risk factors associated with common multifactorial conditions; it suggests that anyone who intends to offer genetic tests directly to the public should first submit a proposal to the Advisory Committee, which would assess the quality of the proposal. The Committee would also publish 'white' and 'black' lists of testing service providers. Service providers would additionally be required to forward a copy of the test result to the subject's GP. More generally, it is indicated that genetic testing services should not be made available unless adequate information and post-test support were assured. One of the main arguments in favour of this approach is that a genetic test is relevant not only to the interest of the subject, but frequently also to the interests of the subject's relatives. As indicated, the Committee does not favour DNA testing services being made available directly to the public by commercial laboratories. It is partly to prevent such a development that the Committee believes germline DNA diagnostics should for the time being generally remain subject to licensing under Section 2 of the WBMV (see chapter 6).

5.4.2 'DIY testing'

The problem of 'DIY testing' requires special attention. Outside the Netherlands, DNA kits can already be purchased to test for the presence of the most common mutations associated with cystic fibrosis, for example. The market for these tests is not restricted primarily to expert care providers. In view of recent developments, it is time to decide whether the government can and should act to regulate activities of this kind, the problems which have previously been highlighted by the Health Council and others

(GR89, Gev96). One regulatory option would be to make the supply of test kits subject to certain conditions, for instance under the provisions of the Medical Device Act. Another potential problem here is how such controls on the availability of self-diagnostic kits could be harmonized with European law on *in vitro* diagnostics. It is debatable whether in the longer term the introduction of such kits could actually be prevented; the Netherlands is not an island and it cannot stand aside from international developments indefinitely. Indeed, according to the parents' and patients' organization, VSOP, test kits can already be ordered from abroad via the Internet. In spite of these considerations, the Committee is opposed to DIY kits being made freely available in the immediate future. Too much uncertainty still exists about the consequences of self-diagnosis for the subject and the subject's relatives. Furthermore, proper follow-up could not be assured if such tests entered widespread use. The provision of consultative services by the CGCs is expensive and there is not presently the capacity to cope with an upsurge in demand; in first-line health care, there is currently insufficient expertise in the field of (clinical) genetic problems. In the next five years or so, the emphasis must be on coordinating the activities of GPs, psychosocial care providers, the medical specialists involved in DNA diagnostics and the CGCs. Only once coordination has been achieved and care providers in the various fields are fully conversant with and able to devote their time to post-test matters should the marketing of DIY test kits for specified risk factors be considered.

It may be that circumstances will change in due course, making a review of this issue appropriate. At such a time, each type of test should be considered individually and consideration should be given not only to the potential disadvantages of unrestricted availability, but also to the potential benefits. These include the individual's freedom of choice and access to information about the consequences of and options associated with a particular outcome, based not merely upon a physician's assessment but upon an independent personal risk evaluation. It is likely that patients' and consumers' organizations, who are already becoming organized at a European level, will press for the availability of DIY test kits. If, therefore, the government intends to prevent the sale of such kits in the longer term, it must at least be able to justify its stance.

5.4.3 Treatment methods

Pharmaceutical companies expect modern DNA technology to be very useful in the development of new medicinal products. Medicinal products nowadays are often designed to interact effectively with specific molecular processes inside or outside the cell and, where possible, to act only upon certain types of cell or tissue. The level of expectation is reflected in the number of biotechnology companies that have sprung

up, especially in the United States. In the US alone, there were already about 1,100 such companies by the end of 1996, most of them quite small (less than a hundred employees). By 2003, these firms are expected to turn over 12.5 billion dollars (Dib96). Compared with North America, Europe currently has around half as many biotechnology companies, which together employ only a quarter of the number of people.

It is estimated that the average cost of developing an effective medicinal product is five hundred million guilders, and it takes at least ten years before a patented new product can be launched onto the market. Since eight or nine out of every ten medicinal products fail to sell well enough to cover the cost of development, those that do prove popular tend to be (very) expensive. Not surprisingly, the pharmaceutical industry tends to concentrate on common, multifactorial diseases. Using knowledge of the most important molecular and cellular mechanisms involved in a disease, therapeutic strategies are sought with a view to negating or limiting the main functional problems. These strategies do not always address the problems associated with defective genes; in many cases, they seek to make use of alternative biochemical routes or to employ substances which are more effective than normal (extra)cellular components in promoting or inhibiting particular reactions.

In future, medicinal products will be targeted more and more specifically; not only will they be designed to control specific genetically determined disease risks and associated molecular mechanisms, but they will also be adapted to certain hereditary factors which influence the side-effects or efficacy of the medicinal product itself (as in the example given earlier, where a particular genetic defect can inhibit the function of cholesterol-reducing drugs). It is likely that, in the future, the prescription of medicines will be individualized, partly on the basis of genetic profile.

The question is, how expensive will such developments be, and what ramifications will the cost have for the availability of medicinal products? The cost problem is already making itself felt on a small scale with the treatment of patients with certain rare hereditary metabolic diseases, who are kept relatively healthy by the regular administration of a protein which they cannot produce themselves due to a genetic defect. For example, in the Netherlands there are a few dozen people with a form of Gaucher’s disease who benefit from regular doses of the enzyme beta glucocerebrosidase. Production and purification of this protein are expensive and it is available only from a single American company. Although the cost of treatment varies from one country to another, it is usually tens of thousands of dollars a year.

By modifying animal genes in a particular way (transgenesis), it is possible to breed animals whose milk contains a particular human protein, simplifying production and purification and providing for availability on a larger scale. However, transgenesis

and animal cloning is not universally regarded as ethically acceptable. Various countries, including some European countries, have or are preparing legislation in this field. In the Netherlands, the genetic modification of animals is subject to a general prohibition with certain exceptions (see the Decree on Animal Biotechnology). It is important that the application of such legislation takes account of the need to develop efficacious and cost-effective therapies. This aspect was given due consideration in the Health Council's reports 'Research with embryonic stem cells' (GR97a) and 'The transplantation of foetal material' (GR97b).

It is open to question whether, as increasing attention is devoted to common multifactorial conditions such as cancer, cardiovascular disease, diabetes, rheumatism, multiple sclerosis, asthma and neurodegenerative disease, enough is being done to improve treatment prospects for patients with rare hereditary diseases. Discussions involving the medical profession, the government and the business community would appear to be warranted in the near future. Both nationally and internationally, the authorities are looking to encourage research into (therapies for) rare diseases. The EU, for instance, has a rare diseases action programme and is preparing a draft directive on 'orphan drugs'. The Committee would like to see rare hereditary diseases addressed through such initiatives.

Chapter 6

Organization and regulation: recommendations

This chapter sets out the Committee's recommendations regarding the future organization and regulation of DNA diagnostics. These recommendations are based on the developments outlined in the preceding chapters, on the possibilities they create and on their implications. Certain points should be made at the outset. Two categorical clinical centres, on a par with university hospitals, have traditionally played a major role in the field of oncology, which is very important in relation to DNA diagnostics. These are the Daniel den Hoed Clinic (DDHK) and the Dutch Cancer Institute/Antoni van Leeuwenhoek Hospital (NKI/AvL). The DDHK is now organizationally part of a university hospital, but the NKI/AvL is not. In the following paragraphs, the term 'university hospital' is intended to include the oncological centres.

6.1 The present situation

6.1.1 Organizational arrangements

Under the existing statutory regulations (see 6.1.2), diagnostic DNA testing for monogenic diseases and certain hereditary cancers is concentrated largely in and around the CGCs, although some tests for hereditary cancers are conducted at one of the oncological centres. Several other large laboratories, including the CLB and the Anthropogenetic Laboratory in Leiden, are involved in DNA testing for hereditary blood diseases. Diagnostics in connection with hereditary eye conditions is concentrated primarily in the Inter-university Ophthalmology Institute. Now that some

DNA tests are relatively simple to perform, clinical diagnostics laboratories are starting to show an interest in adding the relevant analyses to the range of services they provide. Thus, it would appear that the statutory prohibition on such testing can be ignored or circumvented.

The CGCs are not heavily involved in diagnostic testing for genetic risk factors. Testing for mutations such as factor V Leiden and for the APOE and HLA genes is conducted at various centres. No clear organizational or financial structure is yet in place for DNA diagnostic activities in connection with these risk factors. To date, most of the testing carried out in this field has been in the context of research projects, but a gradual shift towards patient care is now taking place. For both practical and financial purposes, chromosomal examinations performed in connection with 'proliferative bone marrow malfunctions' (see 3.5) fall within the CGCs' remit, on the basis that the technology involved is comparable with that used for other CGC activities. However, the Ministry of Health, Welfare and Sport, the CGCs and the care insurers agree that the present financing arrangements are inappropriate, since the testing is not a form of heredity analysis. The logical follow-on from this chromosome research, DNA diagnostics, is not covered by these arrangements and is proving hard to get off the ground: the organizational arrangements vary and there is no systematic financing.

