

Genetic Tests and Future Need for Long-term Care in the UK

Report of a Work Group of the Continuing Care Conference Genetic Tests and Long-term Care Study Group, chaired by Dr Virginia Warren, BUPA

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Foreword

Our knowledge of genetic science is expanding rapidly. Genetic testing could grow rapidly over the early decades of the next century. The overall result will be of benefit to people since those people with a predisposition to a certain disease or a combination of impairments could take preventative measures. They could make life-style changes or receive medical treatment or therapy earlier and thus defer the onset of disease, or significantly reduce the risk.

Widespread genetic testing of the population would raise many issues for the insurance industry. Would people with a predisposition to a disease take out insurance more readily and in larger amounts than the average? Would people who know that they have a predisposition to a disease fail to reveal the fact, and thereby adversely select against the insurance office which could lead to substantial underwriting losses?

The public also has worries and doubts about the relationship between genetic testing and insurance. Would some people with a particular genetic profile be denied insurance cover completely? Would some people only obtain insurance at a very high cost that only a few people can afford?

A joint seminar of the Royal Society and the actuarial profession in September 1996 considered the implications for life assurance. The general feeling was that there were some problems associated with high sums assured, but there were unlikely to be adverse effects for either the insurance industry or the general public. For normal cases of average size, life assurance cover could be obtained by proposers without increases in premium and without reference to genetic test results.

The Association of British Insurers has drawn up guidelines and a Code of Practice on how member offices should use genetic information. Several researchers have suggested that, though the impact of genetic testing will be relatively slight for life assurance, it could have a serious impact on other classes of insurance in future years – medical fees insurance and long-term care insurance have been quoted as particular cases.

The Continuing Care Conference (CCC) is a unique coalition of commercial, charitable and public service organisations with a common purpose to ensure that the public and private funding of long-term care needs of elderly people meets their reasonable expectations and preserves their dignity in old age. Several prominent insurance offices are members. Research, advice and recommendations of good practice are a fundamental part of CCC's *raison d'être*. CCC has sponsored a distinguished multi-disciplinary team of medical doctors, actuaries, geneticists and consultants to consider the effects of genetic testing on long-term care and insurance. CCC was aware that in North America there were calls for making it illegal for insurance offices to take notice of genetic test results when underwriting or pricing long term care insurance. CCC wants to promote a reasoned discussion in the United Kingdom.

The Study Group's report is not exhaustive and concentrates principally on Alzheimer's disease, though outlines are given for diseases which lead to the requirement for long-term care, or are thought to be significantly influenced by the genetic profile. The

relationship between genetic and other (environmental) risk factors is explored. This shows that for most diseases which are significant for long-term care, environmental factors are more important than genetic factors.

An actuarial model developed by Dr A S Macdonald was used to estimate the likely long-term care cost that results from susceptibility to Alzheimer's disease according to the Apolipoprotein E (ApoE) gene. For a small percentage of people, around 2%, there is a higher long-term care cost, at just over 10% higher than the average for males, and below 10% for females. Insurance offices and the Association of British Insurers (which has drawn up guidelines and a Code of Practice on how member offices should use genetic information) will now need to consider whether this degree of 'extra' risk can be absorbed into the standard underwriting pool. Under current underwriting practice for long-term care insurance, 10% of extra risk is generally taken as the boundary at which extra underwriting terms are imposed. Many insurers are likely to absorb this degree of extra risk within the standard underwriting pool.

The Study Group members, under the leadership of Dr Virginia Warren, are to be congratulated on accomplishing this wide-ranging and important study. This study, which concentrates on Alzheimer's disease, will serve as a model for gauging underwriting terms for other diseases and may be of use in care planning. It will encourage other bodies and other study groups to extend the research to other classes of insurance.

Desmond Le Grys
Director of Research, Continuing Care Conference

1. The Project: Scope, Summary and Conclusions

1.1 Terms of Reference

"To research and evaluate the significance of diagnostic and prognostic genetic markers in the financing (both private and state) of long-term care of the elderly, and in relation to the provision of care." CCC Genetic Tests and Long-term Care Study Group minutes 22.5.98

Objective: to take what information is available on this topic, and present it in a form useful to funders and providers of care.

1.2 Scope of the study

This is a pragmatic piece of work. We have sought to find relevant information, and to collate and present it in a way which is accessible to funders and providers of long term care. We have aimed to give you a valid impression, not a detailed appreciation, of the present state of play.

We have done this to the best of our ability, within the constraints of the time and skills available. As you read and use the booklet, please remember that the work was undertaken by a group of active geneticists and insurance specialists, none of whom could make its production a main task. We have been able to work up the section on late-onset Alzheimer's most fully. For all the conditions we would wish the "provider" aspect and also the ethical context to have been more fully explored. For the latter, you may like to

see Mental disorders and genetics: the ethical context, the report of the Nuffield Council on Bioethics, published in September 1998, and available on the web. (Nuffield, 1998)

Similarly, apart from Angus Macdonald's model of Alzheimer's, we are conscious of the absence of a "healthcare economics" input. You might like to see Alzheimer's Disease in the United Kingdom: Burden of disease and future care by Bosenquet N, May J and Johnson N (Health Policy Review paper 12, London: Imperial College School of Medicine Health Policy Unit, 1998) (Bosenquet, N et al, 1998) and Fit for the Future: The prevention of dependency in later life: a Report of the Prevention of Dependency in Later Life Study Group chaired by Elizabeth Mills (ed Prophet H, London: Continuing Care Conference, 12, Little College Street, SW1P 3SH) (Prophet, H (ed) 1998)

In this text, abbreviations and acronyms, listed in 6.1, are given in italics. We realise that many readers will not be familiar with the vocabulary of genetics and hope that you will find helpful the following informative introduction to genetics and a glossary available on the Internet:

- *Genetics: Basis for medicine in the 21st century*, pages 53-56. Published by Munich Reinsurance Company, 1998. Copies are available from Munich Re, 154 Fenchurch Street, London EC3M 6JJ (Tel: 0171 626 2566)
- <http://www.hhmi.org/GeneticTrail>

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1.4 Executive summary

Genetics is advancing rapidly as a laboratory science, and will enhance our understanding of the causes and modulators of all diseases. It can be expected to contribute to the treatment (avoidance, amelioration or cure) of many of the conditions which give rise to a need for long-term care. However, it is clear that these advances are not imminent but will start to bear fruit in the medium to long term (ie 5-20 years).

- Increasing genetic knowledge impacts in four ways on conditions that give rise to a need for long term care:

- it may allow confirmation of diagnosis in affected people
- it may allow predictive testing in healthy people
- increased understanding of genetic factors may allow environmental triggers to be identified, hopefully leading to preventive measures

- new genetic knowledge may lead to new forms of treatment.

- Diagnostic genetic testing of people who are already showing symptoms is already widespread and is increasing. It has implications for long-term care if it helps define the prognosis. It may have repercussions for healthy family members if they choose to be tested.

- For predictive testing of healthy people it is important to distinguish two cases:

- Some tests lead to useful preventive action. Insofar as the preventive measures are effective, these tests are uncontentious, and have no implications for long-term care

- Some tests simply indicate the probability of future disease without allowing the risk to be modified. Such tests are relevant to long-term care but are fraught with ethical difficulties

- For conditions that are entirely genetically determined, most of the genes have now been identified. Predictive testing is technically possible, and is available, for example for Huntington's disease, within a tightly controlled ethical framework.

- Few conditions are exclusively due to inherited genetic factors. Most are due to a mixture of inherited genetic factors and lifestyle and environmental factors. The genetic variants that confer some of the susceptibility to common conditions such as heart disease, diabetes and schizophrenia are proving difficult to identify, but there is gradual progress with many diseases. Our current knowledge does not allow predictive or diagnostic genetic testing and our knowledge of the lifestyle and environmental risk factors is not complete either. Nevertheless, understanding of the two areas is sometimes sufficient to allow us to indicate to the public and patients how they could reduce their risk of developing disease or alter its course for the better.

- Increasing genetic knowledge will refine health professionals' advice to the public and patients. Three ways in which this might happen can be envisaged:

- (i) it will be feasible to avoid or ameliorate some diseases by altering genes directly.

- (ii) it will be feasible to avoid or ameliorate some diseases by altering gene products (proteins) by diet or medication

- (iii) the main impact of genetic knowledge on treatment over the next few years is likely to be through drug development. We know that some drugs are more effective, or cause fewer side effects, in some patients than others. Often, the explanation of this will turn out to be genetic. Genetic testing should allow some currently available drugs to be used with greater precision, and may be a prerequisite for using some new drugs.

- A small proportion of some cancers is due to pre-conceptual genetic changes (eg up to 10% of all breast cancer). The identification of such a genetic change allows the estimation of the lifetime risk of someone with that genetic constitution developing that disease. Characteristically, early studies are conducted with affected families, and the estimated lifetime risk is high (eg 85% for breast cancer for women with BRCA1). Further studies, which are population based, are then carried out, and the estimated risk falls (eg to 55% in the case cited). This happens because the number of people in the general population with the genetic susceptibility but no disease becomes apparent. This effect will almost certainly be seen with the e4 allele for ApoE 4 in relation to Alzheimer's disease.

- Long-term care is labour-intensive, whether delivered formally or informally. The demography of the UK is changing. Until about 2011 the increase in the working age population will keep pace with the increase in the 'dependent' population. After that, the ratio will become unfavourable and there will be progressively fewer people to provide formal or unpaid care.

- The Study Group's report is not exhaustive and concentrates principally on Alzheimer's disease, though outlines are given for the major groups of diseases which lead to the requirement for long-term care, or are thought to be significantly influenced by the genetic profile. The relationship between genetic and other (environmental) risk factors is explored. This shows that for most diseases which are significant for long-term care, environmental factors are more important than genetic factors.

- For a small percentage of people with Alzheimers disease, around 2%, there is a higher long-term care cost, at just over 10% higher than the average for males, and below 10% for females. Insurance offices and the Association of British Insurers (which has drawn up guidelines and a Code of Practice on how member offices should use genetic information) will now need to consider whether this degree of 'extra' risk can be absorbed into the standard underwriting pool. Under current underwriting practice for long-term care insurance, 10% of extra risk is generally taken as the boundary at which extra underwriting terms are imposed. Many insurers are likely to absorb this degree of extra risk within the standard underwriting pool.

1.5 Recommendations

- 1) The Genetics and Insurance Committee (GAIC) note that the same genetic test can have different relevance for different insurance products. A test which predicted a long period of morbidity associated with normal, or near normal, life expectancy would have different meaning for long term care insurance than life insurance. GAIC should make

multiple assessments of each test, classifying them as appropriate for use, or not appropriate for use, for each class of insurance product.

2) That long-term care insurers should not plan to rate applicants for risk of genetically complex disease unless:

a) it becomes clear that consumer-driven “right to know” testing has become sufficiently common in the UK for serious anti-selection to take place if applicants are not rated,

AND

b) actuarially sound data are available to relate the risk of a particular genotype to the risk being insured, and not just to the risk of a specific disease.

3) That those in all sectors involved in funding and providing long term care use the forthcoming years before genetic susceptibility testing has a major influence on clinical practice to introduce relevant teaching. This needs to be a component of all relevant professional training courses, and of current practitioners’ continuing professional development.

4) That research into the interactions between genetic and lifestyle risk factors for disease is supported, with a view to finding the most cost effective way to reduce that risk. More actuarial research is needed.

5) Our model has suggested that 2% of people could possibly be asked a higher premium for long-term care cover on the basis of genetic understanding of their susceptibility to Alzheimer’s disease. The implications of this need exploration.

1.6 Key Points about Specific Conditions (listed alphabetically)

Diseases giving rise to the need for long-term care, and those which produce symptoms in the elderly and which have interesting genetics, were considered. In our full report we codified the information gleaned onto a standard template and have abstracted the key points here.

Alzheimer’s Disease, familial early onset

- This is very rare, comprising only about 2% of all Alzheimer’s disease.
- Some families show autosomal dominant inheritance with near 100% penetrance, so an individual with an affected parent can deduce that they have a 50/50 chance of developing the disease personally. Conversely, a family member whose parent (or grandparents) on the affected side is well and aged more than 70 can reassure themselves that they are very unlikely to be at risk.
- Mutation screening is difficult and not currently routinely available in the UK.
- From an insurance viewpoint, this presents similar underwriting problems for family members as Huntington's disease.

Alzheimer's Disease, late onset

Key points relating to Alzheimer's disease and genetic testing

- Late-onset Alzheimer's Disease (AD) is common but genetically complex. The only unambiguously identified genetic factor is ApoE.
- ApoE4 is associated with an increased likelihood of Alzheimer's. ApoE2 may be protective. This risk or protection is thought to act through an effect on time of onset.
- Susceptibility must be due to a combination / some combinations of other genes and lifestyle risk factors. At present, we have limited information on these.
- Although ApoE4 genotyping is simple, several authoritative recent reports have warned against using it for diagnostic or predictive purposes. In addition to the poor predictive value for an individual, it is a general ethical principle of genetic testing that it should be performed only when a positive result leads to some useful intervention.
- Although in principle undisclosed ApoE testing could allow substantial anti-selection in long-term care insurance, such testing is not generally available within the UK, either over the counter (which would contravene the guidelines of the Advisory Committee on Genetic Testing (ACGT) or clinically. Family history is the major risk factor: an affected first-degree relative doubles the risk of late-onset disease.

Key points relating to the actuarial model

- According to our model, long-term care costs vary depending on ApoE status. The magnitude of the variation depends on assumptions about a number of factors. Those we have considered are (i) the frequency of the different genotypes in the population, (ii) the extent to which a given genotype is protective against, or risky for, Alzheimer's, (iii) the overall age/sex-specific mortality rate, (iv) how this is modulated in those with Alzheimer's by being in an institution and (v) whether genotype influences mortality rate. We have presented tables which show the effects of varying the assumptions made. These are capitalised at age 60.
- For context, we have also calculated the overall costs of a pension starting at £10,000 per year from age 60, increasing at 3% per year.
- The modelled overall care costs are about 60% of the pension costs for males, and over 90% for females. Females suffer several financial disadvantages; they live longer (so pension costs are higher) and require more long term care on average. Considering the genetic risk, the e4 allele puts females at greater risk of AD. In addition, the majority of unpaid carers, whose economic value is included in the care costs, are female.
- Pension costs are not very dependent on ApoE genotype. It is clear that increased care costs will not be significantly offset by reduced pension costs.

Cancer: Breast Cancer

- Little breast cancer is due to known genes.
- Even with a strong family history, women reaching late middle age without developing the disease become not much more likely to get it than a woman without such a family history - they “grow out of” their risk.
- Women can potentially reduce the risk of breast cancer by eating healthily, exercising regularly and moderating alcohol intake.

Cancer: Colorectal Cancer

- About 10% of colorectal cancers are largely genetic and a further 10-15% are associated with strong family history or with ulcerative colitis. The remaining 75-80% of cases are sporadic.
- Acquired genetic changes associated with the development of colorectal cancer are increasingly being understood.
- A predominantly vegetable diet would probably reduce risk.
- Population screening for early disease, rather than genetic susceptibility, may be introduced in the UK.
- For genetic cases, predictive DNA testing is possible, but would only be offered to a healthy person if the family history suggested there was a high risk.