Diagnostic DNA testing for somatic mutations associated with solid tumours is presently in a developmental phase and therefore financed from research funds. As with testing in connection with haemato-oncological conditions, the introduction of somatic mutation testing for normal patient care purposes is hampered by the absence of systematic financing.

DNA analyses in connection with patient-related scientific research are conducted at numerous locations. The organizational arrangements differ considerably from one clinical specialism to another and from one university hospital to another, depending on the emphasis, the size of the relevant research group, the available expertise, the level of interest from the various parties and the developmental history of DNA testing and cooperation.

The Committee concludes that the present organizational provisions for DNA diagnostics are no longer appropriate for or adequate to cope with the growing demand and the broadening indication range, with all its implications for treatment and prevention. The CGCs are not in a position to meet the anticipated demand, either in quantitative or qualitative terms. DNA testing for common multifactorial diseases needs to be more closely linked to the clinical centres where indication, treatment and follow-up also take place. Laboratory expertise in this field must also be integrated. Systematic financing arrangements are required for diagnostic DNA testing in

connection with acquired abnormalities of the genetic material, in particular somatic mutations.

6.1.2 *The existing regulatory system*

Until the new Special Medical Services Act (WBMV) came into force in November 1997, postnatal DNA diagnostics, as an activity within the field of 'clinical genetic testing and heredity advice', fell within the scope of Section 18 of the Hospital Provision Act (WZV). These regulations have been applied because of the "significant social implications" of the activities in question and in order to achieve "managed and regulated implementation" with a view to controlling quality, costs and efficiency. The wording of the planning decree introduces a number of specifications and restrictions: postnatal (chromosome and) DNA testing comes within the scope of the regulatory system if it is conducted "in connection with the diagnosis of congenital or hereditary abnormalities, the identification of carriers or the diagnosis of abnormalities in sexual development or function". The practical expression of this requirement in the 1996 covenant between the CGCs and the health insurers restricts DNA diagnostics largely to testing in connection with monogenic conditions (Ver95). Thus, the position of testing for hereditary risk factors is unclear, since individual risk factors are passed on in accordance with a Mendelian pattern, but in most cases the associated diseases are multifactorial and brought about by a combination of various genes and environmental factors.

Heredity advice came within the scope of the provisions insofar as it was "of a complex nature". The pre-test and post-test support activities referred to in this report can be seen as an extension of heredity advice, necessitated by the increasing diversity of the advisory tasks and of the consequences of testing; support activities now extend beyond heredity advice.

The long-term clinical follow-up sometimes necessary for individuals who carry genetic risk factors is outside the scope of the provisions and no alternative regulatory arrangements have been made. In the field of acquired abnormalities of the genetic material, only "postnatal *chromosomal* examinations for diagnostic and prognostic purposes in connection with proliferative malfunctions of the bone marrow" have been brought within the scope of Section 18. Thus, DNA testing for somatic mutations is not covered by the present planning decree.

The statutory prohibitions contained in Section 18 of the WZV have now been superseded by comparable provisions in Section 2 of the WBMV, but the criteria for application remain unchanged. Under the new legislation, controls are applied to diagnostic and therapeutic activities:

- whose application in the field of patient care is to a significant extent in a developmental phase, but which cannot any longer properly be regarded as experimental
- which, from the point of view of quality, efficiency and cost management, are best confined to a sufficiently small number of locations that provision may be regarded as supra-regional or national
- which, without the safeguards made possible by application of Section 18, would entail unacceptable risk, insofar as the quality of the functions could not be sufficiently assured, given the social and ethical issues associated with application of those functions or which would not be undertaken at all or not to a sufficient extent, due primarily to the expensive nature of the functions (financial risk).

6.1.3 Developments and changes in the regulatory system

The Committee has observed a change in departmental policy on application of the prohibition provisions: on the basis of the Quality of Care (Institutions) Act and the Individual Health Care Professions Act, responsibility for the quality of care is being shifted primarily to the field. A new procedure for making decisions regarding the financing of activities which then came under Section 18 of the WZV, was agreed in 1995 and implemented through the Outline Agreement between the Minister and the Association of University Hospitals. Under this procedure, the allocation of additional financial resources for Section 18 activities requires retrospective justification. It is expected that the prohibition provisions will be applied mainly on the basis of prescribed quality conditions which necessitate concentration and supra-regional arrangements. Exceptional social or ethical considerations are also likely to be taken into account. By pursuing this policy, the Minister appears to wish to give the parties active in the field a greater say in defining indication ranges and the requirements. This necessitates stricter self-regulation within the profession and amongst the care institutions, with scope for binding agreements on the division of responsibilities and on concentration. At the same time, health insurers are being given the additional responsibility of finding ways of funding new, medically justified forms of care.

The Committee has established that, since the introduction of the new financing arrangements, the inclusion of new diagnostic and care procedures within the scope of Section 18 of the WZV or Section 2 of the WBMV still seems, in practice, to provide safeguards. In the absence of arrangements for dedicated financing, this approach has the advantage that the procedures in question are at least included in the negotiations on the Outline Agreement and in the talks with the health insurers. Against this background, the extended scope for regulation provided by the WBMV is welcome. Section 8 of the Act provides for the targeted promotion of functions which are not

classed as “specific medical procedures”, but which are deemed to require promotion in one or more centres with a view to bringing the quality of care, or certain care aspects, up to a higher level, and which are felt to warrant a degree of control. According to the explanatory notes, Section 8 can also be used to ease the transfer of a procedure out of the licensing regime, thereby making it more likely that procedures will be ‘declassified’.

6.2 Controlled development: quality requirements and regulation

The Committee believes that in future DNA diagnostic techniques will quite properly be used for a wider range of purposes than at present. In view of the individual and social implications, the necessity of gaining knowledge regarding the clinical consequences, the cost and the pressure to introduce new techniques generated by medical research and exerted by the business community, the Committee believes it is necessary to create the conditions under which controlled development can take place. To this end, the Committee recommends the imposition of general quality requirements on DNA diagnostics, the definition of complex forms of DNA diagnostics whose concentration in one or more centres is desirable and the identification of certain forms of complex DNA diagnostics which require statutory regulation.

6.2.1 Quality requirements

The Committee believes that special quality requirements should be introduced, covering not only the technical aspects of testing, but also the circumstances under which testing is indicated, integration in clinical management, consultation and follow-up. The requirements should at least relate to the following matters:

- the expertise and facilities necessary for:
  - determining whether diagnostic DNA testing is indicated for a patient and whether a given test is appropriate, necessary and sufficient to provide the information sought
  - performing and interpreting the analysis
  - interpreting the clinical significance of the findings
- participation in mutual quality control schemes
- the availability of sufficient expertise in the field of molecular genetics
- cooperation with other laboratories
- the involvement of or referral to a more specialized laboratory or department in appropriate circumstances.

DNA testing for hereditary mutations should additionally be subject to special requirements covering the pre-test and post-test trajectories and dealing with matters such as the following:

- the expertise and facilities for:
  - determining the risk
  - determining whether diagnostic DNA testing is indicated for healthy individuals
  - the scope for influencing the risk within the relevant clinical field
  - informing, advising and, where appropriate, supporting index patients and their healthy relatives both when testing is being considered and after testing
- reporting and recording data
- ensuring provisions for and quality of that family research, if desired
- ensuring provisions for participation in a follow-up programme remains an option.

The Committee would like to see detailed quality requirements based on the above integrated within quality policy by hospitals, laboratories and professional bodies; the requirements should also serve as a point of reference for the agreements made with health insurers. The requirements regarding diagnostic testing for hereditary mutations should also apply to DNA diagnostics in clinical research, wherever such research involves consultation and family investigation.

6.2.2 *The distinction between complex and non-complex forms of testing*

The various diagnostic DNA tests differ considerably in terms of their complexity. This not only applies to the technical aspects; there can also be marked differences in the complexity of determining whether testing is indicated, of interpreting the findings and of the implications for patients, their relatives and other individuals at increased risk of disease. The Committee therefore believes that it is necessary to classify tests on the basis of complexity*. Where relatively 'simple' tests are concerned, the general quality requirements should provide sufficient safeguards; where complex tests are concerned, however, explicit concentration is necessary in the interests of quality, efficiency and the management of the implications. The following criteria should be used for the classification of a test:

- the complexity of determining whether a test is indicated, of the technical aspects and of interpreting the findings
- the frequency with which the test is performed
- the complexity of clinical interpretation

* In this report, the term 'complex' does not have the same meaning as in the Decree on Clinical Genetic Testing and Heredity Advice (see 6.1.2).

- the speed of scientific developments and the importance of linking DNA diagnostics to clinical research and evaluation
- the extent to which the test is linked to forms of treatment and follow-up which themselves warrant concentration

Where tests for hereditary mutations are concerned, the following criteria should be used as well:

- the levels of relative and absolute risk and the extent to which risk data is available
- the nature and seriousness of the consequences for index patients and healthy carriers, including the infrastructural and capacity implications of providing information, advice and support
- the existence and nature of post-test options for the reduction of disease risk and the desirability of involving healthy risk carriers in follow-up programmes
- the nature of other post-test options
- the desirability of predisposition testing on children
- the importance of links with genetic epidemiological research and the associated requirements regarding expertise and infrastructure in the field of information and computer technology.

At present, the Committee believes that most diagnostic DNA tests should be classed as complex. In the future, the expectation is that decisions regarding the need for concentration will depend less on the technology involved in a test, and more on the circumstances under which patient testing is indicated and on the consequences for patients and, where hereditary mutations are concerned, patients' healthy relatives and subsequent generations. Judged on this basis, diagnostic DNA tests for monogenic diseases and monogenic variants will generally be regarded as complex; so too, for a while at least, will somatic DNA diagnostics. Tests for hereditary risk factors may be complex or non-complex. Non-complex tests of this kind include those for the factor V Leiden mutation and HLA-B27 classification tests, used in suspected cases of Bechterew's disease. In due course, the Committee expects that most diagnostic DNA tests for the prediction of therapy response and HLA tissue classification tests used for patient diagnostics can be treated as non-complex as well.

The Committee would ultimately like to see dynamics in the division of responsibilities; however, given the issues outlined above, a considerable degree of concentration is desirable for the time being. Under the present government policy, concentration must be effected through agreements between the main actors in the field (the medical professions, the hospital and laboratory organizations and the health insurers), except in cases where grounds exist for statutory control in the form of

prohibitions or targeted promotion. The following subsection is devoted to the areas in which government involvement is considered necessary or desirable by the Committee.

6.2.3 Recommendations regarding statutory regulation

Bearing in mind the criteria for application of Sections 2 and 8 of the WBMV, the Committee would make a number of recommendations, which are set out in the paragraphs below.

Complex DNA diagnostics in connection with germline mutations

In terms of the interests and issues involved, tests for germline mutations have a significance which goes beyond the immediate individual request for assistance; such tests are potentially significant for people other than the subject. An individual who is informed about his or her genetic make-up may be obliged to make some very difficult decisions regarding what course of action to take, and these decisions can sometime have implications for the offspring. A test for an inheritable mutation always yields information which is relevant to the subject's relatives. In view of these considerations, such testing should be subject to special requirements concerning the provision of information, counselling, registration, the protection of privacy and data retention. Given the special social, ethical and psychological issues at stake, the Committee believes that complex germ line DNA diagnostics should be subject to statutory control under Section 2 of the WBMV. Various other arguments also apply. With a few exceptions, this field of DNA diagnostics is still complex, both in terms of the test technology and in terms of the interpretation of test data in relation to other diagnostic information. While more and more is being learned about the mutations associated with various diseases, relatively little is yet known about the clinical interpretation of the available information or about the consequences for treatment and follow-up. Furthermore, the concentration of expertise *and* patient material is necessary for the development of insight into each type of disease; supra-regional arrangements are therefore required in this area. In the field of predisposition testing, the boundary between family research carried out as a consequence of an individual request for assistance and population screening needs to be carefully monitored. Furthermore, DNA testing for germline mutations can have very considerable financial consequences for health care, arising out of the cost of the tests themselves, out of the need to provide information and advice and out of the need to provide post-test medical care and clinical follow-up in some cases; testing may also generate new groups of potential test subjects.

Complex somatic DNA diagnostics: general

Complex somatic DNA diagnostics does not entail the sort of social and ethical issues which require statutory regulation. The concentration of expertise, facilities and infrastructure with a view to controlling quality, efficiency and cost is primarily the responsibility of the parties active in the field. There is no difference in principle between DNA test techniques and other new diagnostic laboratory techniques. The Committee therefore began by considering whether the field was capable of independently achieving the necessary concentration and coordination. Compulsory licensing to ensure that the relevant quality and efficiency requirements are met will be needed only in circumstances where the necessary conditions for self regulation of the field are absent and where there are far-reaching consequences for patient care. Statutory control may also be desirable for forms of DNA diagnostics which are of major significance for the patient, if government intervention appears necessary to secure appropriate and adequate developmental progress.

The Committee has observed that DNA diagnostics has developed further in some fields than in others. Furthermore, differences exist in the views of various disciplines and in the extent to which their professional bodies have developed quality policies that include binding arrangements on the division of responsibilities.

Complex somatic DNA diagnostics: solid tumours

Most testing for the somatic mutations associated with solid tumours is conducted in pathology laboratories. DNA testing has only comparatively recently been introduced into pathology, and there is no history of statutory regulation. The first steps towards concentration have since been taken, with the launch of an internal scheme under which laboratories are ‘accredited’ on the recommendation of the Molecular Pathology Working Group and the Professional Practice Committee of the Dutch Pathology Association (NVVP).

Accreditation depends on meeting criteria on the availability of technological infrastructure and molecular biological expertise, the availability of expertise in clinical pathology, links with a CGC, the minimum number of procedures, participation in quality assurance programmes and membership of the NVVP’s molecular diagnostics network. A similar system has been set up by the Dutch Clinical Chemistry Association.

Although potentially great, the demand for DNA testing for the somatic mutations associated with solid tumours is currently quite low. The Committee therefore believes that the quality policies pursued in the field provide a suitable basis for proper development. Application of Section 2 of the WBMV is consequently not considered

appropriate at present. Nevertheless, the Committee considers that the process of controlled development is much more likely to succeed and lead to the efficient general clinical introduction of this form of DNA diagnostics if use is made of the statutory provisions for encouraging centres which commit themselves to agreements on indication ranges and the division of responsibilities. The Committee would also like to see actual progress reviewed in a few years' time.

Complex somatic DNA diagnostics: haemato-oncology

The situation in the field of haemato-oncology is somewhat different. Cytogenetic (chromosome) testing in connection with myeloproliferative conditions is quite well established; being covered by Section 2 of the WBMV, most of this testing is carried out in the laboratories of the CGCs, under the clinical responsibility of the haemato-oncologist. Although DNA diagnostics is an extension of this kind of testing, it is not confined to the CGCs, but takes place in pathology, haematology, immunology and clinical chemistry laboratories as well. In this field, no collective schemes are in place comparable with those which operate in the pathology and clinical chemistry disciplines.

With no sign of the parties active in this field reaching agreement amongst themselves or with the insurers regarding quality, indication ranges or the division of responsibilities, certain forms of haemato-oncological diagnostic testing clearly require statutory control. The forms of testing in question are mainly those designed to detect somatic mutations consistently associated with rare types of leukemia, whose results have significant consequences for treatment, in particular decisions regarding bone marrow transplantation and intensive chemotherapy. Data from such tests is highly significant for both primary therapy and for the policy adopted in the event of the disease recurring. Haemato-oncological tests need to be repeated more frequently than tests for solid tumours and can be repeated relatively easily because of the ready availability of blood cells. However, the sensitivity requirements and other conditions that repeat tests must meet are very strict, because it is vital that recidivism is detected and treated as early as possible. In a given year, there are about four hundred new patients, who will require between three and ten tests each. Uncontrolled growth in the volume of testing is not expected, since the numbers of patients concerned are small and each type of test is comparatively rare.

In view of the requirements regarding test quality, the level of expertise needed for correct interpretation, integration with other diagnostic activities and linkage with specialized forms of treatment currently regulated under Section 2 of the WBMV, this type of DNA testing needs to be concentrated in the university hospitals. The importance of the tests for individual patients is such that adequate financial provisions

need to be made to enable repeat testing at various expertly determined points in the course and the follow-up of the disease. It may be that both concentration could be effected and adequate finance secured by bringing the relevant tests within the scope of the new statutory promotional scheme. If cytogenetic testing in this field were also brought under Section 8, it could be readily removed from the scope of Section 2 and a coherent policy could be established in the field of haemato-oncology. However, given that the promotional scheme is aimed at future development, it would not be logical to maintain the present distinction between solid tumours and haematological cancers within the field of complex somatic DNA diagnostics. With the previously outlined considerations in mind, the Committee believes that any promotional scheme should cover the entire field of somatic DNA (and chromosome) diagnostics.