Cancer: Endometrial Cancer

- Little endometrial cancer is due to pre conceptual changes in genes.

Cancer: Liver and Pancreatic Cancer

- Inherited genetic contribution to these cancers is small.
- Primary liver cancer is very rare in this country - largely because hepatitis B is not prevalent. Continuing control of this infection rather than anything genetic is the way to keep it rare.
- Secondary liver cancer is very common in the UK, but is a different entity.

Cancer: Ovarian Cancer

- Approximately 5% to 10% of ovarian cancers are familial and three distinct hereditary patterns have been identified. Limited predictive testing is possible in families with breast-ovarian cancer.

Cancer: Prostate Cancer

- Prostate cancer is very common in elderly men. It is often asymptomatic, or causes few problems.
- Many men die with prostate cancer, rather than of prostate cancer.
- In some, it does follow an aggressive course, with local symptoms and distant metastases giving eg bone pain.
- Some initial progress has been made in identifying susceptibility genes, but as yet no predictive testing is available.
- We do not know how best to treat disease of the various degrees of aggressiveness and spread.

Cataract

- About 50 purely genetic forms of cataract have been described, but they are very rare and constitute only a small proportion of all cataracts.
- Cataract should not generate demand for long-term care because it is so treatable.

Diabetes Mellitus: Type 1

- Type 1 diabetes is genetically complex.
- Environmental factors must interact with genetic factors in its causation.
- We do not at present know how to prevent it; this is a research priority as prevalence is rising rapidly and diabetes is an unpleasant and costly condition with many complications.

Diabetes Mellitus: Type 2

- Type 2 diabetes is common (approx 4% of the population).
- At present there is no place for genetic testing in determining susceptibility to Type 2 diabetes. Family history and ethnic identity are the main predictors of risk.
- Heart disease is a common complication (8% of people with diabetes): it is estimated that a quarter of this is attributable to the D allele of the ACE gene. People with type 2 diabetes and at least one copy of this allele can potentially reduce their risk.
- Avoidance of obesity, and adequate exercise are protective.

Fragile X

- There are many causes of mental retardation, including chromosomal, single gene and non-genetic causes.
- Fragile X is the commonest known single-gene cause of moderate-severe mental retardation in males. Females are more mildly and variably affected.
- Various characteristic physical features can suggest the diagnosis in an affected boy; the diagnosis can be confirmed in either sex by a DNA test.
- Fragile X follows a well defined but complex inheritance pattern in families; careful assessment of the full pedigree and DNA data is needed to calculate risks of affected children.
- Examination of the X chromosome may cut short months of uncertainty, developmental assessment and worry for the parents, and inform further reproductive choices.

Haemorrhagic Stroke

- Haemorrhagic stroke comprises about 10% of stroke in the UK. It does not share the genetic causes of blood lipid abnormalities with IHD and ischaemic stroke. It looks similar clinically because the resultant brain damage causes similar patterns of disability in movement, speech etc. • The major risk factor for “primary” haemorrhagic stroke is high blood pressure. “Secondary” haemorrhagic stroke is mainly due to brain tumours, or abnormalities of the blood.
- At one year after first ever haemorrhagic stroke, approx 65% of people will have died, 10% will be alive and dependent, and 25% alive and independent.
- Any genetic influence is via any genetic influence on high blood pressure.

Huntington’s disease

- Huntington’s disease is entirely genetically determined. A person who carries the HD mutation will inevitably develop HD, if they live long enough.
- The age of onset is very variable, and cannot be predicted for individuals.
- All affected people carry the same mutation, for which a simple DNA test is available.
- Predictive testing is strictly controlled, limited to a few specialist genetics centres using internationally agreed protocols.

Ischaemic Heart Disease

- This is a very common disease and if genetics can be used to allow a proportion of people at risk to avoid the onset of the disease or to reduce the severity of the disease they have got, it will be very important to society as well as to individuals. • It has long been apparent that there were symptoms and signs in common between IHD and

ischaemic stroke, and increasing genetic knowledge is confirming the overlaps between the two conditions.

- It has long been apparent that there were symptoms and signs in common between IHD and ischaemic stroke, and increasing genetic knowledge is confirming the overlaps between the two conditions.
- While we have gone some way to understanding the genetics of IHD, there is still a long way to go. We are very well informed about the environmental factors that play a part, and people can reduce their risk without waiting for the genetics by addressing them.
- Where the same molecule seems to play a major role in the development of two diseases, (IHD/ischaemic stroke and Alzheimer's), genetic testing for it in one context could bring unwelcome news in the other context. Society needs to consider the ethical and practical implications, including implications for insurance practice.

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Manic Depression

- Family, twin and adoption studies support an effect of genetic susceptibility, but to date no susceptibility genes have been conclusively identified.
- Information that is available supports the view that some psychiatric disease has a molecular basis, so that in the medium term we can reasonably hope for effective drugs whose design is tailored to the underlying pathogenesis.

Multiple Sclerosis

- A condition which must result from an interplay of genetic and environmental factors.
- We do not currently understand enough to prevent it, or to treat it well.

Osteoarthritis

- A very common condition in which it seems likely that a number of genes will be shown to be involved, together with lifestyle factors.
- It is likely that it will be divided into a number of separate diseases by genetic pathology.

Osteoporosis

- It is likely that osteoporosis is a complex disease which will be revealed to have specific genetic as well as lifestyle components.

Parkinson's disease

- A disease with a genetic element where occupational medicine has given specific clues regarding the interaction of industrial chemicals with genetics, and quite a good understanding of the biochemistry of how symptoms are produced.
- We should know how to ameliorate or avoid disease as understanding develops.

Rheumatoid Arthritis

- A fairly common disease which affects people in young adult life and therefore causes many years of disability. Its drug treatment is not particularly targeted or effective, and tends itself to have serious side effects. So, an insight from genetics could be particularly valuable.
- It appears that certain HLA types confer susceptibility to rheumatoid arthritis.

Schizophrenia

- A moderately common (1% of population) disease with a peak of incidence in young adults.
- Family, twin and adoption studies support an effect of genetic susceptibility, but to date no susceptibility genes have been conclusively identified.
- Information that is available supports the view that some psychiatric disease has a molecular basis, so that in the medium term we can reasonably hope for effective drugs whose design is tailored to the underlying pathogenesis.

- Following concerns about care in the community, the balance of public provision between community psychiatric and institutional care is currently under review. It must be remembered that some ‘long-term residential care’ for people with schizophrenia happens within the prison service, where cases may not actually be recognised and therefore appropriate treatment not given.

1.7 Summary of Relevant Population Attributable Risks

Introduction

We sought published estimates of the population attributable risk (PAR) due to inherited genetic change, and present these here. The PAR is defined as the proportion of new cases of a disease in a population that can be attributed to a given risk factor. It can be seen that inherited genetic change is responsible for relatively little of the need for long-term care amongst older people generally, and for little of the illness they experience which, while it may not lead to the need for long-term care, reduces their quality of life. It would be inappropriate to set our expectations of ‘genetic medicine’ very high in these respects. However, in some cases it may be revealed that an inherited genetic change is a ‘necessary’ prerequisite for the development of a disease along with a handful of environmental and lifestyle risk factors, each one of which is only ‘optional’. In that case the genetic risk factor will take on disproportionate importance.

Positions on spectrum

The following numbers refer to positions on a scale where 100% preconceptual is represented as zero, and 100% post-conceptual is represented as 100. The position on the spectrum is estimated rather than absolutely defined. It is represented as a single number or as a range. These numbers have been estimated from a graphical representation in the original report.

AD: early onset	65
AD: late onset	83
Cancer: Breast Cancer	83-98
Cancer: Colorectal Cancer	80-85
Cancer: Liver and Pancreatic Cancer	100
Cancer: Ovarian Cancer	85
Cancer: Prostate Cancer	90-100
Cataract	70
Diabetes Mellitus, Type 1	50-60
Diabetes Mellitus, Type 2	40-45
Fragile X	0
Haemorrhagic Stroke	67-77

Huntington's Disease	0
Ischaemic Heart Disease	63-77
Ischaemic Stroke	63-83
Manic Depression	40-50
Multiple Sclerosis	52-58
Osteoarthritis	53-75
Osteoporosis	70
Parkinson's Disease	75-90
Rheumatoid Arthritis	45-60
Schizophrenia	40-65

2. Genetic Tests and Long-term Care: background to the study

2.1 Placing genetics in context: demographic predictions

In looking at the relevance of genetic tests to long-term care, we took account of the changing context within which care is provided. Clearly, demographic changes were key areas for consideration.

The population of the United Kingdom is projected to increase gradually from 58.8 million in 1996 to over 62 million by 2021. Longer-term predictions suggest the population will peak at nearly 63 million in 2031 and then gradually start to fall.

“Dependency” rates will fluctuate; in 1996 there were 632 dependents per 1000 people of working age. This figure is predicted to fall gradually to about 580 per 1000 in 2020 when the increase in women's retirement age is complete. It will then increase rapidly, with longer-term projections suggesting a levelling off around 700 per 1000 from the mid 2030s. The figures are similar those in the early 1970s, but then it was children who comprised the majority of dependents. Note that without the planned change in women's retirement age, the proportion of dependents would have risen earlier and further as indicated by the dotted lines in the figure. (NB Between April 2010 and March 2020, state retirement age will change from 65 for men and 60 for women to 65 for both sexes. One should always beware of interpreting “dependency” too literally; children and the elderly both drive the economy. Equally, many are relatively self-reliant, and indeed care for others.)

There is a flex point in the dependency ratio at around 2011; it is important to remember that this figure has a denominator as well as a numerator. The size of the population of working age is predicted to rise until then, and then decline as the post-war bulge reaches the retirement ages. Up to 2011 the working population's increase is enough to match the increase in the elderly so the resulting ratio is nearly constant. The declining number of children means the ratio with them falls sharply, so the combined ratio also falls.

After 2011 the changeover to a declining working population transforms the picture. The ratio in respect of the elderly rises to a new high while that in respect of children levels off, despite their falling numbers. The underlying trend is an increase in the combined ratio, moderated for a decade by the artefact of the change in women's pensionable age. Sources: Shaw (1998); Craig (1997).

Figure 1: Projected age distribution, United Kingdom, 1996-2036

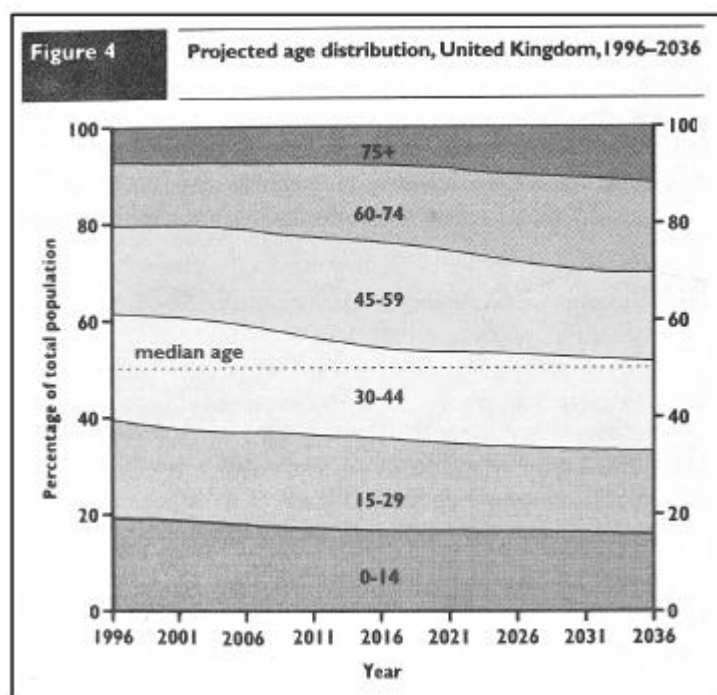


Figure 2: Actual and projected dependency ratios, United Kingdom, 1971-2036

Source: Population Trends, Spring 1998, Office for National Statistics, © Crown Copyright 1998. Data supplied by Government Actuary's Department, from 1996-based national population projections.

2.2 Placing Genetics in Context: Attributable Risk

Genetic factors probably play some role in every disease, but the overall importance of any given factor can be summarised by the population attributable risk (PAR). Verbally, this is the proportion of new cases of a disease in a population that can be attributed to a given risk factor - in this case, an undesirable genome. It is usually quoted as a percentage.

$$\text{Mathematically: PAR\%} = \frac{[Pe (Ie - Iu) \times 100]}{(Pt \times Iu)}$$

where Pe = number of persons exposed

Pt = persons in the population

Ie = incidence rate among the exposed

Iu = incidence rate among the unexposed

It = incidence rate for the total population

(Last (1988); Khoury et al (1991); Khoury and Wagner (1995)).

Thus, with greater understanding we will be able to place diseases on a continuum between those at one end which are largely due to preconceptual changes in genes eg coeliac disease and those at the other end which are largely due to environmental exposure eg bacterial meningitis. In the former, exposure to gliadin (a protein found in wheat and barley but not oats or rice) in the diet “switches on” the disease only in genetically susceptible individuals; treatment is currently by diet, but this is difficult to manage and socially disruptive. Genetic therapy would hugely improve people’s quality of life. In the latter, the ability to carry the relevant bacteria in the throat without succumbing to meningitis, as many adults do, and to survive if an overwhelming number of bacteria does produce the disease, is associated with the genetics of the immune system, eg Westendorp RGJ et al (1997). This knowledge does not currently contribute to the care of those with the disease, but does explain the superficially odd observation about bacterial carriage.

Note however that even for a disease with a low population risk attributable to undesirable genes, a few people with the disease may have a major genetic component. Breast cancer is an example; fewer than 10% of people with the disease have known undesirable genes (the population genetic attributable risk is low) but, if your family has a mutant version of the BRCA1 or BRCA2 gene, you may have a 55-85% lifetime risk of developing the disease (high personal genetic attributable risk).

2.3 Aspects of genetic disorders: genetically simple and complex diseases

Examples: Huntington’s Disease and Coronary Artery Disease

Some diseases depend entirely on mutations in one specific gene. Such diseases are called mendelian. Within families they are inherited according to specific rules. Clinical geneticists are skilled in recognising these patterns (autosomal dominant, autosomal recessive or X-linked) and can give exact probabilities of a person being affected. In Huntington’s disease the child of an affected person has a 50% chance of inheriting the causative mutation, and anybody carrying that mutation who lives long enough will eventually develop the disease, although the age of onset cannot be predicted.

Most diseases are not mendelian. Coronary Artery Disease (CAD), which gives rise to ischaemic heart disease, provides a good example. There are many genes and conditions that predispose to CAD. In the table, the first four disorders are caused by rare mutations in certain genes, and are found to have strong family histories. The disease susceptibility follows the rare mutation through the family. But additionally, even in a single patient, most diseases requiring long-term care are not caused or promoted by single gene mutations. Rather, a complex sequence of inherited (pre-conceptual) and/or acquired (post-conceptual) changes in DNA, and exposure to environmental risk factors is necessary. The last two disorders in the table do not show a pattern of positive family history. In each case there is an association with commonly found gene variants, but being a carrier of one of these variants merely elevates the probability of developing the condition. In the case of coronary thrombosis the mutation associated with the disease is

found in 20% of the general population but in 40% of those with coronary thrombosis. The association is statistically valid, but most people with the mutation do not develop coronary thrombosis. The increased probability is significant in public health (and possibly insurance) terms, but is not predictive for an individual.