The Committee would therefore suggest that consideration be given to applying the provisions of Section 8 of the WBMV to the "complex diagnostics of acquired abnormalities in the genetic material": a coherent package of chromosomal examinations and DNA diagnostic procedures involving somatic cells. If such an approach is not adopted, or until it is, a small number of clearly defined somatic DNA tests (those concerned with rare leukemias) should, in the Committee's view, be kept within the scope of Section 2 of the WBMV.

If complex diagnostic DNA testing for hereditary mutations, including hereditary risk factors, remains or is brought under Section 2 of the WBMV, the present arrangements will need to be modified. To this end, an appropriate balance will have to be struck between two conflicting considerations. As things stand, the expertise of the CGCs is the basis upon which heredity analysis, DNA diagnostics, family contact programmes and counselling are organized. It is very important, the Committee believes, that this expertise and the coherent body of functions and activities performed by the CGCs is preserved. However, as the range of conditions for which DNA diagnostics is indicated widens to include more multifactorial diseases, it becomes less desirable that only the CGCs are licensed to perform all the tests. There are several reasons for this. First, the conditions for which testing is or will be indicated are very diverse and great differences exist in the roles that hereditary risk factors play in their occurrence. Second, the pre-test and post-test trajectories are properly clinical responsibilities. Third, differences exist in the extent to which departments and laboratories are involved and in the likely demand for testing. Nevertheless, the expertise of the CGCs should be available to practitioners in the various clinical fields where DNA diagnostics is introduced.

The Committee would therefore suggest that consideration be given to applying the provisions of Section 2 of the WBMV to a single function, "heredity analysis and consultation of a complex nature", responsibility for which would be divided between

the CGCs and the university hospitals. The CGCs would broadly retain responsibility for the activities already undertaken, so that the cohesion between chromosomal examinations, biochemical testing, DNA diagnostics, prenatal diagnostics and counselling would be maintained; for their part, the university hospitals would be responsible for DNA diagnostics and consultation in connection with multifactorial diseases, subject to certain organizational conditions listed below and with scope for collaboration with non-university departments and laboratories. The Committee assumes that the planning decree bringing the relevant forms of testing under the scope of the Act could be worded in a general way, so that its practical implementation could regularly be adapted to take account of developments. An important role is foreseen for the profession in identifying DNA procedures which should be regarded as complex and therefore considered for concentration. The involvement of parties active in the field would be in line with government's general wish to move towards deregulation and with the quality policy currently pursued, but it would represent a new approach. Appropriate organizational arrangements would therefore have to be developed. Similar problems are found in other fields of clinical care which are subject to statutory regulation. Procedural and practical requirements could be imposed to control the way decisions on the complexity of test procedures are arrived at. Experts from the various disciplines involved in defining indication ranges, in laboratory analysis, in treatment and in post-test activities should be involved in the determination of complexity, as should experts in the fields of counselling and psychological support.

Naturally, the minister could also ask the Health Council for advice at any point.

6.3 Organizational, training and financial arrangements

6.3.1 Network formation

Developments in DNA testing for multifactorial conditions (including monogenic variants of such conditions) are presently taking place within a wide range of different disciplines, with the emphasis differing from one university or categorical oncology centre to another. If a research group, clinical department or diagnostic laboratory has a particular interest or expertise in a given field, this often provides an excellent basis for further development; the Committee therefore believes that organizational arrangements should be facilitative rather than restrictive. Accordingly, the Committee would suggest that the licensing of a university hospital under Section 2 should be subject to the conditions that the general quality requirements are met and that a network structure is established within the hospital, linking all departments and laboratories involved in DNA diagnostics. The local CGC should also be linked to the network, so as at least to be able to contribute expertise in the fields of DNA

diagnostics, family investigation and genetic counselling. Thus, no changes would be required in the organization, remit and financing of the CGCs. It should also be possible for licensed centres to collaborate with non-university departments and laboratories.

The function of a network is to promote and monitor the quality of DNA diagnostics and of all related activities. It is important that formal arrangements are made regarding responsibility for network function, quality policy, the care provided and the division of responsibilities between network members. Agreements can also be made regarding consultation arrangements and referral patterns and the organization of family contact and follow-up programmes. In this way, optimal use can be made of the available expertise and the overlap between monogenic and multifactorial diseases (including the familial and monogenic variants of multifactorial diseases) can be determined.

If the minister should decide to bring diagnostic testing for somatic abnormalities in the genetic material within the scope of the promotional scheme, participation in a network might be made a precondition for assistance. Forms of diagnostic DNA testing which are not subject to statutory regulation could in principle be conducted outside the networks, provided that the quality requirements are met. Parties active in the field would collectively have to decide how the necessary division of responsibilities, concentration and network ties were to be effected.

The precise nature of each network could be determined by the relevant university hospital, taking account of the regional situation. The Committee would also favour participation by the few groups and laboratories which, although not part of a particular university hospital, do operate at a similar level; these include the CLB and the Inter-university Ophthalmology Institute. Cooperation should additionally be possible with peripheral laboratories and other institutions or departments which meet the quality requirements in a particular field of DNA diagnostics.

Each network could determine which of its member-departments or groups is best placed to undertake each form of DNA testing. The difficult question of where to draw the line between somatic mutations and germline mutations could be decided in consultation with the laboratories performing research into somatic mutations. Agreements would be needed regarding intra-network working practices. To this end, a protocol should be drawn up for each test performed for general clinical purposes within the network, covering the circumstances under which the given test is indicated and appropriate follow-up. Laboratories operating within the network should be involved in the procedures for reasons of quality control and annual production arrangements should be agreed. National harmonization amongst the (networks in the) university centres should be sought on matters relating to new developments and rare tests.

The Committee would emphasize that these recommendations relate to the testing of individual patients and the predisposition testing of index patients' immediate relatives. Sometimes, DNA testing may be indicated for a patient or possibly his or her relatives on the basis that the patient belongs to a particular population group. In the Committee's view, activities involving entire risk groups or population (sub-)groups, which are classed as population screening under the WBO, require additional organizational and financial arrangements.

6.3.2 *Consequences for the remit of CGCs*

For the time being, demarcation between the CGCs' DNA laboratories and non-CGC laboratories will continue to be based on the distinction between monogenic and multifactorial diseases. However, it is anticipated that other criteria frequency, test complexity, nature of the genetic risk and significance for relatives will become increasingly important. Consequently, it is quite possible that some tests for monogenic abnormalities could be allocated to non-CGC laboratories, while complex polygene interactions would require the expertise of a CGC.

For a network system to be successful, it is essential that various responsibilities and duties are clearly defined. Given their specialist expertise, the CGCs are expected to play an important role in relation to the following:

- the expertise in counselling matters
- the expertise concerning testing which involves several generations of a family, as opposed to individual-oriented molecular diagnostics in various clinical specialisms
- training and consultation
- quality control in the fields of indication definition, laboratory analysis and follow-up, inside and outside the CGCs
- training for GPs, clinical specialists and paramedics
- prenatal diagnostics.

6.3.3 *Training*

It has been established that medical practitioners in other countries tend to lack sufficient knowledge of genetic matters to inform patients properly, to determine whether testing is indicated or to provide good advice (Ano98, Cho97, Gia97, McK97). A similar situation probably exists in the Netherlands at present. It will therefore be necessary to ensure that training programmes better reflect the increasing interest in and knowledge of the genetic aspects of disease. The need for clinical genetic expertise will increase, especially in relation to multifactorial diseases. This

need could be met by training more clinical geneticists with specialist expertise in particular clinical fields, or by creating recognized genetic sub-disciplines within various clinical specialisms or by establishing so-called double-specialisms. No consensus on this matter has yet been reached within the profession.

GPs too will increasingly find themselves having to answer questions about genetic risks, the practical significance of such risks and the difficult decisions facing their patients where genetic matters are concerned. The more that is learned about the genetic aspects of disease, the greater the GP's role will become in various areas including the provision of information and advice. The basic and in-service training given to GPs will therefore have to systematically address not only advancing medical knowledge in this field, but also strategies for dealing with uncertainty, the psychological impact of testing on families and the dilemmas which testing creates.

In other countries, specially trained paramedics have successfully been used to provide advice, especially regarding hereditary forms of cancer. A research project has been started in the Netherlands and the Dutch Clinical Genetics Association has drafted training requirements for so-called genetic assistants.

6.3.4 *Financial issues*

Although the detailed consideration of financial issues was not part of the Committee's remit, certain matters are relevant in the present context.

Predisposition testing aimed at prevention and early treatment is only responsible and efficient if adequate provision is made for the long-term medical supervision of risk carriers. The health 'gain' is not a product of testing, but of the post-test trajectory. Follow-up activities could generate an additional workload which is too great for the available capacity. These knock-on effects must be taken into account when considering the financial implications of testing.