Table A: Examples of genetically simple and complex diseases: coronary artery disease

Condition	Gene	Frequency	Characteristics
Familial hypercholesterolaemia (Autosomal Dominant)	LDLR (58 pathogenic mutations)	1:500 in west	Avg. age of infarct 46 Elevation of LDL bound to cholesterol
	Polygenic	1:25	Avg. age of infarct 58
Familial combined Hyperlipidaemia (Autosomal Dom)	ApoC3 Plus several unknown genes	1-2:100 in west	Avg. age of infarct 52 Elevated LDL and VLDL accounts for 10% of premature CAD
Familial hypertriglyceridaemia (Autosomal Dom)	Pepsinogen	rare	Avg. age of infarct 57 Environmental influences alcohol and carbohydrates
Hyperlipoproteinaemias Types I to V	Many ApoE 29 mutations ApoB 17 mutations		Types II, IV & V autosomal dominant Types I & III complex autosomal recessive 20-60% will get CAD
Coronary thrombosis	glycoprotein IIIa association with One mutation PI ^{A2}	Mutation found in 20% normals 40% in CAD	Mainly premature CAD
Angina pectoris	ACE association with Allele D (not as strong as above)		Appears to cause infarct and unstable angina when homozygous

(Sources: ACE: Leatham et al, (1994))

It also needs to be kept in mind that it is naive to regard any given genetic variant as “desirable” or “undesirable”. Any variant that persists in the population at high frequency is likely to be beneficial to more people (of reproductive age) than it is harmful to, or it

would have been eliminated by evolution. This is a powerful argument for not seeking to alter the DNA in germ cells. Having two copies of the gene for sickle cell anaemia is undesirable; having one is very desirable in the tropics because it helps protect you against malaria. Similarly, a story may be emerging of a protective role against typhoid played by the cystic fibrosis gene. Humans' relationship with infectious diseases is an uneasy battle; given rising antibiotic resistance, we could again be glad of such effects.

2.4 The rationale of genetic testing and its relevance to long term care

Almost all genetic tests test DNA rather than chromosomes or a gene product (RNA or a protein). With a few exceptions, especially tumour cells, every cell of a person contains almost exactly the same DNA, so any accessible source of cells can be used for DNA testing. Each human cell contains 6,000,000,000 base-pairs of DNA. A typical gene contains 1,000 – 100,000 base pairs of DNA. Current mutation detection technologies target between 1 and 500 specified base pairs from the total DNA for examination. Thus screening for mutations depends on knowing in advance where to look.

- Testing for a known specific sequence change (eg a specific single base-pair on chromosome 4 that is always abnormal in achondroplasia) is quick and cheap.
- Testing for any pathogenic change within a specified gene (eg screening for mutations in the BRCA1 breast cancer gene) stretches current technology to the limit. It is routine in research but is not generally practicable in day-to-day clinical genetics. For many genes, routine service testing should become feasible over the next 5 years with the development of gene chip technology.
- Searching for any pathogenic change in any gene is quite impossible now and for the foreseeable future.

Single-gene diseases are usually caused by obvious mutations with high predictive value.

When mutations in a single gene cause a disease (these are the diseases called mendelian, like cystic fibrosis or haemophilia), the mutations, once found, are usually easy to recognise. Most often the mutation will completely inactivate the relevant gene. Such mutations, when detected, are good predictors of genetic risk. But there are many ways of inactivating a gene, and so for most such diseases, unrelated affected people have different mutations (but in the same gene). Screening a patient for mutations entails screening the whole gene for any suspicious-looking DNA sequence change.

The DNA sequence changes conferring susceptibility to complex diseases are probably not classical mutations, but common and usually non-pathogenic variants.

At present very few susceptibility genes for common, genetically-complex diseases like diabetes have been definitely identified. However, it is thought

that the DNA sequence variants that confer susceptibility to these common diseases will mostly turn out to be minor changes that slightly alter the activity of a gene, or its response to physiological controls, rather than “classical” mutations that totally inactivate a gene. These variants are expected to be common in the general population, and to be pathogenic only when combined with similar changes in several of the other susceptibility genes.

It is hoped (but not proven) that only one or a few sequence variants in a given gene would act as susceptibility factors. If true, it would follow that susceptibility testing would need to look for only one or a few particular DNA sequence variants when testing a given gene. Thus we could imagine a panel of cheap and simple specific tests covering dozens of different susceptibility genes, perhaps all on one gene chip, that would map out a person’s overall susceptibility to a given disease. Interpreting the results would depend on extensive epidemiological and genetic data defining the risk conferred by each particular combination of factors. This will require very large, very detailed studies in diverse settings, possibly running over as long as a generation. All this lies some way in the future, and depends on current speculation about the nature of genetic susceptibility factors turning out to be correct. This research may turn out to be more useful for tailoring specific drug treatments for affected people, rather than for assessing the risk that an unaffected person will develop a disease – in other words, there may be few implications for predicting the likelihood that somebody will require long-term care, not least because improved treatment will change the natural history of the disease, so past data will not be valid for predicting the future.

2.5 Integration of genetic and other risk factors

Many of the more common diseases will follow the type of complex inheritance seen for coronary heart disease. We might also find that some “non-genetic” forms of diseases, that show no family history, are in fact caused by combinations of common mutations in many different genes acting in tandem with environmental factors. There is a need for epidemiological as well as genetic work, and for effort in integrating the two. Likely environmental factors include lifestyle choices such as smoking and lack of exercise, as well as contact with harmful bacteria and viruses and exposure to radiation (naturally from granite, cosmic rays etc, or from medical imaging) and toxic chemicals (eg petrol and diesel fumes as well as specific occupational hazards). Clarifying these is not a task for geneticists alone. Further work will be required on the epidemiology of the environmental exposures, and in understanding the interactions between them. (See McMichael (1994) for a useful conceptual diagram.)

It might be harder to detect genetic contributions to these diseases if they do not have any genes of major effect in their catalogue and all of the genes carry equal weight. The ability to predict future disease states in these conditions is likely to be quite limited unlike the predictive value of known mutations in diseases with simple modes of inheritance such as Huntington’s disease and cystic fibrosis.

Breast cancer provides examples of the sorts of questions that need answering. Are the approximately 90% of cases which apparently arise in response to environmental factors (eg excessive oestrogen exposure and late first full term pregnancy) a different disease from the approx 10% largely due to genetic causes, but one which has the same final common pathway? Are the 15-45% of people with the undesirable BRCA status who not develop the disease protected by their reproductive life history?

2.6 Common questions, fears and misconceptions about genetics and genetics and insurance

Q: If I have the gene will I develop the disease?

A: For a few rare diseases, this is true. In these cases the gene is said to be 100% penetrant. But for the great majority of diseases, genes are just like any other susceptibility factors: having the “disease” gene increases your risk, but does not inevitably predestine you to get the disease.

Q: If I do not have the gene I will not get the disease?

A: This again this is not generally true. There is a degree of uncertainty as many genetic diseases have sporadic, non-genetic forms. If you do not possess the gene causing the disease in your family you are still at the same risk of developing the non-genetic form of the disease as the general population.

Q: If I have a disease gene will this affect my insurance policies?

A: No. Currently there are many restrictions on the use of genetic testing for insurance purposes. The ABI, HGAC and ACGT have all issued guidelines on this point, and until the reliability, relevance and actuarial significance of each test has been proven they can not be taken into account for insurance purposes. The HGAC and ACGT have set up an independent group, the Genes and Insurance Committee (GAIC), to assess each test in relation to each form of insurance. There is a long-standing tradition of use of family history information for assessing applicants for some types of insurance.

Q: If I reveal a genetic test result will it affect other members of my family?

A: No. All genetic test results are confidential and can not be used to assess another individual's application.

Q: Will I be asked to reveal any genetic test results from my relatives?

A: No. Genetic test results can not be linked to another person for insurance purposes.

Q: If I reveal a genetic test result to one insurance company can they pass it to others?

A: No. This is against the confidentiality agreement signed by you as an applicant and also against the guidelines of the ABI, HGAC and ACGT.

Q: How many tests can be done currently?

A: Tests are possible for several hundred diseases, but these are all rare. Mostly these

diseases have their onset in childhood. Even for those adult-onset diseases where a genetic test is possible, the use of such tests is confined to people who have a strong family history of the disease.

Q: Will population screening for genetic diseases ever occur?

A: It already occurs. Babies born in the UK have a heel prick test for Phenylketonuria (PKU) and the test has been used for at least 30 years. This is a quick and easy test. Screening is used if it results in people getting effective treatment who would otherwise suffer some severe disease – babies with PKU would be severely mentally retarded, but if they are detected by early screening and put on a special diet, they grow up normal. This test meets the classic requirements for responsible detection of pre-symptomatic disease (Wilson & Jungner, 1968).

Q: What if people get themselves tested by buying a test ‘over the counter’?

A: For ethical, (and, secondarily, financial) reasons, the NHS will not introduce widespread testing services unless knowledge of the result can be used to alter the natural history of the disease for the better. For example; the NHS will not seek to identify those at increased risk of Alzheimer’s unless care can be offered to mitigate this risk. If “right-to-know” testing becomes widespread, then, in relation to private insurance and Alzheimer’s (and assuming that GAIC validates the test for use in place of family history), it may be appropriate for two risk pools to be used. This arrangement would allow the industry to protect itself from adverse selection, be practical and efficient to administer. It would, however, be disadvantageous to a small proportion of the population, and UK society and the Government will need to consider how the services this group may need will be funded.

Q: Will all this genetic testing lead to a “cure”?

A: Hopefully: if a genetic test has been developed this means that a genetic cause of a particular disease has already been found and this may lead to novel cures to correct the defect and prevent symptoms for developing. For example in PKU the “cure” is a dietary one which prevents any symptoms from developing if specific foods are avoided.

Q: Can genetic tests predict how severely I will be affected if I get a genetic disease?

A: Sometimes, but usually not. Most genetic diseases are variable, even when people carry exactly the same mutation.

2.7 Future prospects?

When an understanding of genetics, environmental factors and their interaction is gained, new tools will be able to be developed for clinical medicine:

- some diseases will be able to be avoided or ameliorated by altering genes eg introduction of functioning genes into stem cells in the lungs of people with cystic fibrosis.
- some diseases will be able to be avoided or ameliorated by altering gene products eg a

high homocysteine level in the blood is a risk factor for ischaemic heart disease. It appears that eating more folate would reduce this risk in many people by boosting a faulty enzyme (methylentetrahydrofolate reductase) which in other people keeps the homocysteine level low. Equally, new drugs will be able to be developed to achieve this sort of effect.

- some diseases will be able to be treated with greater precision with currently available drugs. It is observed that some drugs are more effective, or cause fewer side effects, in some individuals than others. Often, the explanation for this will turn out to be genetic.
- drugs will be able to be designed to treat specific conditions in people with specific genomes.

Some of these will reduce demand for long term care. None are currently available.

3. Condition-specific Information

3.1 Criteria for inclusion

The group considered conditions that are likely to lead to a (short) timespan of long-term care among many people. We took note of the list of disabling chronic conditions considered in 'Fit for the Future: The prevention of dependency in later life', viz

- Dementia
- Stroke
- Osteoporosis
- Urinary incontinence
- Joint pain and stiffness, eg osteoarthritis and rheumatoid arthritis
- Cataract

Given our brief to look at genetic tests and future need for long-term care, we put aside urinary incontinence as it is usually a long term side effect of childbirth, or a symptom of another pathology (eg benign prostatic hyperplasia, diabetes), rather than a disease in its own right, the genetics of which could be considered. We included cataract, although the causes are highly heterogeneous and mostly non-genetic, because there are rare genetic forms.

To the list we added:

- other fairly common causes of disability, eg Parkinson's, multiple sclerosis.
- common conditions causing significant morbidity, if not always dependency, particularly if their genetics are of interest and illuminate general understanding, eg ischaemic heart disease, diabetes, cancers, schizophrenia.
- rare conditions which can cause individuals many years of dependency, eg Fragile X, manic depression.
- rare conditions of late onset which can cause individuals some years of dependency, eg Huntington's.

We are aware of the ABI's list of seven genetic tests considered relevant to underwriting for life insurance. Our brief is future need for long-term care, a context in which time of

onset and duration of dependency is a more important consideration than prediction of age of death.

We are aware that chromosomal disorders, eg Down's syndrome, may give rise to many years' need for long-term care for some affected people. We have not addressed it here as the genetics of this is well understood.

The Template

The findings of the background research on the diseases included in our study have been laid out in a consistent format, given overleaf. This will enable the reader to assess and compare information relating to causation and prevalence, and the potential for reducing the burden of disease.

Disease name and brief description

(from the Oxford Reference Dictionary, 1986, when available)

Key points:

Causation:

- Known genes
- Likely genetic risk factors
- Known environmental and lifestyle risk factors
- Likely environmental and lifestyle risk factors

Position on spectrum (population attributable risk):

The numbers quoted refer to positions on a scale where 100% preconceptual is represented as zero, and 100% post-conceptual is represented as 100. The numbers are approximations only: they are estimated from an original graphical representation.

(NB: The position on the spectrum is estimated rather than absolutely defined. It is represented by a single figure or, where a range is given, by figures at the lower and upper ends of the range.)

Method

The estimates of population attributable risks were retrieved by performing Medline searches using GratefulMed and PubMed, using "and" operators between these search terms: disease name, population attributable risk, genetics. In GratefulMed, human subjects and English language were specified. OMIM was found to be too laborious, and to have a lower yield of relevant information.

Prevalence

- Age sex table from the 4th National Morbidity Study, conducted in 1991 by the OPCS and RCGP, published by them with the DoH in 1995 (National Morbidity Study, 1995) Rates are per 10,000 person-years at risk.

Potential for reducing burden of disease

- Environmental and lifestyle risk factors
- Drug therapy -
 - increased coverage of current therapy (British National Formulary section references will be given; this is published twice a year by the BMA and Royal Pharmaceutical Soc. of GB)
 - genetically targetted conventional therapy
 - genetic therapy
- Invasive interventions

NB When individual papers are quoted the detailed reference will follow; where information is not attributed, it is taken from the Oxford Textbook of Medicine, third edition, 1996.

4. The Costs of Care: Case Study – Alzheimer’s Disease

4.1 Introduction

Geneticists divide Alzheimer’s disease into two quite different categories, although the clinical and pathological features of the two types are identical. For the purposes of this study we have concentrated on late-onset Alzheimer’s disease (as defined below) because of its central relevance to the long-term care of older people and its associated costs, the focus of CCC’s activity. The case study is in two parts:

- condition-specific information contributed by Professor Andrew Read of Manchester University (you might like to see section 3.1 for an explanation of the way this information is laid out), and
- an actuarial model, contributed by Dr Angus Macdonald of Heriot-Watt University, that estimates the likely costs of future care arising from the disease and indicates what proportion of costs may be associated with different ApoE alleles.