The Committee cautiously estimates that the number of DNA analyses with consequences for subjects' relatives will at least double in the next five years. Beyond 2003, (much) more rapid growth may be expected, the management of which requires the immediate creation of a clear framework for financial and indication-related decisions.

The financial arrangements must distinguish four categories of test: heredity analyses conducted by the CGCs (including complex diagnostic DNA testing in connection with monogenic diseases), complex diagnostic DNA tests conducted at the university hospitals in connection with multifactorial diseases, complex (haemato-)oncological diagnostic tests for acquired chromosome and DNA abnormalities and non-complex diagnostic DNA tests. Where the first two categories are concerned, allowance should be made for the often involved pre-test and post-test

trajectories. Diagnostic testing for the hereditary mutations associated with breast and bowel cancers, which is currently financed through the CGCs, could then be funded under the arrangements for multifactorial disease testing; any such funding arrangements would need to cover the infrastructure for the pre-test and post-test trajectories and assured (where necessary, lifelong) follow-up.

The Committee believes that the development and use of DIY tests should be discouraged for the time being. However, this requires that proper provision is made for the testing of everyone for whom it is genuinely indicated. The Committee believes that the government and the health insurers have a responsibility to ensure that diagnostic DNA tests are available wherever warranted on the basis of indication definitions carefully formulated by the medical profession.

6.4 Future developments

The Committee expects that in the long term there will be less need for concentration in DNA diagnostics. Clinical understanding of the hereditary factors associated with multifactorial conditions will increase, as will knowledge of the benefits and limitations of predisposition testing and the associated post-test trajectory. As a result of these processes, DNA diagnostics will increasingly become a normal part of a very diverse range of clinical disciplines. Already, certain technological developments in the field of DNA chips are nearing fruition, which will allow simultaneous testing for a large number of different mutations, or for a few mutations in a large number of samples. Such developments should be accompanied by changes in medical training, so that explicit attention is given to the genetic aspects of disease. First-line health care practitioners will frequently have to tackle questions from patients and healthy individuals regarding hereditary risks and their consequences. In many such cases, it will fall to the GPs or specially trained paramedics to provide appropriate advice and, where appropriate, to refer the individuals in question for testing. The university-based networks will retain responsibility primarily for those diagnostic DNA tests which are technically very complex or new, which involve very difficult decisions and serious consequences, or which need to be tied in with clinical evaluation testing and epidemiological research.

Numerous areas of uncertainty remain, however, both in relation to clinical and technological development and in relation to the roles that the government and the parties involved in the field should play in bringing about the necessary and desirable concentration of procedures and care. The Committee therefore considers that both scientific developments in DNA diagnostics and the quality and implementation of test procedures should be reviewed again in another few years.

Rijswijk, 28 April 1998,
on behalf of the committee
(signed)

DCM Gersons-Wolfensberger,	professor H Galjaard,
Secretary	Chairperson

Literature

ACGT97 Advisory Committee on Genetic Testing (ACGT). Code of practice and guidance on human genetic testing services supplied direct to the public. London: Health Departments of the United Kingdom, 1997.

ACMG95 American College of Medical Genetics. Statement on use of Apolipoprotein E testing for Alzheimer disease. JAMA 1995; 274: 1627-9.

Ano97 Anonymous. The Future of asthma. Lancet 1997; 350: 1113.

Ano98 Anonymous. Artsen en genen. Aanbevelingen inzake genetica van het hoofdbestuur van de KNMG voor de Algemene Vergadering. Medisch Contact 1998; 53: 551-6.

ASCO96 American Society of Clinical Oncology (ASCO). Statement o the American Society of Clinical Oncology: Genetic testing for cancer susceptibility. J Clin Oncol 1996;14: 1730-6.

ASCO97 American Society of Clinical Oncology (ASCO). Task force on cancer genetics education: resource document for curriculum development in cancer genetics and cancer predisposition testing. J Clin Oncol 1997; 15: 2157-69.

ASHG95 American Society of Human Genetics (ASHG). Report from the ASHG Information and Education Committee: medical school core curriculum in genetics. Am J Hum Genet 1995; 56: 535-7.

Bar96 Barton JC, Bertoli LF. Hemochromatosis: the genetic disorder of the twenty-first century. Nature Med 1996; 2: 394-5.

Bar97 Barcellos LF, Thomson G, Carrington M, *et al.* Chromosome 19 single- locus and multilocus haplotype associations with multiple sclerosis; evidence of a new susceptibility locus in caucasian and chinese patients. JAMA 1997; 278(15): 1256-61.

Bee96 Beemer FA. Multiple endocriene neoplasie type 2a.In: Presymptomatische DNA-diagnostiek voor erfelijke, later in het leven optredende, ziekten. Rotterdam: PAOG, 1996: 34-5.

Bee97 Beemer FA. Van poortwachter tot Mendel. Utrecht: Wetenschappelijke uitgeverij Bunge, 1997.

Bijl98 Bijl RV, van Zessen G, Ravelli A. Psychiatrische morbiditeit onder volwassenen in Nederland: het NEMESIS-onderzoek. II. Prevalentie van psychiatrische stoornissen. Ned Tijdschr Geneeskd 1997; 141: 2453-60.

Blo92 Bloch M, Adam S, Wiggins S, *et al.* Predictive testing for huntington disease in Canada; The experience of those receiving an Increased risk. Am J Med Genet 1992; 42: 499-507.

Blo95 Bloemenkamp KWM, Rosendaal FR, Helmerhorst FM, *et al.* Enhancement by factor V Leiden mutation of risk of deep-vein thrombosis associated with oral contraceptives containing a third-generation progestagen. Lancet 1995; 346: 1593-6.

Bol97 Bolt I. 'Goede raad. Over autonomie en goede redenen in de praktijk van de genetische counseling', (dissertatie). Thesis Publishers, Amsterdam, 1997.

Cho97 Chorley W, MacDermot K. Who should talk to patients with cancer about genetics? Br Med J 1997; 314: 441.

Cod94 Codori AM, Brandt J. Psychological Costs and benefits of predictive testing for huntington's disease. Am J Med Genet 1994; 54: 174-84.

Col96 Collins F. Commentary on the ASCO statement on genetic testing for cancer susceptibility. J Clin Oncol 1996; 14: 1738-40.

Col97 Collins FSC. Preparing health professionals for the genetic revolution. JAMA 1997; 278: 1285-6.

Cou97 Couch FJ, DeShano ML, Blackwood MA, *et al.* BRCA1 mutations in women attending clinics that evaluate the risk of breast cancer. N Engl J Med 1997; 336: 1409-15.

Cro95 Cromme PVM, van Eijk JThM, van der Veen EA, *et al.* Glucose- intolerantie bij ouderen in Nederland; het Twello-onderzoek. Ned Tijdschr Geneeskd 1995; 139: 2558-64.

Dah96 Dahlback B. Are we ready for factor V Leiden screening? Lancet 1996; 347: 1346-7.

Des96 Desmarais S, de Moerloose P, Reber G, *et al.* Resistance to activated protein C in an unselected population of patients with pulmonary embolism. Lancet 1996; 347: 1374-5.

Dev96 Devilee P. Moleculaire genetica bij erfelijke vormen van borst- en ovariumkanker. In: Presymptomatische DNA-diagnostiek voor erfelijke, later in het leven optredende, ziekten. Rotterdam: PAOG, 1996: 8-10.

Dib96 Dibner M. Biotechnology's promise and future. Montreal: NRC Biotechnology Research Institute, 1996.

Dud94 Dudok de Wit AC, Meijers-Heijboer EJ, Tibben A, *et al.* Effect on Dutch family of predictive DNA-testing for hereditary breast and ovarian cancer. Lancet 1994; 344: 197.

Dud97 Dudok de Wit AC. To know or not to know. The psychological implications of presymptomatic DNA testing for autosomal dominant inheritable late onset disorders. (Proefschrift). Rotterdam: EUR, 1997

Dud97 Dudok de Wit AC, Tibben A, Duivenvoorden HJ, *et al.* Psychological distress in applicants for predictive DNA testing for autosomal dominant, heritable, late onset disorders. J Med Genet 1997; 34: 382-90.

Eve97 Evers-Kiebooms G. Psychological consequences of presymptomatic testing for Huntington's disease. Lancet 1997; 349: 8089.

Fed96 Feder JN, Gnirke A, Thomas W, *et al.* A novel MHC class I-like gene is mutated in patients with hereditary haemochromatosis. Nature Genet 1996; 13: 399.

Fer95 Fermo I, Vigano'D'Angelo S, Paroni R, *et al.* Prevalence of moderate hyperhomocysteinemia in patients with early-onset venous and arterial occlusive disease. Ann Intern Med 1995; 123: 747-53.