Early onset Alzheimer’s disease is discussed, in less detail, together with other conditions listed in the section Other Condition-specific Information (5)

4.2 Alzheimer’s Disease (AD): Condition-specific Information

Alzheimer’s is a progressive physical disease of the brain. It affects a person’s ability to remember, speak, think and make decisions. (Source: Alzheimer’s Disease Society)

Key points:

Key points relating to Alzheimer’s Disease and genetic testing

- Late-onset AD is common but genetically complex. The only unambiguously identified genetic factor is ApoE.
- ApoE 4 is associated with an increased likelihood of Alzheimer’s. ApoE 2 may be protective. This risk or protection is thought to act through an effect on time of onset. Susceptibility must be due to a combination / some combinations of other genes and lifestyle risk factors. At present, we have limited information on these.

- Although ApoE genotyping is simple, several authoritative recent reports have warned against using it for diagnostic or predictive purposes. In addition to the poor predictive value for an individual, it is a general ethical principle of genetic testing that it should be performed only when a positive result leads to some useful intervention.
- Although in principle undisclosed ApoE testing could allow substantial anti-selection in long-term care insurance, such testing is not generally available within the UK, either over the counter (which would contravene the guidelines of the Advisory Committee on Genetic Testing (ACGT)) or clinically. Family history is the major visible risk factor: an affected first-degree relative doubles the risk of late-onset disease (Blacker et al, 1998).

Key points relating to the actuarial model

- According to our model, long-term care costs vary depending on ApoE status. The magnitude of the variation depends on assumptions about a number of factors. Those we have considered are (i) the frequency of the different genotypes in the population, (ii) the extent to which a given genotype is protective against, or risky for, Alzheimer's, (iii) the overall age/sex-specific mortality rate, (iv) how this is modulated in those with Alzheimer's by being in an institution and (v) whether genotype influences mortality rate. We have presented tables which show the effects of varying the assumptions made. These are capitalised at age 60
- For context, we have also calculated the overall costs of a pension starting at £10,000 per year from age 60, increasing at 3% per year.
- The modelled overall care costs are about 60% of the pension costs for males, and over 90% for females. Females suffer several financial disadvantages; they live longer (so pension costs are higher) and require more long-term care on average. Considering the genetic risk, the e4 allele puts females at greater risk of AD. In addition, the majority of unpaid carers, whose economic value is included in the care costs, are female.
- Pension costs are not very dependent in ApoE genotype. It is clear that increased care costs will not be significantly offset by reduced pension costs.

Causation:

- Known genes

ApoE is a serum protein that has three forms made from three alleles, e2 (8%), e3 (77%) and e4 (15%). The frequencies of these alleles (in Caucasians; (see Farrer et al, 1997)) imply that 23% of people carry one copy of e4 and 1.8% carry two copies. 34-65% of people with late-onset AD have at least one copy of e4 and many studies have shown a statistical association between e4 and AD. Analysis of data on 6000 patients (Farrer et al, 1997) suggested odds ratios (OR) for Caucasians of 3.2 (95% confidence interval 2.8-3.8) for e3/e4 and 14.9 (95% CI 10.8-20.6) for e4/e4. e2 may be protective (OR 0.6, 95% CI 0.5-0.8). e4 is also a risk factor in other ethnic groups, but the risk is less well defined because of the smaller number of cases studied. Attempts have been made to construct a more specific predictor by subdividing e4 genes into high-risk and low-risk

classes according to the nature of nearby DNA sequences, but the results are unconfirmed. Our understanding will be further refined as results become available from population based studies rather than hospital clinic or brain bank based studies. The OR for e4 will probably fall as it is likely to be more common in people without the disease than we at present appreciate. This phenomenon has already been seen with BRCA1 and breast cancer.

Many e4 individuals do not develop AD, and many non-e4 individuals do. Meyer et al (1998) presented data on an elderly population suggesting that ApoE type did not influence whether subjects will develop AD, but rather when susceptible individuals would do so. Regardless of ApoE genotype, more than half of the population will develop AD by age 100, suggesting that some other factors govern susceptibility. In a French study (Bickeboller et al, 1997), the risk of e3/e4 individuals developing AD by age 85 was 14% for men and 17% for women, which could be low, as it equates to what is expected in the general population. ApoE genotype does not affect the rate of clinical decline in affected people.

Although ApoE genotyping is simple, several authoritative recent reports have warned against using it for diagnostic or predictive purposes (American College / Society, 1995; McConnell et al, 1998). In addition to the poor predictive value for an individual, it is a general ethical principle of genetic testing that it should be performed only when a positive result leads to some useful intervention.

As well as modifying risk of AD, ApoE genotype affects the risk of some types of hyperlipidaemia and possibly of atherosclerosis and macular degeneration. For insurance purposes this brings possible problems. The AD risk cannot be considered in isolation from other effects of ApoE type on health and longevity. There is the potential for people in lipid clinics to be typed for ApoE. Generally they would be unaware of any implication of the result for their risk of AD. Thus they would probably not disclose the result of this genetic test on any insurance proposal. However, having received signed consent from the patient to release details of medical history to the insurance industry, the GP might do so. This scenario is believed currently to be hypothetical rather than a real risk in the UK. Under current ABI guidelines, the insurer should not use such information as a further indicator of risk.

Although in principle undisclosed ApoE testing could allow substantial anti-selection in long-term care insurance, such testing is not available within the UK, either over the counter (which would contravene the guidelines of the Advisory Committee on Genetic Testing (ACGT)) or clinically outside the possible context of lipid clinics. Family history is the major visible risk factor: an affected first-degree relative doubles the risk of late-onset disease (Blacker et al, 1998).

- Likely genetic risk factors

Reports of other susceptibility genes (some specified, e.g. bleomycin hydrolase, butyrylcholinesterase, alpha-2 macroglobulin alpha-antichymotrypsin (Ezquerria et al, 1998; others defined only by chromosomal location) are controversial and unreliable.

- Known environmental and lifestyle risk factors

None

- Likely environmental and lifestyle risk factors

Head injury

Basic levels of education only

Occupational exposure to glues, pesticides, fertilisers, particularly in those with less education. (Canadian Study, 1994; Jorm, 1997; Schofield et al, 1997)

Use of non-steroidal anti-inflammatory drugs, use of hormone replacement therapy and having achieved a high educational level may all be protective. (Canadian Study, 1994; Jorm, 1997; Schofield et al, 1997)

- Position on spectrum (population attributable risk)

PAR for the e4 allele of apolipoprotein E: 20% (in Rotterdam) (Slooter et al, 1998); 13.7% (in East Boston, Mass) (Evans et al 1997).

On a scale from zero (100% preconceptual) to 100 (100% postconceptual), Alzheimer's disease is about 83.

Prevalence estimates (%) for all types of dementia from the MRC Cognitive Function and Ageing Study.

Age	Male	Female
65-69	1.4	1.5
70-74	3.1	2.2
75-79	5.6	7.1
80-84	10.2	14.1
> 85	19.6	27.5

Note: these rates are not based on a physician diagnosis of dementia, but on a well validated questionnaire used in a standardised way by trained interviewers in five centres across the UK. It does not discriminate between people with problems due to Alzheimer's and people with dementia due to other causes. These caveats apart, this study gives the most robust estimate to date of the prevalence of dementia syndrome for England and Wales, and should be regarded as reliable and representative for use in planning services. (MRC CFAS, 1998). This is why it is used here rather than the National Morbidity Study.

Death Rate

'The age standardized death rate from Alzheimer's disease apparently increased from less than 1 per 100,000 in 1979 to 19 for men and 21 for women in 1996. This may be due to a true increase in incidence, or to greater recording of dementias and neurodegenerative disorders on death certificates by doctors (for which there is clear evidence, although it is also clear that it often happens that dementia is still not mentioned

on the death certificates of many people who have had it diagnosed), or a mixture of both. (Kirby, L et al, 1998)

Potential for reducing burden of disease

- Environmental and lifestyle risk factors
Head injury avoidance may modify the risk.
- Drug therapy
 - Increased coverage of current therapy: several drug trials are underway, but there is at present no treatment or prevention.
 - Genetically targetted conventional therapy. None
 - Genetic therapy
- Invasive interventions

4.3 A Simple Actuarial Model of Alzheimer's Disease

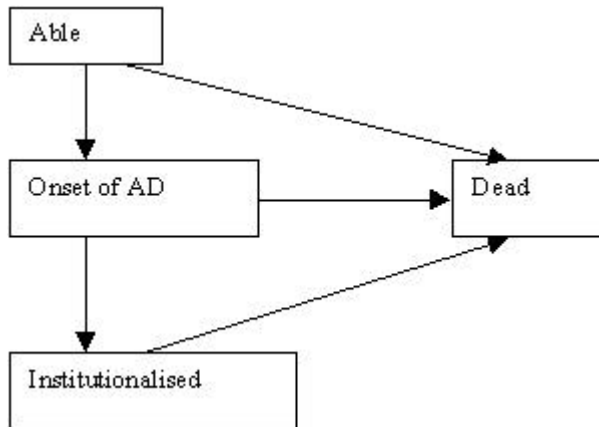
The purpose of this model is twofold: to estimate likely costs of future care arising from Alzheimer's Disease (AD); and to indicate what proportion of these costs might be associated with the different ApoE alleles. Currently, ApoE is the most-studied gene known to indicate susceptibility to AD at older ages, and we can use epidemiological studies to estimate: (i) the prevalence of different genotypes in the population; and (ii) the rate of onset of AD for each genotype. That said, the available evidence does not allow us to attach great certainty to any estimates.

Although there is clear evidence of an association between certain alleles of the ApoE gene and AD, the mechanism is unknown, and it is quite likely that other genes will turn out to be involved. In future, it will be possible to determine genetic component(s) of AD in much more detail. The current work illustrates a methodology for translating such information into components of care costs, which will help in assessing the value of new clinical approaches based on genetics.

The model considers a person who is healthy at age 60. This is a convenient starting point, for two reasons: (i) it is a typical retirement age; and (ii) roughly speaking, occurrences of AD at younger ages are rare 'early onset' cases, while occurrences after age 60 represent the bulk of cases. To make AD-related care costs meaningful, we will compare them with the cost, on retirement at age 60, of a pension.

The model represents the 'life history' of a person in relation to AD, as movements between the states shown in Figure 3. The model allows for movements to take place at different ages, reflecting the distribution of age at onset of AD, for example. Associated with each state in the model is an annual cost of care, allowing the cost of care associated with a 'life history' to be calculated. We are interested in the average of these costs over the population, or equivalently the average cost in respect of a person who is healthy at age 60. Obviously, this crude model could be elaborated to represent in more detail the development of AD, but we have had to restrict the representation to those events, modelled by movements between states, that have been studied in the epidemiological literature.

Figure 3.



Calibrating the Model

In order to calibrate the model, we need to refer to the extensive medical literature on AD; this will be covered in Macdonald & Pritchard (forthcoming) and we will not describe it here. We just note the following:

- (1) Quite a lot is known about the epidemiology of AD through large-scale studies, although the direct causes remain unclear. This situation will change as the MRC Cognitive Function and Ageing Study progresses, and more papers are published.
- (2) Much uncertainty remains in the estimates used in the model. It is estimated that AD accounts for roughly half of all dementias, but accurate diagnosis of AD is difficult, and so is the determination of the time of onset.

Allowing for the ApoE Genotype

The ApoE e4 allele has been found to be associated with increased susceptibility to AD at older ages. This enters the model in two ways:

- (1) The population is divided into different risk pools according to ApoE genotype. In the model, individuals are randomly allocated to genotypes according to the frequencies of the genotype in the whole population; e.g. 1.8% are allocated two copies of e4.
- (2) While the e4 allele puts people at risk of earlier AD, it is unclear whether or not it alters the course of the disease, once it has begun. On balance it probably does not and our model follows that assumption.

Prevalence of ApoE Genotypes

To allow for the different ApoE genotypes, we represent each by a separate model as shown in Figure 1. This allows us to represent the different risks of onset of AD, and premature mortality, in respect of each genotype. To obtain results in respect of a person chosen at random, we combine the outcomes of the different models, in proportion to the population frequencies of the genotypes. These frequencies are roughly as in Table 1, at age 60 (Farrer et al, 1997): because of rounding, these add up to 100.1%, but we have ignored this slight discrepancy.

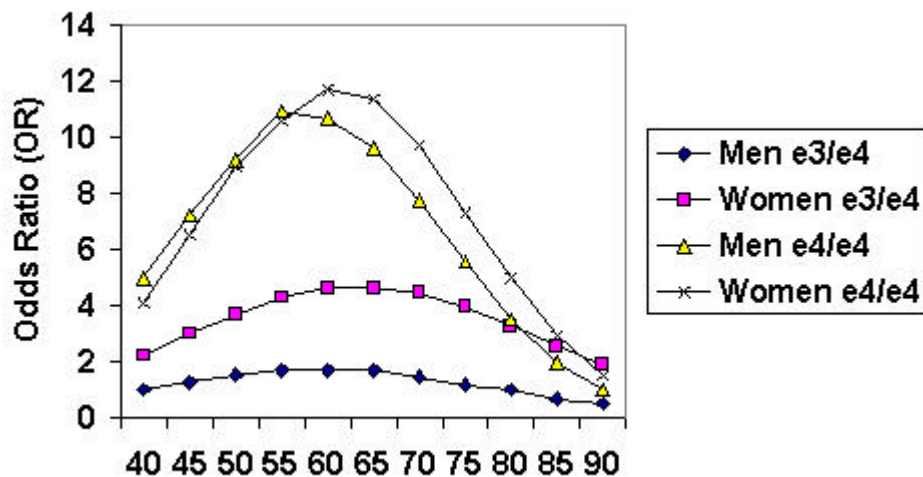
Table 1: Prevalence of ApoE genotype in population at age 60

ApoE genotype	frequency
e2/e2	0.8%
e2/e3	12.7%
e3/e3	60.9%
e2/e4	2.6%
e3/e4	21.3%
e4/e4	1.8%

People with two copies of the e4 allele are at greatest risk, but this genotype is relatively rare. People with one copy of the e4 allele are subject to some extra risk (women much more than men), and are much more common. People with the e2/e2 genotype are too uncommon for even the meta-analysis of Farrer et al (1997) to distinguish their AD risk from that of e2/e3, and we combine these two in the model.

Figure 4:

Odds Ratio (OR) Relative to ApoE Genotype e3/e3 (e3/e4 and e4/e4).



(Source: Farrer et al, 1997)

Figure 5:

Odds Ratio (OR) Relative to ApoE Genotype e3/e3 (e2/e4 and e2/e3)

(Source: Farrer et al, 1997)

Prevalence of AD in Relation to ApoE Genotype

Figures 4 and 5, taken from Farrer et al (1997), show the odds ratios relative to the e3/e3 genotype at different ages. They all show a peak, at ages around 60-70. Generally speaking, an odds ratio greater than 1 indicates more genetic risk than the e3/e3 genotype, while an odds ratio less than 1 indicates less risk than the e3/e3 genotype. The most interesting odds ratios are e2/e4 and (for males) e3/e4. These peak above 1, but then fall away to less than 1. This suggests that the presence of a single e4 allele does not confer greater risk at all ages. In particular, it suggests that the e2 allele confers a protective effect that is only exceeded by the adverse effect of the e4 allele at certain ages. This feature has a significant effect on the care costs calculated by the model.

However, it is very likely that the odds ratios indicated by Farrer et al. (1997) are on the high side, possibly very much so. This is because they are derived from case-based studies; that is, studies which take as their starting point people who are known to have AD, or to have a familial risk of AD. More reliable estimates of population risk are obtained from prospective studies of a sample of people representative of the “ordinary” population. For example, in the case of the BRCA1 and BRCA2 genes associated with breast cancer, risk estimates based on case-studies were very high, but are being revised downwards as more representative data become available. Unfortunately, it is nearly always the case that case-study data become available before prospective studies are carried out, and at present we do not know what results a prospective study of ApoE might yield. As a rough assumption, we have cut the odds ratios in Farrer et al (1997) by a factor of 4, but we will also show what the effect would be if the odds ratios in Farrer et al were about right.

Incidence of AD in Relation to ApoE Genotype

No reliable information is available on the precise relative risks suffered by people with the different ApoE genotypes. By “relative risks” we mean the chances that someone with a given genotype will develop AD by any given age, compared with someone with a different genotype. What are available, from the meta-analysis of Farrer et al, are odds ratios¹ at ages up to 90. At ages where the incidence of AD is low (say, below age 70) these approximate the relative risks quite well, but at higher ages they are not such good approximations, especially in a study based on cases rather than a prospective survey.

The odds ratios in Farrer et al. (1997) rise to a peak at about age 60, falling quite steeply at older ages. This is consistent with a similar rising and falling pattern of relative risks.

We have found simple formulae for the relative risks (relative to the e3/e3 genotype) that reproduce closely the reported odds ratios. From other studies, we have fitted a function representing the aggregate incidence of AD, which is close to that of people with the e3/e3 genotype.

¹ The definition of odds ratio is this: the probability that a life in one group has AD is p_1 , and the probability that a life in another group (e3/e3, taken as the standard) has AD is p_2 . Then the relative risk is p_1 / p_2 , the odds in the first group is $p_1 / (1 - p_1)$, the odds in the second group is $p_2 / (1 - p_2)$, and the odds ratio is:

$$[p_1 / (1 - p_1)] / [p_2 / (1 - p_2)]$$

Mortality

We need to consider separately the premature mortality of those who do not have AD, those who have AD but have not yet been institutionalised, and those who are institutionalised.

(a) We have to consider the fact that premature death has been becoming rarer during all of this century, and might continue to do so. This means that the mortality rates in the tables currently used by actuaries are probably much too high. This would tend to underestimate costs which are payable as long as someone survives, including the costs of pensions and long-term care. As a basic assumption, we have cut the mortality rates of people who do not yet have AD to 65% of those of the standard mortality tables AM80 (males) and AF80 (females), published by the Faculty and Institute of Actuaries. This represents quite light mortality by current standards. While this study was in preparation, the Faculty and Institute of Actuaries have published updated tables, which indicate that the trend towards fewer premature deaths is continuing.

(b) Those who have AD, but are not yet institutionalised, are assumed to suffer relatively low mortality rates. The exact assumption varies with sex and the 'background' mortality in (a) above, but is around 20% of the AM80 or AF80 tables. This is supported by Jost & Grossberg (1995), a brain-bank analysis which found that very few lives with AD died outside an institution. It seems intuitively reasonable that this should be so, since deteriorating health could itself result in a person with AD becoming institutionalised.

(c) Several studies offer indirect evidence that people with AD in institutions experience mortality rates rather higher than normal, possibly more severe at relatively younger ages, but no clear conclusion emerges. In connection with (b) above, we have assumed that these people suffer relatively high extra mortality, namely an addition of 0.2 to the force² of mortality. Later, we will also show the effect of a smaller additional mortality (0.02) while institutionalised.

There is much uncertainty about the appropriate mortality to assume. Later, we show the effects of varying the assumptions we made above.

AD Care Costs

Holmes et al (1998) surveyed the costs of care of 655 persons diagnosed as having AD, during March and April 1997. They included the opportunity costs of unpaid care, but excluded state benefits (to avoid double counting). This study, therefore, gives a more complete picture of the societal costs than others that only consider institutional care costs. The costs per head were found to be as follows (in 1997 money):

(a) £41,794 per year; PLUS

(b) £436.6 per year, for each year since the diagnosis of AD; MINUS

(c) £336.0 per year, for each year of age; PLUS

(d) £17,840 per year, if institutionalised.

² Some technical jargon is unavoidable in describing exactly what we mean by 'high' and 'low' mortality of institutionalised people. The 'force of mortality' is an actuarial term for the probability of dying in the next instant, but expressed in yearly time units (rather as we would measure the speed of a car over the next instant in miles per hour). The 'high' and 'low' mortality assumptions are an addition of 0.2 and 0.02 respectively, to the force of mortality of people unaffected by AD.

The second of these causes some mathematical difficulty in the model we have used; we have replaced it by assuming that, on average, costs corresponding to this factor are incurred at the rate of 5×436.6 per year, roughly equivalent to deaths being spread over the 10 years after diagnosis. This is probably an understatement.

We suppose that care costs increase by about 5% per year, representing earnings inflation, since a significant portion of the costs relates to labour.

Total Care Costs

The estimates calculated as above are care costs in respect of AD only. That is, the cost of care arising from other dementias, or loss of physical function, are not included. Direct estimation of the expected total care costs for a 60 year-old person in good health is a difficult problem, for three reasons:

(a) there are few reliable data, either on the progression of a healthy 60 year-old through various states of disability, or of the costs associated with those states of disability (especially opportunity costs of unpaid carers);

(b) it is likely that different systems of delivering long-term care will give rise to different costs; people's behaviour will depend on the opportunities available to them; and

(c) the overall level of premature deaths is falling, and might continue to do so; this must translate into changes in patterns of disability, but just how is unknown. It is possible that longer lifetimes will result in more time spent in good health, followed by a speedy decline (so the cost of care will fall) or more time spent being cared for (so the cost will rise).

No-one knows.

Because of these difficulties, we show the magnitude of overall care costs in a very simple way. Currently, AD accounts for approximately 25-33% of total care costs, based on U.S. figures (Watson, 1998). We estimate overall care costs by applying a multiplier of 3 to the estimated AD costs.

Comparison with Pension Costs

To give a basis for comparison, we have also used the model to calculate the cost, at age 60, of a pension starting at £10,000 per year, and increasing at 3% per year (representing Retail Price inflation). Historically, price inflation has usually been about 2% less than earnings inflation, so care costs should rise faster than pension costs.

Results

Table 2 shows the results of these assumptions for males and females. The first line shows, in 1997 money, the expected care costs in respect of AD alone, for each ApoE genotype, and the average of these, weighted by the genotype frequencies in Table 1. The figure in the second line represents the overall care costs, estimated as three times the average care costs of AD alone. This is equivalent to the hypothetical lump sum (in 1997 money) that each healthy 60 year old would have to save should such care costs be met by means of a universal levy. The third line shows the cost of a pension starting at £10,000 per year, increasing at 3% per year. (All costs are shown rounded to the nearest £100.)

Table 2: Estimated expected lifetime costs at age 60, with low overall mortality and high mortality while institutionalised (equivalent to single premium costs).

	e2/e3	e3/e3	e2/e4	e3/e4	e4/e4	Weighted Average	Estimated overall care costs
Men	£	£	£	£	£	£	£
AD costs only	31,000	35,900	33,400	34,700	47,000	35,200	
Overall costs							105,600
£10,000 pension	171,900	171,400	171,400	171,300	168,800	171,600	
Women	£	£	£	£	£	£	£
AD costs only	52,300	56,300	65,900	66,900	72,800	58,600	
Overall costs							175,800
£10,000 pension	201,500	200,900	198,100	198,200	195,800	200,500	

The main features of this comparison are:

- Care costs in respect of AD depend upon genotype, in roughly the proportions expected on the basis of relative risks.
- Given the rarity of the e4/e4 genotype, the average AD care costs for males are little greater than those for the low-risk genotypes, but for females the increase is about 10%, because the e3/e4 genotype confers significantly higher risk.
- Overall care costs are about 60% of the pension costs for males, and 90% for females. Females suffer several financial disadvantages; they live longer (so pension costs are higher) and require more long-term care on average. Considering the genetic risk, the e4 allele puts females at greater risk of

AD. In addition, the majority of unpaid carers, whose economic value is included in the care costs, are female.

(d) Pension costs are not very dependent on ApoE genotype. It is clear that increased care costs will not be significantly offset by reduced pension costs.

(e) With the possible exception of the e4/e4 genotype most UK insurers would include all the other genotypes within the standard underwriting pool and would charge the same premium rate (females have higher premium rates than males) and underwriting terms even for the slightly elevated cost for e3/e4.

If the proposer had previously undergone a genetic test which revealed the e4/e4 genotype, and if the results were shown to the insurer, then the insurer would need to consider if it was beyond the boundary of the standard underwriting pool. The extra risk is just over 10% of estimated overall cost for males and just below 10% for females. Under current underwriting practice for long-term care insurance, 10% extra risk is generally taken as the boundary at which extra underwriting terms are imposed. Insurers would need to decide if this extra degree of risk for e4/e4 could be included in the standard underwriting pool. Many insurers are likely to absorb this degree of risk within the standard underwriting pool.

Sensitivity Tests

Given the great uncertainty about the assumptions we have made, we show the effects of varying some of these in this section. Table 3 shows the effect of higher average mortality. Specifically, we assume that mortality follows that of the AM80 and AF80 mortality tables, which represent the years 1979-82, so are rather high by today's standards.

Table 3: Estimated expected lifetime costs at age 60, with high overall mortality (100% pf AM80 and AF80), that is, more of the population are supposed to die prematurely.

	e2/e3	e3/e3	e2/e4	e3/e4	e4/e4	Weighted Average	Es ov co
Men	£	£	£	£	£	£	£
AD costs only	19,500	22,800	21,600	22,400	33,000	22,400	
Overall costs							67
£10,000 pension	148,800	148,600	148,500	148,500	147,000	148,800	
Women	£	£	£	£	£	£	£
AD costs only	36,100	39,200	48,600	49,100	55,300	41,500	
Overall costs							12
£10,000 pension	181,200	181,000	179,000	179,200	177,300	180,700	

Compared with Table 2, care costs decrease by 30-40%, while pension costs decrease by only 10-15%. This effect arises because, if overall mortality is higher, more people die before the onset of AD, and less time is spent in care. However, it is not clear to what extent this feature of the model we have used is realistic; it amounts to an assumption that longer lifetimes mean that more time will be spent in care, rather than more time being spent in good health.

We assumed before that people in institutions suffered substantially worse mortality than average, represented by an addition of 0.2 to the overall force of mortality. This acts to reduce care costs, by removing people from the most expensive state more quickly. Table 4 shows the effect of a much smaller increase, an addition of 0.02 to the overall force of mortality. In other words, people in institutions still have above-average mortality, but not so much as before. The pension costs are omitted, since the comparison in this case would be misleading.

Table 4: Estimated expected lifetime costs at age 60, with low additional mortality risk while institutionalised.

	e2/e3	e3/e3	e2/e4	e3/e4	e4/e4	Weighted Average	Es ov co
Men	£	£	£	£	£	£	£
AD costs only	50,000	57,900	54,500	56,700	81,100	56,900	
Overall costs							17
Women	£	£	£	£	£	£	£
AD costs only	88,600	95,800	117,900	119,000	134,500	101,100	
Overall costs							30

Compared with Table 2, care costs are considerably higher. Longevity of people in institutions is (not surprisingly) a key determinant of costs.

Finally, recall that we cut the relative risks based on the odds ratios for the risk of AD from Farrer et al (1997) (the largest recent study, see Table 1) by a factor of 4. This was to allow for possible (substantial) overestimation of risks arising from case-based studies, rather than prospective population-based studies. Table 5 shows what would happen if we used the odds ratios in Farrer et al without adjustment (all other assumptions are as in Table 2).

Table 5: Estimated expected lifetime costs at age 60, with relative risks given by the odds ratios at age 60 in Farrer et al (1997).

	e2/e3	e3/e3	e2/e4	e3/e4	e4/e4	Weighted Average	Es ov co
Men	£	£	£	£	£	£	£

AD costs only	16,100	41,200	26,400	34,900	87,300	37,000	
Overall costs							11
£10,000 pension	172,900	170,900	170,300	170,100	159,400	170,900	
Women	£	£	£	£	£	£	£
AD costs only	35,500	52,800	85,900	88,900	106,700	60,000	
Overall costs							18
£10,000 pension	203,400	210,400	191,800	192,100	184,300	199,400	

The changes in overall care costs are modest, and there is a small decrease in the pension costs. The overall care costs for males actually fall, because of the fact that three genotypes (e2/e3, e2/e4 and e3/e4) are less risky than the e3/e3 genotype at many ages. Whether this is realistic or not is a question that can only be answered with much more information on the relative risks at higher ages. The most striking feature is (as expected) much greater costs in respect of the e4/e4 genotype, and (for females) the e3/e4 genotype. This could present a significant risk of adverse selection if long-term care were provided primarily through private, voluntary insurance, but in terms of overall costs the rarity of the high-risk genotypes means that the ‘genetic burden’ of AD costs is quite slight.

Figure 6: AD Costs Depending on Level of Relative Risk

Figure 6 shows how the AD care costs for females (by genotype and weighted average) depend on the relative risks; moving from left to right shows the effect of increasing the relative risks from 25% of those implied by Farrer et al (1997), as in Table 2, to 100% of those implied by Farrer et al (1997), as in Table 5. The significant feature is the stability of the weighted average costs, even as the costs of the riskier and less risky genotypes diverge; such a pattern of costs presents significantly fewer problems if care is funded through universal contributions than if care is funded through private, voluntary insurance.

4.4 Scope for Similar Work

The particular model we used was dictated by the available data; the model represents states and movements between states, and we could only use such states and transitions as were covered in the available literature. However, the general form of such a model can be extended to a vast range of other problems, such as genetic conditions and different forms of insurance.

A well-established example is disability insurance (or Permanent Health Insurance) which pays a regular income if the insured person is unable to work. This is represented by a “healthy” (at work) state, an “ill” (off work) state and a dead state, with movements backwards and forwards between “able” and “ill” being possible. This model is already widely used by insurance companies.

Our model only considers AD, and then total care costs are estimated by a crude multiplier of 3. A more advanced model would include extra states, representing in more detail the loss of physical or mental function that introduce a need for increasing levels of care. Such a model, for example, would include the loss of various “Activities of Daily Living” (ADLs) such as dressing and feeding, and would include other cognitive disorders as well as AD. Some of these extensions will be considered in Macdonald & Pritchard (forthcoming).

On the purely genetics side, such models can be used to measure the impact of genetic testing on insurance companies, such as the likely consequences of forbidding insurers to use genetic test information for underwriting. This was in fact the reason for first applying these models to genetic questions (Macdonald, 1997, 1999). More work along these lines is likely to be undertaken in future, in view of the Government’s response to the report of the HGAC and the establishment of the GAIC.