Fre96 Freimer NB, *et al.* Genetic mapping using haplotype, association and linkage methods suggests a locus for severe bipolar disorder (BPI) at 18q22-q23. Nature Genet 1996; 12: 436-41.

Fri97 Frisoni GB, Trabucchi M. Clinical rationale of genetic testing in dementia. J Neurol Neurosurg Psychiatr 1997: 217-21.

Gal97a Galjaard H. De Klinische genetica in Nederland. II. Erfelijkheidsadvisering en prenatale diagnostiek. Ned Tijdschr Geneeskd 1997; 141(49): 2386-91.

Gal97b Galjaard H. Toekomstige ontwikkelingen in het erfelijkheidsonderzoek. I. Technologische mogelijkheden. Ned Tijdschr Geneeskd 1997; 141(50): 2432-7.

Gal97c Galjaard H. Toekomstige ontwikkelingen in het erfelijkheidsonderzoek. II. Psycologische en maatschappelijke aspecten. Ned Tijdschr Geneeskd 1997; 141(50): 2438-44.

Gev96 Gevers JKM, Roscam-Abbing EW. Voorspellend medisch onderzoek. Mogelijkheden, verwachtingen en toegang. Vereniging voor Gezondheidsrecht, 1996: 1- 84.

Gia97 Giardiello FM, Brensinger JD, Petersen GM, *et al.* The use and interpretation of commercial APC gene testing for familial adeno matous polyposis. N Eng J Med 1997; 336: 823-7.

Gio98 Giordano PC, Harteveld CL. Hemoglobinopathieen in Nederland: de rol van de huisarts in dragerschap-diagnostiek en preventie. Huisarts Wetensch 1998: 1-19.

Goo96 van Gool WA, van Crevel H. Nieuwe diagnostische tests voor de ziekte van Alzheimer in de klinische praktijk. Ned Tijdschr Geneeskd 1996; 140: 2071-3.

GR89 Gezondheidsraad: Beraadsgroep Genetica. Erfelijkheid: wetenschap en maatschappij. Over de mogelijkheden en grenzen van erfelijkheidsdiagnostiek en gentherapie. Den Haag: Gezondheidsraad, 1989; publikatie nr 31/89.

GR94 Gezondheidsraad: Beraadsgroep Gezondheidsethiek en Gezondheidsrecht. Genetische screening. Den Haag: Gezondheidsraad, 1994; publikatie nr 1994/22.

GR95 Gezondheidsraad. Niet alle risico's zijn gelijk. Den Haag: Gezondheidsraad, 1995; publicatie nr. 1995/06.

GR96a Gezondheidsraad. Risico, meer dan een getal. Den Haag: Gezondheidsraad, 1996; publicatie nr 1996/03.

GR96b Gezondheidsraad: Commissie WBO. Wet bevolkingsonderzoek: de reikwijdte (2). Rijswijk: Gezondheidsraad, 1996; publikatie nr 1996/24.

GR97a Gezondheidsraad. Onderzoek met embryonale stamcellen. Rijswijk: Gezondheidsraad, 1997; publicatie nr 1997/27.

GR97b Gezondheidsraad. Transplantatie van foetaal materiaal. Rijswijk: Gezondheidsraad, 1997; publicatie nr 1997/31.

Hol97 Holtzman, NA. Testing for genetic susceptibility to common cancers: clinical and ethical issues. Adv Oncology 1997; 13(1): 9-15.

Hol97 Holgate ST. Asthma genetics: waiting to exhale. Nature Genet 1997; 15: 227-9. Jam96Jamison KR, McInnis MG. Genetic studies of manic-depressive illness. Nature Med 1996; 2: 521-2.

Jan90 Janson M, Kock E, Nordenskjold M. Constitutional deletions predisposing to retinoblastoma. Hum Genet 1990; 85: 21-4.

Jon98 de Jong SC. Geen relatie tussen homocysteineconcentratie en coronaire hartziekten Ned Tijdschr Geneeskd 1998; 142: 598.

Kie96 Kiemeney LALM, Witjes JA, Hendrikx AJM, *et al.* Erfelijke prostaatcarcinoom. Ned Tijdschr Geneeskd 1996; 140: 1068-71.

Koo98 Koonin SE. An independent perspective on the human genome project. Science 1998; 279: 36-7.

Kui98 Kuivenhoven JA, Jukema W, Zwinderman AH, *et al.* The role of a common variant of the cholesteryl ester transfer protein gene in the progression of coronary atherosclerosis. N Engl J Med 1998; 338(2): 86-93.

Lan96 Langston AA, Malone KE, Thompson JD, *et al.* BRCAI mutations in a population-based sample of young women with breast cancer. N Engl J med 1996; 334: 137-42.

Lee98 van Leeuwen FW, de Kleijn DPV, van den Hurk HH, *et al.* Frameshift Mutants of B Amyloid Precursor Protein and Ubiquitin-B in Alzheimer's and Down Patients. Science 1998; 279: 242-7.

Ler94 Lerman C. Psychological issues in genetic testing for breast cancer susceptibility. Arch Intern Med 1994; 154: 609-16.

Ler96 Lerman C, Narod S, Schulman K, *et al.* BRCA1 testing in families with hereditary breast-ovarian cancer. JAMA 1996; 275: 1885-92.

Mag96 Maguire CP, Kirby M, Coen R, *et al.* Family members' attitudes toward telling the patient with Alzheimer's disease their diagnosis. Br Med J 1996; 313: 529-31.

Man96 Mandel H, Brenner B, Berant M, *et al.* Coexistence of hereditary homocystinuria and factor V Leiden -effect on thrombosis. N Engl J Med 1996; 334: 763-8.

Man96 Mandel H, Brenner B, Berant M. To the editor. Thrombophilia, homocystinuria, and mutation of the factor V gene. N Engl J Med 1996; 335: 291.

Mar97 Marshall A. Getting the right drug into the right patient. Nature Biotechnol 1997; 15: 1249-52.

McD96 McDonald IG, Daly J, Jelinek VM, *et al.* Opening Pandora's box: the unpredictability of reassurance by a normal test result. Br Med J 1996; 313: 329-32.

McK90 McKusick VA. Mendelian inheritance in Man (9e editie). Baltimore, MD: Johns Hopkins Press, 1990.

McK97 McKinnon W, Baty BJ, Bennett RL, *et al.* Predisposition Genetic Testing for late-onset disorders in adults; a position paper of the national society of Genetic counselors. JAMA 1997; 278(15): 1217-20.

Meij96a Meijers-Heijboer EJ. Erfelijkheidsadvies van erfelijk borst- en ovariumkanker. In: Presymptomatische DNA-diagnostiek voor erfelijke, later in het leven optredende, ziekten. Rotterdam: PAOG, 1996: 15-7.

Meij96b Meijer H, van den Berg MH, Schaap C, *et al.* De moleculair-genetische basis van enkele erfelijk bepaalde hartziekten en de mogelijkheden voor DNA-diagnostiek. Cardiologie 1996; 3: 226-31.

Men95 Menko FH. Erfelijke aspecten van colon- en rectumcarcinoom; risicobepaling voor familieleden van patienten en adviezen voor screening. Ned Tijdschr Geneeskd 1995; 135: 928-31.

Mic97 Michie S, Bron F, Bobrow M, *et al.* Nondirectiveness in genetic counseling: an empirical study. Am J Hum Genet 1997; 60: 40-7.

Mid98 Middeldorp S, Henkens CMA, Koopman MMW, *et al.* The incidence of venous thromboembolisme in family members of patients with factor V Leiden mutation and venous thrombosis. Ann Intern Med 1998; 128: 15-20.

NIA96 National Institute on Aging/Alzheimer's Association Working Group. Apolipoprotein E genotyping in Alzheimer's disease. Lancet 1996; 347: 1091-5.

NVI97 Nederlandse Vereniging voor Immunologie. Moleculaire diagnostiek in de medische immunologie. Amsterdam: NVI, 1997.

Odd96 Oddoux C, Struewing JP, Clayton CM, *et al.* The carrier frequency of the BRCA2 6174delT mutation among Ashkenazi Jewish individuals is approximately 1%. Nature Genet 1996; 14: 188-9.

Olo97 Olopade-Olopade. Genetic testing, guidelines, ethics - When to test and what to do with the results. Am Soc Clin Oncol 1997: 58-62.

Oph97 Ophoff RA. The molecular basis of familial hemiplegic migraine; migraine as a Ca2+ channel disorder (Proefschrift). Leiden: Rijksuniversiteit Leiden, 1997.

Ott97 Otten R. Genetische kennis haalt artsen in. Medisch Contact 1997; 50: 1575-6.