In all cases, the limits on what it is feasible to model are imposed by the available data. Ideally, since the model represents life histories (in terms of events relevant to any given problem), the data should be exactly that: observed life histories of large study populations. These are rarely available. Then we have to rely on published studies, so the models are restricted by events that have been studied; for example, time to onset of AD has been studied, so we can include it in the model. Generally speaking, events are studied because they are of interest, either medically or in terms of health economics, both of which coincide with our interests, so these models can be useful. They could be very much more useful, however, if they could be applied to basic data rather than the bare results that are usually distilled from the data and published.

We must emphasise the many uncertainties that have made this study difficult. None of the figures in the tables should be quoted as exact calculations: that they are not.

Medical and epidemiological studies gather an enormous volume of data, but publications give summary information of limited use to someone seeking to answer a different but related question. The brief statistics that appear in the medical literature, such as means, medians, confidence intervals, odds ratios and lifetime risks, or Kaplan-Meier curves, are not adaptable.

By far the most useful studies are those that provide incidence rates (or transition intensities, in mathematical terms). Our model is based on incidence rates, rather too many of which we have had to guess. A link between the Department of Actuarial Mathematics and Statistics at Heriot-Watt University and the Medical Research Council and Department of Health Cognitive Function and Ageing Study (MRC CFAS) is being nurtured and we hope this will allow us to refine our figures. Many medical and epidemiological studies obtain prevalence rates, based on the number of persons affected at the time of the study because this is more relevant to the provision of services. This is a bit like taking a snapshot instead of a video.

Much more could be done with the data gathered in medical studies, beyond the publication of a few summary statistics in medical journals. We would strongly encourage more collaboration between medical researchers, health economists and actuaries at all stages in the planning and analysis of studies of the conditions listed in the next section of this report.

5. Other Condition-specific information

5.1 Alzheimer's disease: familial early onset

A condition clinically and socially similar to Alzheimer's disease, which has its onset before 65 years of age.

Key Points:

- This is very rare, comprising only about 2% of all Alzheimer's disease.
- Some families show autosomal dominant inheritance with near 100% penetrance, so an individual with an affected parent can deduce that they have a 50/50 chance of developing the disease personally. Conversely, a family member whose parent (or grandparents) on the affected side is well and aged more than 70 can reassure themselves that they are very unlikely to be at risk.
- Mutation screening is difficult and not currently routinely available in the UK.
- From an insurance viewpoint, this presents similar underwriting problems for family members as Huntington's disease.

Causation:

- Known genes
10-50% of early onset cases have mutations in one of three genes: APP, presenilin-1 or presenilin-2 (Cruts et al 1998, Blacker and Tanzi 1998)
- Likely genetic risk factors
None currently
- Known environmental and lifestyle risk factors
None currently
- Likely environmental and lifestyle risk factors
None currently
- Position on spectrum (population attributable risk)

On a scale from zero (100% preconceptual) to 100 (100% postconceptual), familial early-onset Alzheimer's disease is about 65.

Prevalence

Age and sex table for the ICD 9 code most closely approximating the condition of interest, from table 21 (rarely, table 20) of the 4th National Morbidity Study....

- "Senile and prsenile organic psychotic conditions"

Age	Male	Female
25-44	0	0
45-64	4	3

(Rates per 10,000 in each group)

Thereafter, presenile Alzheimer's is subsumed within general Alzheimer's.

Potential for reducing burden of disease

None currently in any of the three categories

- Environmental and lifestyle risk factors
- Drug therapy - increased coverage of current therapy
genetically targeted conventional therapy
genetic therapy
- Invasive interventions

5.2 Cancers

Cancer: "a disorder of the processes of growth, development, and repair during which cells undergo morphological and metabolic deviations from those inherent properties of the cells of the tissue of origin.The cells do not conform to the restraints imposed on the proliferation of normal body cells....spread to distant parts of the body." This potentially fatal cancer arises in the secretory cells of the mammary glands, and characteristically spreads to brain, bone and lung.

5.2.1 Breast and Gynaecological Cancers

Breast Cancer

Key Points:

- Little breast cancer is due to known genes.
- Even with a strong family history, women reaching late middle age without developing the disease become not much more likely to get it than a woman without such a family history - they "grow out of" their risk.
- Women can potentially reduce the risk of breast cancer by eating healthily, exercising regularly and moderating alcohol intake.

Causation:

- Known genes
BRCA1 (on 17q) – in breast and breast-ovarian cancer families, BRCA2 (on 13q) – in breast cancer families (sometimes including cases of male breast cancer), H-ras-1.
BRCA1 PAR: 3.3% (95% confidence interval 0-7.2%) for white women and 0% in African American women. (Newman et al 1998)
BRCA 2 PAR: 10.4% of Icelandic women, and 38% of men with breast cancer occurs in carriers of the 999del5 mutation. (Thorlacius et al 1998)

The proportion of breast cancer cases predicted to be attributable to breast/ovarian cancer gene(s) decreases markedly with age (33% at 20-29 down to 2% at 70-79 when modelled on the CDC Cancer and Steroid Hormone Study. (Claus 1996). No relation between endometrial cancer and a family history of breast or ovarian cancer (Parazzini et al 1994). No interaction with hereditary prostate cancer (Isaacs et al 1995), contested by Thorlacius et al 1998, but they were unable to comment on ovarian cancer risk.

TP53 on 17p – in families with Li-Fraumeni syndrome, which includes premenopausal breast cancer, childhood sarcomas and rhabdomyosarcomas, and other rare cancers.

- Likely genetic risk factors (chromosomal areas being worked on, likely role)
Some “cancer families” have inherited mutations in the BRCA1, BRCA2 or TP53 genes. Some families with pure breast cancer have no mutations mapped to the locations of the known genes. These families account for about 5% of breast cancer. The other 95% of cases appear to be sporadic, without any very strong inherited predisposition. Genes conferring modestly increased susceptibility may include HRAS1.

HRAS1 PAR: 0.092% for breast cancer, the frequency being greater in African Americans than Caucasians. The racial effect is associated with a specific allele (A3.5) (Weston and Godbold, 1997).

- Known environmental and lifestyle risk factors (attributable risk)

Early menarche (eg <12 yrs)

Late first full term pregnancy (eg 30 yrs or older)

No full term pregnancies

“Family history of breast cancer”

Benign breast disease

PAR for unmodifiable risk factors together, as listed above: 15% (Rockhill et al 1998)

High social class 18.9% (High social class together with later age at first birth or nulliparity (29.5%) and “family history of breast cancer” (9.1%) all together account for 47% (CI 17-77) in the NHANES I, as they are not independent risk factors. (Madigan et al 1995)

Duration of lactation (minor protective effect)

Obesity after the menopause PAR: 10.2% (CI 0.2-20.2%)

Prescribed oestrogens : the Pill is not a risk factor for death from breast cancer (Beral et al, 1999)

High alcohol intake (>20g/day) PAR: 10.7% (CI: 4.4-17.05; premenopausal women at higher risk than post)

Low levels of physical activity PAR:11.6% (CI:-0.1-23.35; postmenopausal women at greater risk than pre)

Low beta-carotene intake (<3366microg/day) PAR:15.0% (CI: 7.4-22.95; premenopausal women at higher risk than post)

Low vitamin E intake (<8.5mg/day) PAR: 8.6% (CI:-0.4-17.5%) (Mezzetti et al 1998)

- Likely environmental and lifestyle risk factors (status)
Dietary phyto-oestrogen intake (legumes, pulses) may be protective.

- Position on spectrum (population attributable risk)

On a scale from zero (100% preconceptual) to 100 (100% postconceptual), breast cancer is about

83-98.

For women aged 30-55 initially, ageing to 42-67 (Nurses' Health Study), only 2.5% of breast cancer cases are attributable to a positive family history (Colditz et al 1993).

Prevalence

- Age table for each gynae cancer from the 4th NMS.

Prevalence - rates per 10 000 women

	Breast	Ovary	Endometrium
25-44	10	01	00
45-64	61	11	04
65-74	81	07	11
75-84	88	06	08
85+	87	10	02

- Secular/geographic trends

Migration studies show geographic differences to be more influenced by environmental than genetic factors.

Potential for reducing burden of disease

- Environmental and lifestyle risk factors

Avoid overweight and obesity, excessive alcohol, eat fruit and veg, exercise, specifically legumes and pulses.

- Drug therapy -

- increased coverage of current therapy (BNF 8.3.4.1, 8.2.2, 8.1.3, 8.1.2)

- Tamoxifen as treatment for 1st cancer
- Tamoxifen in preventing 2nd cancers
- Potential for restrogen analogues, eg Raloxifene

- genetically targeted conventional therapy

- genetic therapy

- Invasive interventions

Mastectomy and reconstruction as treatment by age 70. These investigators remind us that prophylactic mastectomy might be considered, but there are two problems: penetrance of the gene and lack of information about the outcome of the procedure. Estimates of how many people with an undesirable gene will get breast cancer are falling as population rather than family studies are done: 0.6% of Icelanders carry the 999del5 mutation of BRCA2. Amongst the women, only 17% get breast cancer by age 50, rising to 37.2% by age 70. The paper reminds us that earlier point estimates of the penetrance (not Icelanders) were 70-90% lifetime risk. (Thorlacius et al, as above) No studies have reported the consequences, over years let alone decades, of prophylactic mastectomy.

Ovarian cancer - in brief

Key Points:

- Approximately 5% to 10% of ovarian cancers are familial and three distinct hereditary patterns have been identified. Limited predictive testing is possible in families with breast-ovarian cancer.
- Some common genes with breast cancer.
- The proportion of ovarian cancer cases predicted to be due to the susceptibility gene ranges from 14% among patients diagnosed in their thirties to 7% among those diagnosed in their fifties (Claus, 1996).

Approximately 5% to 10% of ovarian cancers are familial and three distinct hereditary patterns have been identified: ovarian cancer alone, ovarian and breast cancers, or ovarian and colon cancers (Lynch, Watson, Lynch et al, 1993). The most important risk factor for ovarian cancer is a family history of a first-degree relative (mother, daughter or sister) with the disease. The highest risk appears in women with two or more first-degree relatives with ovarian cancer (Piver, Baker, Jishi et al, 1993). The risk is somewhat less for women with one first-degree and one second-degree (grandmother, aunt) relative with ovarian cancer. In most families affected with the breast and ovarian cancer syndrome or site-specific ovarian cancer, genetic linkage has been found to the BRCA1 locus on chromosome 17q21 (Miki, Swensen, Shattuck-Eidens et al, 1994; Easton, Bishop, Ford et al, 1993; Steichen-Gersdorf, Gallion, Ford et al, 1994). The lifetime risk of developing ovarian cancer in patients harbouring germ-line mutations in BRCA1 is substantially increased over the general population (Easton, Ford, Bishop, 1995).

- Position on spectrum (population attributable risk)

On a scale from zero (100% preconceptional) to 100 (100% postconceptional), ovarian cancer is about 85.

Endometrial cancer - in brief

(cancer of the lining of the womb)

Key Points:

Little endometrial cancer is due to pre conceptual changes in genes.

- Nearly 5% of endometrial cancer arising in women aged 20-54 may be attributable to a family history, and 2% may be related to colorectal cancer, according to the Cancer and Steroid Hormone Study Group (Gruber and Thompson, 1996).
- No relation between endometrial cancer and a family history of breast or ovarian cancer (Parazzini et al, 1994).
- In comparison with women with no family history of endometrial cancer, those with a first degree relative with the diagnosis have an odds ratio of 1.5 (CI 1.0-2.3). However, in this Greater Milan

study, less than 1% of endometrial cancers were attributable to familial (and hence potentially genetic) factors (Parazzini et al, 1994).

5.2.2 Cancers: Digestive tract cancers

Colorectal Cancer

Cancer: “a disorder of the processes of growth, development, and repair during which cells undergo morphological and metabolic deviations from those inherent properties of the cells of the tissue of origin.The cells do not conform to the restraints imposed on the proliferation of normal body cells....spread to distant parts of the body”.

This potentially fatal cancer arises in the glands of the lining of the bowel, and characteristically spreads to the liver.

Key points:

- About 10% of colorectal cancers are largely genetic and a further 10-15% are associated with strong family history or with ulcerative colitis. The remaining 75-80% of cases are sporadic.
- Acquired genetic changes associated with the development of colorectal cancer are increasingly being understood.
- A predominantly vegetable diet would probably reduce risk.
- Population screening for early disease, rather than genetic susceptibility, may be introduced in the UK.
- For genetic cases, predictive DNA testing is possible, but would only be offered to a healthy person if the family history suggested there was a high risk.

Causation:

- Known genes

Adenomatous polyposis coli (APC) or familial adenomatous polyposis (FAP). Chromosome 5q21. Associated with large numbers of polyps and can be diagnosed by sigmoidoscopy. Genetic predictive testing is available in families with a history of APC.

HNPCC – hereditary non-polyposis colon cancer – may be caused by mutations in several genes, usually MSH2 on chromosome 2p, and MLH1 on chromosome 3p. Can present as Lynch I syndrome (site-specific colorectal cancer) or Lynch II (associated with uterine, gastric, ovarian and other malignancies). Definitive diagnosis by DNA testing; criteria for selecting patients for testing are agreed but arbitrary.

Mutations in the APC gene are found in both the rare inherited and common sporadic forms of colorectal cancer, but in the common form the mutations occur in somatic cells of the affected person, and are not passed on to children. The progression from normal epithelium to adenoma, to carcinoma

is among the best understood of cancers, and some of the genes responsible have been identified. However, these changes occur within the developing tumor, and are unrelated to inherited predisposition.

- Likely genetic risk factors

“Colorectal carcinogenesis is increasingly understood, and involves a number of genetic events, which, in a generally stepwise manner, cumulatively result in the progression from normal epithelium to adenoma (polyp) and finally to invasive adenocarcinoma. The changes include activation of the dominantly acting oncogenes regulating cell division and differentiation (k-ras and possibly c-myc) and inactivation of tumour suppressor genes, including APC and MCC (both on chromosome 5), DCC (chromosome 18) and p53 (chromosome 17). In addition, some colorectal carcinomas may show deletions, insertions and mutations on chromosomes 1,4,6,8,9 or 22 suggesting that other tumour suppressor genes may sometimes be inactivated.”

- Known environmental and lifestyle risk factors

Poor diet

- Likely environmental and lifestyle risk factors
- Position on spectrum (population attributable risk)

On a scale from zero (100% preconceptual) to 100 (100% postconceptual), colorectal cancer is about 80-85.

Prevalence

- Age sex table from the 4th NMS, rates per 10,000 in each group

		Colon	Rectosigmoid, rectum and anus
M	25-44	00	00
M	45-64	07	04
M	65-74	23	14
M	75-84	35	30
M	85+	24	30
F	25-44	00	00
F	45-64	06	03
F	65-74	14	07
F	75-84	29	10
F	85+	35	18

Potential for reducing burden of disease

- Environmental and lifestyle risk factors

- Population screening; the case for introducing population screening using faecal occult blood is being considered, but is not decided. Following recommendations from the National Screening Committee, pilot studies of colorectal cancer screening, one in England and one in Scotland, will evaluate over 2-3 years whether a population-based screening programme would be feasible, acceptable to the public and cost-effective. A proposal document was circulated in September 1998 and an announcement made early in 1999, with a view to pilot schemes starting in 1999/2000. The sites for the pilot study (Coventry and Warwickshire, in England; Tayside, Grampian and Fife, in Scotland) were announced on 2 March 1999. It was also confirmed that a single evaluation project will review the results and report to the National Screening Committee in 2001/2.

- Case finding: recommendations for colonoscopic surveillance on the basis of personal medical history, and of family history are available eg Gastroenterology 1997. (Winawer et al, 1997)

- Diet

An intake of five to six portions of fruit and vegetable a day is desirable, both for the micronutrient content and the fibre (which avoids slow colonic transit times).

A low animal fat intake is desirable; bacterial metabolism may produce carcinogens from it.

- Drug therapy

Increased coverage of current therapy BNF 8.1, 8.2.

- Genetically targetted conventional therapy

Potential for genetic markers to be used to improve case finding in cancer families.

- Genetic therapy

None yet

- Invasive interventions

Polypectomy via colonoscope (daycase procedure)

Tumour resection through abdominal incision or abdomino-peroneal resection.

Liver and pancreatic cancer - in brief

Key points

- Inherited genetic contribution to these cancers is small.

- Primary liver cancer is very rare in this country - largely because hepatitis B is not prevalent. Continuing control of this infection rather than anything genetic is the way to keep it rare.

- Secondary liver cancer is very common in the UK, but is a different entity.

Causation

- Position on spectrum (population attributable risk)

On a scale from zero (100% preconceptional) to 100 (100% postconceptional), liver and pancreatic cancer is close to 100.

- Genetic PAR for liver and pancreatic cancer together: approximately 3% (Fernandez et al, 1994)

Prevalence

Age sex table from the 4th NMS

		Liver	Pancreas
M	45-64	00	01
M	65-74	01	03
M	74-84	01	05
M	85+	00	06
F	45-64	00	00
F	65-74	00	03
F	75-84	00	06
F	85+	02	06

5.2.3 Cancers: Cancer in Men

Prostate Cancer

Cancer in the gland which makes the fluid in which the sperm swim in the ejaculate.

Key points:

- Prostate cancer is very common in elderly men. It is often asymptomatic, or causes few problems.
- Many men die with prostate cancer, rather than of prostate cancer.
- In some, it does follow an aggressive course, with local symptoms and distant metastases giving eg bone pain.
- Some initial progress has been made in identifying susceptibility genes, but as yet no predictive testing is available.
- We do not know how best to treat disease of the various degrees of aggressiveness and spread.

Causation:

- **Known genes**

None yet.

Genealogical studies provide evidence of an inherited predisposition to prostate cancer. The magnitude of the effect may be similar to breast cancer.

Hereditary prostate cancer appears to be a relatively site-specific disease, and does not seem to be part of other hereditary cancer syndromes eg breast/ovary (Isaacs et al, 1995).

- **Likely genetic risk factors**

Two different loci on chromosome 1 (HPC1 and PCAP) and one on the X chromosome (HPCX) have been suggested by family studies, but none of the genes has yet been identified. Genes on 10q25 (MXI1) and 11p11 (KAI1) are involved in the progression of an initial lesion to advanced cancer, but have not been implicated in susceptibility.

High incidence in black populations throughout the world, and a low incidence in Japanese. Both may be partly due to genetic factors, but not wholly so, as both groups have higher rates in the US than in Africa or Japan respectively.

- **Known environmental and lifestyle risk factors**

None

- **Likely environmental and lifestyle risk factors**

Hormonal status

Sexual activity

Western lifestyle

- **Position on spectrum (population attributable risk)**

On a scale from zero (100% preconceptual) to 100 (100% postconceptual), prostate cancer is about 90-100.

Prevalence

Age	Males
25-44	0
45-64	7
65-74	45
75-84	137
85+	155

Viewed in one light, these figures are an underestimate. In 1990/91, cases were diagnosed when they caused clinical symptoms, or when cancerous cell were found incidentally in the tissue removed at operation for benign prostatic enlargement. In the subsequent years, usage of a blood test (PSA) indicating increased likelihood of a diagnosis of prostate cancer has increased, so a higher proportion

of “cases” which would never have given symptoms is now recognised. This artefactually increased prevalence is not relevant from the point of view of provision of long-term care, but is from that of provision of primary care, as these men require on-going monitoring, guidance and reassurance.

Potential for reducing burden of disease

- Environmental and lifestyle risk factors

None known to avoid disease

The possible role of population PSA estimation in detecting pre-symptomatic disease is not clear, and there is no UK screening programme. This is partly because there is no good quality evidence on the optimal treatment path for PSA detected cases.

- Drug therapy - increased coverage of current therapy.

None to avoid disease

Hormonal control of established disease: 8.3.4.2

genetically targetted conventional therapy

None yet

genetic therapy

None yet

- Invasive interventions

?Radical prostatectomy

?External beam radiotherapy

?Conformal radiotherapy

?Brachytherapy

Note that there is controversy as to the relative effectiveness of these invasive options for prostate cancers of varying aggressiveness and state of spread.

5.3 Cataract: adult-onset cataract

Cataract is defined as the presence within the crystalline lens of any opacification.

Key points:

- About 50 purely genetic forms of cataract have been described, but they are very rare and constitute only a small proportion of all cataracts.
- Cataract should not generate demand for long-term care because it is so treatable.

Causation:

The causes of cataract are legion and include genetic, inflammatory, and traumatic causes. About 50 purely genetic forms of cataract have been described, but they are rare and constitute only a small proportion of all cataracts. The prevalence increases substantially with age. Age-related cataract is

itself heterogeneous with respect to the region of the lens affected and comprises three main groups: nuclear sclerosis, posterior subcapsular and cortical opacification.

Cataract appears to occur secondary to one or several of such things as dehydrational crises (severe diarrhoea), glaucoma, ultraviolet B radiation, smoking, trauma, intra-ocular inflammation, and chronic steroid use.

- Known genes

Age-related cataract – None

Genetic forms of cataract include non-syndromic, autosomal dominant forms

Linked to 1p36 (Eiberg, 1995), centromic region of chromosome 13 (Mackay et al, 1997), 17p12-13 (Berry, 1996), 17q11-q12 (Padma, 1995) and 17q24 (Armitage, 1995)

Genes – crystallin family which represent attractive candidates which have been implicated in the aetiology of human inherited cataract (eg Cartier, 1992; Rodriguez, 1992; Chambers and Russell, 1991; Brakenhoff, 1994). Recently mutations have been described in the beta B2 crystallin gene at 22q11.2-q12.2 (Litt et al, 1997) and GJA8 gene on 1q21-25 (lens fibre cell membrane gene GJA8) (Shiels et al, 1997)

Syndromic forms of cataract. Many genetic conditions carry cataract as part of their phenotypic spectrum. The vast majority do not form part of the reservoir of patients with age-related cataract. However, occasionally cataract will be the initial presenting factor for conditions such as myotonic dystrophy (eg Cobo et al 1996)

- Likely genetic risk factors

Poor

- Known environmental and lifestyle risk factors

Age

Smoking (eg Solberg et al, 1998)

Nutrition (eg Leske et al, 1997)

- Likely environmental and lifestyle risk factors

Light (Javitt et al, 1994-5)

- Position on spectrum (population attributable risk)

On a scale from zero (100% preconceptual) to 100 (100% postconceptual), cataract is about 70.

Prevalence

50% 65-74 years

70% 75+

Depends on definition – presence of opacification – causing visual disability etc

Potential for reducing burden of disease

- Environmental and lifestyle risk factors

Extremely complex and loose

- Drug therapy
- increased coverage of current therapy
- genetically targeted conventional therapy

None

- genetic therapy

None

- Invasive interventions

Already extremely effective

5.4 Diabetes mellitus

Type 1 diabetes mellitus

“A disease in which sugar and starch are not properly metabolised by the body.” A condition in which the pancreas becomes unable to manufacture insulin; glucose remains in the blood stream rather than being cleared from it by the muscles and liver. This damages the lining of blood vessels, itself causing heart, kidney, eye, nerve and skin disease. These can be severe, requiring coronary artery bypass grafting, dialysis, laser treatment, cataract surgery and amputation. The disease affects 0.4% of the UK population.

Key points:

- Type 1 diabetes is genetically complex.
- Environmental factors must interact with genetic factors in its causation.
- We do not at present know how to prevent it; this is a research priority as prevalence is rising rapidly and diabetes is an unpleasant and costly condition with many complications.

Causation:

- Known genes and genetic prospects: IDDM is genetically complex (Tisch & McDevitt, 1966; Vyse & Todd, 1996). There is 50% concordance in monozygotic twins, showing that IDDM is dependent on environmental factors as well as genes. The risks to the child or the sib of a person with IDDM in the UK are 2-5% and 6% respectively. Intensive research over many years has defined a large number of chromosomal regions suspected of harbouring susceptibility genes (labelled IDDM1 – 18; Davies et al, 1994), but as is usual with such research, many of these are unconfirmed and few genes have been identified.
- The major inherited predisposition maps to the region of the HLA class II genes on chromosome 6 (IDDM1 locus). An association with HLA types DR3 and DR4 has long been known, but it appears that susceptibility is largely determined by the nature of aminoacid 57 of the HLA-DQb molecule

(aspartic acid determines resistance, other amino acids determine susceptibility (Todd et al, 1987)). A second well defined susceptibility is associated with a common DNA sequence variant near the insulin gene on chromosome 11 (IDDM2 locus (Vafiadis et al, 1997)). The effect of this variant appears to depend on which parent it is inherited from, and even on the nature of the non-transmitted allele in that parent. Other susceptibility loci have been suggested on many other chromosomes.

In summary, many genes, each of individually small effect, are believed to govern susceptibility to unidentified environmental triggers. Genetic testing is not predictive in individuals from the general population. Family history is the main predictor of risk. For a person with an affected sib, DNA testing could indicate a risk higher or lower than the average 6%, but again genetic testing will not give a definitive prediction.

- Known environmental and lifestyle risk factors

The further north you live in Europe, except Sardinia.

- Likely environmental and lifestyle risk factors (status)

Childhood viral infection (?Coxsackie, mumps, rubella when congenital)

?Role of milk protein in setting up autoimmunity

?Nitrates and nitroso compounds in foods

- Position on spectrum (population attributable risk)

On a scale from zero (100% preconceptual) to 100 (100% postconceptual), type 1 diabetes mellitus is about 50-60.

Prevalence

- These figures are for “diabetes mellitus” overall; type 2 is very rare before 45, then rapidly comes to predominate over type 1.

Prevalence rates per 10,000 men or women

Age	Male	Female
0-4	1	1
5-15	8	7
16-24	24	15
25-44	49	34
45-64	217	154
65-74	428	337
75-84	475	374
85+	327	238

Potential for reducing burden of disease

IDDM is probably triggered by some aspect of a Western hygienic lifestyle. In the UK the prevalence is increasing fast, while IDDM occurs about 20 times more frequently among children in the United States than among those in China. The precise triggers have not been identified and there is no known way of reducing the risk of getting IDDM.

- Environmental and lifestyle risk factors

- ?Breast feeding

- ?Avoidance of smoked foods

In those with the disease, not smoking protects blood vessels.

- Drug therapy

See BNF 6.1.1 to 6.1.6, and the Diabetes Control and Complications Trial publications (early-mid 1990s).

See also BNF 2.5, 2.6 and 2.12 for treatment of the risk factors for heart disease.

- Genetically targetted conventional therapy; potential for immunisation against the specific viral infection (when identified) in genetically susceptible individuals

- Genetic therapy: None

- Invasive interventions

For treatment of complications: laser destruction of new (superfluous) blood vessels growing in the back of the eye, angioplasty and coronary artery bypass grafting for heart disease, peripheral vessel surgery/amputation for maintenance of circulation to/minimisation of damage to feet and lower legs.

Type 2 diabetes mellitus

“A disease in which sugar and starch are not properly metabolised by the body”. Failure of muscles to respond normally to insulin (insulin resistance) by removing glucose from the bloodstream is as important as reduced insulin production in contributing to high blood glucose. This damages the lining of blood vessels, itself causing heart, kidney, eye, nerve and skin disease.

Key points:

- Type 2 diabetes is common (approx 4% of the population).

- At present there is no place for genetic testing in determining susceptibility to Type 2 diabetes. Family history and ethnic identity are the main predictors of risk.

- Heart disease is a common complication (8% of people with diabetes): it is estimated that a quarter of this is attributable to the D allele of the ACE gene. People with type 2 diabetes and at least one copy of this allele can potentially reduce their risk.

- Avoidance of obesity, and adequate exercise are protective.

Causation:

- Known genes (identity)

MODY (maturity onset diabetes of the young) is a rare, mendelian dominant condition. Mutations in

either of three identified genes (glucokinase, HNF4A, TCF1) can cause MODY. Clinically it behaves like Type 2 diabetes, but the age of onset is typical of Type 1. Different mutations in the same genes may predispose to maturity-onset NIDDM.

- Likely genetic risk factors (chromosomal areas being worked on, likely role)

NIDDM is genetically complex and heterogeneous. Evidence for genetic susceptibility is provided by the high risk to first-degree relatives of NIDDM patients (10-15% for children or sibs of an affected person), as well as the high concordance in identical twins (claimed by Tattersall and Pyke (1972) to be 100% for identical twins) in which the index case had onset of diabetes after age 45 years.

Identifying susceptibility genes is made more difficult by the arbitrary diagnostic definition of NIDDM (unlike IDDM, which is generally unambiguous). Intensive genetic research has indicated chromosomal locations of several putative susceptibility genes, but these seem to differ in different ethnic groups (Finns vs Mexicans vs Pima Indians).

In rare cases mutations have been found in the same genes as are implicated in MODY (see below), but the common determinants of susceptibility have not been identified.

Position 16189 in the first hypervariable region of mitochondrial DNA is associated with insulin resistance; the variation is a T to C transition. (Poulton et al, 1998).

Position 3243 of mitochondrial DNA is associated with “maternally inherited diabetes and deafness”(MIDD): insulin secretion by the pancreas is impaired. Approximately 1.3% of all diabetic cases in the Netherlands have MIDD. The variation is an A to G transition. (Maassen et al, 1998)

Position 8296 (A to G transition) is associated with impaired insulin secretion. The mutation can explain approx 1% of diabetes. (Kameoka et al, 1998)

The angiotensin-converting enzyme (ACE) gene D (deletion) allele is an independent risk factor for coronary heart disease in NIDDM patients, the effect being mediated through high blood pressure (Huang et al, 1998); (Pujia et al, 1994). The percentage of CHD attributable to the ACE deletion allele was 24% in a Type 2 population (Ruiz et al 1994). The role of the D allele is controversial (Panahloo et al, 1995)

At present there is no place for genetic testing in determining susceptibility to Type 2 diabetes. Family history and ethnic identity are the main predictors of risk.

- Known environmental and lifestyle risk factors (attributable risk)

Obesity, and within that “apple” rather than “pear” shape.

Lack of exercise

Ethnic identity

- Likely environmental and lifestyle risk factors (status)

- Position on spectrum (population attributable risk)

On a scale from zero (100% preconceptual) to 100 (100% postconceptual), type 2 diabetes mellitus is about 40-45.

Prevalence

- These figures are for “diabetes mellitus” overall; Type 2 is very rare before 45, then rapidly comes to predominate over type 1.