Per95 Perry IJ, Refsum H, Morris RW, *et al.* Prospective study of serum total homocysteine concentration and risk of stroke in middle-aged British men. Lancet 1995; 346: 1395-8.

Pol96 Polonsky KS, Sturis J, Bell GI. Non-insulin-dependent diabetes mellitus - a genetically programed failure of the beta cell to compensate for insulin resistance. N Engl J Med 1996; 334: 777-83.

Reg95 Regelink-van der Lee JH, Schulpen TWJ, Memer FH. Incidentie en prevalentie van hemoglobinopathieen bij kinderen in Nederland. Ned Tijdschr Geneeskd 1995; 139: 1498-501.

Rid95 Ridker PM, Hennekens CH, Lindpaintner K, *et al.* Mutation in the gene coding for coagulation factor V and the risk of myocardial infarction, stroke, and venous thrombosis in apparently healthy men. N Engl J Med 1995; 332: 1-14.

Ris97 Risch N. Haemochromatosis, HFE and genetic complexity. Nature Genet 1997; 17: 375-6.

Ros97 Rosenberg RN. Editorials; Molecular Neurogenetics; the genome is settling the issue. JAMA 1997; 278(15): 1282-3.

Ros98 Rosenthal N, Schwartz R. In Search of perverse polymorphisms. N Engl J Med 1998; 338(2): 122-4.

Sar98 Sarasin FP, Bounameaux H. Decision analysis model of prolonged oral anticoagulant tratment in factor V Leiden carriers with first episode of deep vein thrombosis. Br Med J 1998; 316: 95-9.

Sko96 Skolnick M. Commentary on the ASCO statement on genetic testing for cancer susceptibility. J Clin Oncol 1996; 14: 1737-8.

Slo96 Slooter AJC, Gool WA van, van Duijn CM. De plaats van apolipoproteine-E- genotypering in de differentiaaldiagnostiek van dementie. Ned Tijdschr Geneeskd 1996; 140: 2073-6.

Sol96 Solymoss S. Factor V Leiden: Who should be tested? Can Med Assoc J 1996; 155: 296-8.

Ste94 van der Steenstraten IM, Tibben A, Roos RAC, *et al.* Predictive testing for Huntington disease: nonparticipants compared with participants in the Dutch program. Am J Hum Genet 1994; 55: 618-25.

Ste95 Stefanek ME. Bilateral prophylactic mastectomy: Issues and concerns. Monogr Natl Cancer Inst 1995; 17: 37-42.

Ste97 Stephenson J. As discoveries Unfold, a New Urgency to bring Genetic Literacy to Physicians. JAMA 1997; 278(15): 1225-6.

STO95 Stichting Opsporing Erfelijke Hypercholesterolemie. Jaarverslag 1995. Amsterdam: Stichting Opsporing Erfelijke Hypercholesterolemie, 1995.

Str95 Struewing JP, Abeliovich D, Peretz T, *et al.* The carrier frequency of the BRCA1 185delAG mutation is approximately 1 percent in Ashkenazi Jewish individuals. Nature Genet 1995; 11: 198-200.

Str97 Struewing JP, Hartge P, Wacholder S, *et al.* The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among ashkenazi jews. N Engl J Med 1997; 336: 1401-8.

Swi97 Swinkels DW, Cooreman MP, van Solinge WW. Hereditaire hemochromatose: recente ontwikkelingen in de diagnostiek. Ned Tijdschr Geneeskd 1997; 141(28): 1373-4.

Taa96a Taa BG. Behandelingsopties na presymptomatische diagnostiek voor erfelijke darmkanker. In: Presymptomatische DNA-diagnostiek voor erfelijke, later in het leven optredende, ziekten. Rotterdam: PAOG, 1996: 29-30.

Taa96b Taal BG. Hereditary gastric cancer. Richtlijnen voor beleid in families met erfelijke kanker. Lustrumsymposium Stichting Opsporing Erfelijke Tumoren, Utrecht, 9 februari 1996. Amsterdam: STOEH, 1996.

Tac95 Tack CJJ. Recente ontwikkelingen op het gebied van diabetes mellitus type II op jonge leeftijd (MODY). Ned Tijdschr Geneeskd 1995; 139: 2127-30.

Tem91 Temple WJ, Lindsay RL, magi E, *et al.* Technical considerations for prophylactic mastectomy in patients at high risk for breast cancer. Am J Surg 1991; 161: 413-5.

Tib96 Tibben A, Beemer FA, Brunner HG, *et al.* Presymptomatische DNA- diagnostiek voor erfelijke, later in het leven optredende, ziekten. Rotterdam: Bureau PAOG, 1996.

Tib97a Tibben A, Stevens M, de Wert GMWR, *et al.* Preparing for presymptomatic DNA testing for early onset Alzheimer's disease/cerebral haemorrhage and hereditary Pick disease. J Med Genet 1997; 34: 63-72.

Tib97b Tibben A, Roos RAC, Niermeijer MF. Psychological consequences of presymptomatic testing for Huntington's disease. Lancet 1997; 349(9054): 809.

Tod96 Todd JA, Farrall M. Panning for gold: genome-wide scanning for linkage in type 1 diabetes. Hum Mol Genet 1996; 5: 1443-8.

Tod97 Todd JA. Genetics of type 1 diabetes. Pathol Biol 1997; 45: 219-27.

Van96 Vandenbroucke JP. Screening op familiaire hypercholesterolemie. Ned Tijdschr Geneeskd 1996; 140: 944-8.

Vas96 Vasen HFA. Vroege opsporing van familiaire adenomateuze polyposis. In: Presymptomatische DNA-diagnostiek voor erfelijke, later in het leven optredende, ziekten. Rotterdam: PAOG, 1996: 24-5.

Ver95 Vereniging van Stichtingen Klinische Genetica i.o., Zorgverzekeraars Nederland. Klinische Genetica in Nederland anno 1996. Houten: Vereniging van Stichtingen Klinische Genetica i.o., Zorgverzekeraars Nederland, 1995.

Ver96 Verhoef P. Homocysteine, B-vitamins and cardiovascular disease: epedemiologic evidence (proefschrift). Wageningen: Landbouwuniversiteit Wageningen, 1996.

VGR91 Vereniging voor Gezondheidsrecht. Wat mag en wat moet bij erfelijkheidsonderzoek? Richtlijnen Vereniging voor Gezondheidsrecht. Tijdschr Gezondheidsr 1991: 481-8.

Vis96 Visser-O, Coebergh-JWW, Schouten LJ. Incidence of cancer in the Netherlands 1993. Fifth report of the Nederlands cancer registry. Utrecht: Vereniging van Integrale Kankercentra (VIK), 1996.

Vog98 Vogel G. Neurodegenerative Diseases; Possible new cause of alzheimer's Disease found. Science 1998; 279: 174.

Vri97 de Vries B. The fragile x-syndrome. Clinical, genetic and large scale diagnostic studies among mentally retarded individuals. (Proefschrift). Rotterdam: Erasmus Universiteit, 1997.

Wag95 Wagner A, Tibben A, Bruining GJ, *et al.* Preliminary experience with predictive testing for insulin dependent diabetes mellitis. Lancet 1995; 346: 380-1.

Wal97 van der Wall, EE.. Internationale workshop familiaire hypercholtesterolemie en LDL-receptor-afwijkingen (maart 1997, Amsterdam): een verslag. Leiden: STOEH, 1997; (Nieuwsbrief EHC 34, juli 1997).

Wap90 Wapnir IL, Rabinowitz B, Greco RS. A reappraisal of prophylactic mastectomy. Surg Gynecol Obstet 1990; 171-84.

Wei96 van der Weide J, Steijns LSW. Cytochroom-P450 afhankelijk geneesmiddelmetabolisme: invloed van genetische aanleg, co-medicatie, ziekte, dieet en roken op CYP-enzymactiviteit. Ned Tijdschr Klin Chem 1996; 21: 290-6.

Wer90 de Wert G. Erfelijkheidsadvisering. Taak en kopzorgen van de counselor. In: ten Have HAMJ, Blijham GH, Engberts DP, *et al.*, red. Ethiek en recht in de gezondheidszorg. Deventer: Kluwer, 1990: XVI: 101-18.

WVC94 Ministerie van Welzijn, Volksgezondheid en Cultuur, Staatssecretaris van Onderwijs en Wetenschappen. Regeling klinisch genetisch onderzoek en erfelijkheidsadvisering. Staatscourant 1994, 68.

Annexes

Annex **A**

Request for the report

On 28 October 1994, the Minister of Health, Welfare and Sport wrote (under reference ZZT/TOPAZ/944037) as follows to the President of the Health Council:

As you indicated in your report on the clinical genetics planning decree of 4 December 1992, the scope for clinical genetic testing is constantly increasing. This is due partly to work going on around the world to unravel the human genome, which is increasing scientific understanding of the association between, on the one hand, genetic abnormalities and, on the other, disease and physical and mental abnormalities. At the same time, advances in recombinant DNA techniques, in DNA diagnostics and in other such fields mean that the methods used to identify genetic abnormalities are becoming more and more sophisticated or capable of providing ever more precise information. In an increasing number of cases, the techniques in use are also becoming much more simple.

As a result of these developments, clinical genetics is no longer concerned exclusively with identifying the causes of congenital conditions and tracing hereditary abnormalities with a view to providing heredity advice; to an increasing extent, attention is also focused on the identification of genetic abnormalities in patients, for diagnostic, prognostic and therapy-selection purposes.

Furthermore, it is possible to determine a predisposition towards an increasing number of diseases and to ascertain the associated levels of risk by prenatal and postnatal testing.

Under the influence of these developments, the number of clinical genetic tests conducted will rise sharply over the next few years. It seems likely that the existing Clinical Genetics Centres will not be able to meet the growth in demand.

Before formulating a policy on these matters for the period ahead (to be implemented partly through new Section 18 regulations planned for 1997), I would like to hear your views.

More specifically, I would like you to address the following questions:

1 What is the present scientific status of the forms of clinical genetic testing referred to above and what scientific developments may be expected?
2 In light of the expected scientific developments, are there any particular ethical or socially relevant issues which the government should address?
3 Should the forms of clinical genetic testing and heredity advice presently covered by Section 18 of the WZV remain within the scope of the Act's provisions and should the forms of care in question continue to be concentrated in the existing Clinical Genetics Centres?
4 What levels of demand (both in terms of overall volume and in terms of the number of centres required) for the forms of clinical genetic testing and heredity advice referred to in question 3 may be expected in the period up to 2001?
5 How do you anticipate volumes to develop in the period up to 2001 in those fields where clinical genetic testing is undertaken for diagnostic, prognostic or therapy- selection purposes?
6 Do you believe that concentration of clinical genetic testing as referred to in question 5 is desirable in the period ahead? If so, how should this concentration be effected?
7 What preconditions/quality requirements should be attached to the performance of clinical genetic tests of the kind referred to in question 1?

I would like to receive your report before 1 June 1996, partly because the planning horizon of the existing Clinical Genetic Testing and Heredity Advice Regulations is 1997, which implies that the regulations should be updated before that time.

I would be grateful if you would appoint Mr JB van den Wijngaard to assist your deliberations in the capacity of an advisor representing the department.

Dr E. Borst-Eilers,
(signed)
Minister of Health, Welfare and Sport

Annex **B**

The Committee

- H Galjaard, *Chairperson*
  professor of human genetics, Erasmus University, Rotterdam
- EM Bleeker-Wagemakers (to 1 February 1996)
  professor of ophthalmogenetics, University Medical Centre, Amsterdam
- GH Blijham
  professor of internal medicine, Utrecht University Hospital
- FT Bosman
  professor of pathology, University Institute of Pathology, Lausanne
- C van Broeckhoven
  professor of gene technology, University Institution, Antwerp
- HG Brunner
  professor of anthropogenetics, Catholic University of Nijmegen
- RR Frants
  professor of anthropogenetics, University of Leiden
- JKM Gevers
  professor of medical law, University of Amsterdam
- B Löwenberg
  professor of haematology, Erasmus University, Rotterdam
- WJ Mooi (from 1 February 1996)
  professor of pathology, Erasmus University, Rotterdam
- RAC Roos
  professor of neurology, Leiden University Hospital

- MP Springer
  professor of general medical practice, University of Leiden
- H Storm
  clinical chemist, Clinical Chemical Laboratory Foundation, Leeuwarden
- A Tibben
  psychologist-psychotherapist, Erasmus University, Rotterdam
- JB van den Wijngaard, *advisor*
  policy officer, Ministry of Health, Welfare and Sport, Rijswijk
- DCM Gersons-Wolfensberger, physician, *Secretary*
  Health Council of the Netherlands, The Hague

The Committee consulted the following external experts:

Regarding industrial developments:

Roger Craig, Therexsys Ltd, Chief Scientific Officer, Keele, UK
F Grosveld, director of Genexsys Ltd and professor of molecular biology Erasmus University, Rotterdam
Thomas J White, Roche Molecular Systems, vice-president Research&Development, California

Regarding DNA testing outside the CGCs:

EJ Ruitenberg, director of the Blood Transfusion Service's central laboratory, Amsterdam

Regarding developments in oncology:

P Borst, scientific director of the Dutch Cancer Institute, Amsterdam
J Klijn, head of the hereditary tumour out-patients' clinic, Daniel den Hoed Clinic, Rotterdam
EJ Meijers-Heijboer, department of clinical genetics, Rotterdam University Hospital

Regarding cardiovascular disease:

DE Grobbee, epidemiologist, Rotterdam
AM Havekes, chemist, Leiden
AWM van der Kamp, cellular biologist, Rotterdam
JJP Kastelein, internist, Amsterdam

MADH Schalekamp, internist, Rotterdam
AFH Stalenhoef, internist, Nijmegen

Regarding counselling:

CHCM Buijs, Groningen
A van Haeringen,
BCJ Hamel, Nijmegen
LP ten Kate, Free University, Amsterdam
NJ Leschot, Academic Medical Centre, Amsterdam
MF Niermeyer, Rotterdam

Regarding DNA analysis:

E Bakker, Leiden
DJJ Halley, Rotterdam
M Mannens, University Medical Centre, Amsterdam
E Mariman, Nijmegen
B Smeets, Maastricht
JK Ploos van Amstel, Utrecht
H Scheffer, Groningen

Regarding concentration and organization:

CHCM Buijs, Groningen
L ten Kate, Free University, Amsterdam
GJ van Ommen, Leiden
M Breuning, Leiden

Regarding haemato-oncology:

PM Kluin, Leiden
AJP Veerman, Free University, Amsterdam
E Vellenga, Groningen
TJM de Witte, Nijmegen

Regarding thalassemia diagnostics:

PC Giordano, Leiden

Regarding developments in anthropogenetics:

M Breuning, Leiden/Rotterdam
CHCM Buijs, Groningen
LP ten Kate, Amsterdam
GBA van Ommen, Leiden

Annex **C**

Criteria for genetic screening programmes*

Genetic screening programmes must meet the following criteria:

1 The genetic screening programme must address a health problem or a condition which can lead to a health problem for the subject or the subject's offspring.

2 The target group for the screening programme must be clearly defined.

3 The purpose of the programme must be to offer the participants information regarding the presence or risk of a condition or genetic characteristic, and to enable them to make decisions on the basis of this information.

4 Practical post-test options must be open to the participants.

5 Participation in the genetic screening programme must be entirely voluntary and based upon properly informed consent.

6 The target group must be properly informed in a manner which is readily comprehensible for members of the group.

7 The test method used must be appropriate for the purpose of the screening programme.

8 Adequate facilities must be available for repeat testing, for the provision of post-test options and for the provision of information and support to the participants.

9 Adequate steps must be taken to ensure that the privacy of participants is protected and that participants' rights in connection with personal data and cell material are respected during the handling and storage of medical data and cell material.

10 If scientific research is to be carried out in connection with the screening programme, the participants must be properly informed about this research in advance.

* Health Council of the Netherlands: Committee Genetic Screening. The Hague: Health Council of the Netherlands, 1994; publication no. 1994/22.

11 The efficacy, efficiency and safety of the test procedure, any follow-up activities and the arrangements for the provision of information and support to the participants must be subject to constant quality control.

12 The advantages of participation for the participant must clearly outweigh the disadvantages. To enable the advantages and disadvantages to be weighed up, the party proposing the screening programme must provide information on the following matters:

a the prevalence of the disease or condition in the target group

b the natural progression of and variation in the seriousness of the condition

c the target groups for whom testing is potentially appropriate and the basis upon which the proposed target group and subject age (band) were selected

d the specificity, sensitivity and predictive value of the test method to be used and the discomfort involved for participants

e the post-test options open to those for whom the test results are unfavourable

f the length of time which the procedure allows for consideration and possible implementation of treatment options

g the possible favourable and unfavourable psychological, social and other consequences for (potential) subjects and their relatives, as well as for social groups, of being invited to participate, of participating and of not participating

h the likelihood of erroneous results, the possible consequences of erroneous results for participants and the measures to be taken to minimize any adverse consequences;

i the steps to be taken to ensure that the participants' access to the labour market or to private insurance is not unreasonably compromised by participation or non-participation in the programme or any follow-up research;

j the cost of providing the necessary infrastructure and of operating the screening programme.