Prevalence rates per 10,000 men or women

Age	Male	Female
0-4	1	1
5-15	8	7
16-24	24	15
25-44	49	34
45-64	217	154
65-74	428	337
75-84	475	374
85+	327	238

Potential for reducing burden of disease

- Environmental and lifestyle risk factors

Avoidance of obesity

Low fat diet

Adequate exercise (for “muscle health” as well as contributing to weight control)

Avoiding smoking: this will not prevent one getting diabetes, but will help protect blood vessels.

- Drug therapy

See BNF 6.1.1 to 6.1.6, and UK PDS, 1998a; 1998b, the Prospective Study of Diabetes. Increased coverage of current therapy would reduce population burden of disease. There are estimated to be almost equal numbers of undiagnosed people with type 2 diabetes as diagnosed.

See also BNF 2.5, 2.6 and 2. 12 for treatment of the risk factors for heart disease.

- Genetically targetted conventional therapy; treatment of hypertension (BNF 2.5, 2.6) may be especially beneficial in those with D/D or I/D alleles of the ACE gene, in ameliorating their risk of heart disease as a complication of type 2 diabetes.

Genetic therapy: None. At present there is no place for genetic testing.

- Invasive interventions

For treatment of complications: laser destruction of new (superfluous) blood vessels growing in the back of the eye, angioplasty and coronary artery bypass grafting for heart disease, peripheral vessel surgery/amputation for maintenance of circulation to/minimisation of damage to feet and lower legs.

5.5 Fragile-X:

“major cause of mental retardation” IQ 20-80, usually in the range 35-60. Fragile X syndrome is so called because when cells are cultured in special conditions, the X chromosome may appear to have a break in it. Clinically, various physical features in affected males, together with the family history, have a high index of suspicion. DNA testing is needed to confirm the diagnosis.

Key points:

- There are many causes of mental retardation, including chromosomal, single gene and non-genetic causes.
- Fragile X is the commonest known single-gene cause of moderate-severe mental retardation in males. Females are more mildly and variably affected.
- Various characteristic physical features can suggest the diagnosis in an affected boy; the diagnosis can be confirmed in either sex by a DNA test.
- Fragile X follows a well defined but complex inheritance pattern in families; careful assessment of the full pedigree and DNA data is needed to calculate risks of affected children.
- Examination of the X chromosome may cut short months of uncertainty, developmental assessment and worry for the parents, and inform further reproductive choices.

Causation:

- Known genes (identity, nature and magnitude of influence)

FMR1 (Xq27.3) is inactivated in Fragile X syndrome (FRAXA). The usual mechanism of inactivation is a massive expansion of a CGG repeat in the FMR1 gene. Rarely, there is different mutation in the same gene. A similar but much rarer condition, FRAXE, is caused by a similar DNA expansion at a nearby location that affects a different gene, FMR2.

The inheritance is X-linked, but the DNA repeat is unstable, and the risks to family members are not the same as for a normal X-linked disease. Both males and females can carry the condition but be mentally normal. Diagnostic testing, including prenatal testing and testing for normal carrier status, is available.

Familial risks	Normal carrier mother	Retarded carrier mother	Normal carrier father
Risk of retardation to son	0.38	0.5	0
Risk son will be a normal carrier	0.12	0	0
Risk daughter will be retarded	0.16	0.28	0

Risk daughter will be a normal carrier 0.34 0.22 1

(Weaver & Sherman, 1987)

- Likely genetic risk factors (chromosomal areas being worked on, likely role)
Not applicable. FRAXA mental retardation is entirely caused by inactivation of the FMR1 gene.

- Known risk factors (attributable risk)
- Likely environmental and lifestyle risk factors (status)
- Position on spectrum (population attributable risk)

Fragile X is 100% genetic (the variability is caused by genetic instability, not environmental factors).

Incidence

- Probably somewhat less than 1 in 1,000 males, and 1 in 2,500 females (Oxford Textbook). Birth prevalence in New South Wales (before cascade screening programme) 2.5 per 10,000 (Turner et al, 1997).

Prevalence

- Table for mental retardation (all types); rates per 10, 000 in each sex group

Age	Male	Female
0-4	1	0
5-15	1	1
16-24	7	7
25-44	4	3
45-64	3	2
65-74	0	3
75-84	0	0
85+	0	2

Potential for reducing burden of disease

- Environmental and lifestyle risk factors
Some features respond to behavioural management strategies

- Drug therapy – increased coverage of current therapy: None

genetically targetted conventional therapy: None, but examination of the X chromosome may cut short months of uncertainty, developmental assessment and worry for the parents, and inform further reproductive choices.

genetic therapy: None

- Invasive interventions

Carrier testing, if possibility of termination morally acceptable.

Prenatal diagnosis, if possibility of termination morally acceptable.

5.6 Huntington's disease

A very rare condition causing psychiatric symptoms, abnormal movements, dementia and fits

Key points:

- Huntington's disease is entirely genetically determined. A person who carries the HD mutation will inevitably develop HD, if they live long enough.
- The age of onset is very variable, and cannot be predicted for individuals.
- All affected people carry the same mutation, for which a simple DNA test is available.
- Predictive testing is strictly controlled, limited to a few specialist genetics centres using internationally agreed protocols.

Causation:

- Known genes

Autosomal dominant condition carried on chromosome 4q16.3 - the "Huntington" gene. The more repeats there are in the crucial area of the gene, the earlier the onset of the disease is likely to be.

- Likely genetic risk factors

"Ageing" genes generally are probably also involved in the time of onset.

- Known environmental and lifestyle risk factors

No lifestyle risk factors

- Likely environmental and lifestyle risk factors

No lifestyle risk factors

- Position on spectrum (population attributable risk)

On a scale from zero (100% preconceptual) to 100 (100% postconceptual), Huntington's disease is close to 0.

Prevalence

Too rare to be recorded in the National Morbidity Study. Four to seven per 100,000 (OMIM).

Potential for reducing burden of disease

- Environmental and lifestyle risk factors

None to avoid disease

Physiotherapy and occupational therapy measures to ameliorate symptoms

- Drug therapy – increased coverage of current therapy

Symptomatic treatment for specific problems

genetically targetted conventional therapy

None yet

genetic therapy

None yet

- Invasive interventions

None

5.7 Ischaemic Heart Disease

Common condition whereby damage to the lining of coronary arteries impairs their ability to deliver oxygenated blood to heart muscle. This may produce predictable angina when a given amount of exercise produces expected central chest pain. More acutely, if clots form on the damaged areas the blood supply may be completely cut off, resulting in unpredictable pain, abnormal heartbeat, loss of consciousness – a heart attack. Chronically, it may produce heart failure; shortness of breath giving reduced mobility.

Key points:

- This is a very common disease and if genetics can be used to allow a proportion of people at risk to avoid the onset of the disease or to reduce the severity of the disease they have got, it will be very important to society as well as to individuals.
- It has long been apparent that there were symptoms and signs in common between IHD and ischaemic stroke, and increasing genetic knowledge is confirming the overlaps between the two conditions.
- While we have gone some way to understanding the genetics of IHD, there is still a long way to go. We are very well informed about the environmental factors that play a part, and people can reduce their risk without waiting for the genetics by addressing them.
- Where the same molecule seems to play a major role in the development of two diseases, (IHD/ischaemic stroke and Alzheimer's), genetic testing for it in one context could bring unwelcome news in the other context. Society needs to consider the ethical and practical implications, including

implications for insurance practice.

Causation:

- Known genes (identity, nature and magnitude of influence)

Familial hypercholesterolaemia - gene: LDLR (58 pathogenic mutations, auto dom, carriage rate 1 in 500 in Western pops. Average infarct age 46) (OMIM entry nos143890) PAR cannot be more than 0.2%??

Familial hypertriglyceridaemia - gene: pepsinogen (auto dom, very rare. Average infarct age 57)

- Likely genetic risk factors (chromosomal areas being worked on, likely role)

Apolipoprotein A1-CIII-AIV plus several unknown genes give familial combined hyperlipidaemia - elevated LDL and VLDL. Carriage rate 1-2 in 100. Average infarct age 52. PAR for premature coronary artery disease (CAD) = 10%. (Babirak et al, 1989; Pajukanta et al, 1998; Wojciechowski et al 1991)

Glycoprotein IIIa association with one mutation PIA2. Carriage rate 2 in 5 with CAD, 1 in 5 normals.

ApoE (29 mutations) and ApoB (17 mutations) associated with types I to V hyperlipoproteinaemias. 20-60% will get CAD. Types II, IV & V auto dom, I & III complex auto recessive. (OMIM entry nos 107741, 144400, 144600, 144650)

- Known environmental and lifestyle risk factors/markers (attributable risk)

Age: marker of cumulative exposure to all risk factors

Sex: marker for absence of oestrogen protection

Raised serum LDL cholesterol: polygenic association. Carriage rate 1 in 25. PAR for >200mg/dL 27% in men, 34% in women (Wilson et al, 1998).

Raised serum homocysteine: marker for ?? PAR for coronary artery disease = 10% (Boushey, 1995). Inadequate antioxidant intake

Lack of adequate aerobic exercise (>20%)

Hypertension (20%) PAR 30% for myocardial infarction: (Lindholm and Lithman, 1985). PAR for CHD events in men (>130/85) : 28%, in women: 29% (Wilson at al, 1998)

marker for excessive salt intake

?marker for a variant at codon 235 in the angiotensinogen gene (Katsuya et al, 1995) (threonine has a twofold risk over methionine)

? marker for other genes

Smoking (active or passive) (20%) PAR (males) 30% (Davies et al, 1998).

Low birth weight and poor infant growth

Diabetes PAR black women=27%, non-black women=15%, black men=8%, non-black men 12% (Folsom et al, 1997).

Smoking, hypertension, elevated serum cholesterol and diabetes together: PAR = 53% for both sexes. (Davies et al, 1988).

Smoking (1), cholesterol (1), body mass (3), family history of acute myocardial infarction (3), hypertension (3) and diabetes (6) together PAR= 85% for non-fatal myocardial infarction. The figures in brackets give the rank order of the factors (Negri, 1995).

- Likely environmental and lifestyle risk factors (status)

Outdoor air pollution PAR = 2% for major cardiac events. (Poloniecki et al, 1997)

Gum disease/chronic oral infection

Chlamydia pneumoniae

Social exclusion

- Position on spectrum (population attributable risk)

On a scale from zero (100% preconceptual) to 100 (100% postconceptual), ischaemic heart disease is about 63-77.

Prevalence

- Prevalance rates of IHD per 10,000 men or women

Age	Male	Female
16-24	1	0
25-44	23	9
45-64	397	176
65-74	920	498
75-84	915	675
85+	879	597

- Prevalence “essential” hypertension per 10,000 men or women

Age	Male	Female
16-24	9	10
25-44	99	95
45-64	743	849
65-74	1,458	1,757

75-84	1,108	1.584
85+	493	703

- Prevalence rates for disorders of lipid metabolism per 10,000 men or women

Age	Male	Female
16-24	5	6
25-44	53	25
45-64	164	181
65-74	99	151
75-84	11	18
85+	0	0

Secular/geographical trends

IHD prevalence is high in the UK, but death rates have been falling after reaching a peak in the 1970s. Social environment and lifestyle have apparently been the main driving forces behind the changes - dietary choices (saturated fats) and cigarette smoking being important. There is a southeast to northwest gradient across the UK (The Health of Adult Britain, 1994).

Potential for reducing burden of disease

- Environmental and lifestyle risk factors
 - Stop smoking - health protection: increase taxation, extend advertising/sponsorship bans.
 - Encourage exercise - safe cycling to work and school; easy access to cheap, pleasant facilities
 - Stimulate fruit and veg consumption
 - Reduce salt in convenience foods
- Drug therapy – increased coverage of current therapy
 - anti-hypertensives
 - lipid lowering agents
 - genetically targetted conventional therapy
 - genetic therapy
- Invasive procedures - access to angioplasty and CABG.

Ischaemic Stroke

Description

Key points:

- This is a very common disease and if genetics can be used to allow a proportion of people at risk to

avoid the onset of the disease or to reduce the severity of the disease they have got, it will be very important to society as well as to individuals.

- It has long been apparent that there were symptoms and signs in common between ischaemic stroke and IHD, and increasing genetic knowledge is confirming the overlaps between the two conditions. While we have gone some way to understanding the genetics of ischaemic stroke, there is still a long way to go. We are very well informed about the environmental factors that play a part, and people can reduce their risk without waiting for the genetics by addressing them.
- Where the same molecule seems to play a major role in the development of two diseases, (IHD/ischaemic stroke and Alzheimer's), genetic testing for it in one context could bring unwelcome news in the other context. Society needs to consider the ethical and practical implications, including implications for insurance practice.

Causation:

- **Known genes (identity, nature and magnitude of influence)**

Familial hypercholesterolaemia - gene: LDLR (58 pathogenic mutations, auto dom, carriage rate 1 in 500 in Western pops. Average infarct age 46) (OMIM entry no 143890) PAR cannot be more than 0.2%??

Familial hypertriglyceridaemia - gene: pepsinogen (auto dom, very rare. Average infarct age 57)

Likely genetic risk factors (chromosomal areas being worked on, likely role)

Apolipoprotein A1-CIII-AIV plus several unknown genes give familial combined hyperlipidaemia - elevated LDL and VLDL. Carriage rate 1-2 in 100. Average infarct age 52. PAR for premature coronary artery disease (CAD) = 10 % (Babirak et al, 1989; Pajukanta et al, 1998; Wojciechowski et al 1991).

Glycoprotein IIIa association with one mutation PIA2. Carriage rate 2 in 5 with CAD, 1 in 5 normals.

APOE (29 mutations) and APOB (17 mutations) associated with types I to V hyperlipoproteinaemias. 20-60% will get CAD. Types II,IV & V auto dom, I & III complex auto recessive. (OMIM entry nos 107741, 144400, 144600, 144650)

Apolipoprotein E polymorphism is not a risk factor for ischaemic stroke in subjects aged > or = 75, although it might influence survival after stroke occurrence (2/3 and 3/3 more desirable than 3/4) (Basun, 1996)

Apolipoprotein E 4 has a PAR of 33% for vascular dementia amongst those with stroke, and a 44% PAR for Alzheimer dementia amongst those with stroke (Slooter et al, 1997)

- **Known environmental and lifestyle risk factors (attributable risk)**

Hypertension:

All ages PAR 68% (Lindholm and Lithman, 1985); 30% (Nielsen, 1996).

Those aged 18-44: WM 21.7 (6.2-34.6), WW 21.3 (5.4-34.5, BM 53.5 (39.0-64.4), BW 50.5 (37.1-61.1) (Rohr et al, 1996)

Smoking PAR White men = 22.6 (3.1-38.2) White women 17.2 (4.0-34.0), Black men 40.5 (23.1-54.0) Black women 29.1 (13.5-41.9)

Diabetes PAR WM=19.0 (8.2-28.5), WW 15.8 (3.8-26.3), BM13.2 (5.3-20.4) BW 22.1 (12.5-30.7)

High alcohol intake

Arterial emboli eg from diseased heart valves

Atrial fibrillation

Haematological disease

- Likely environmental and lifestyle risk factors (status)
- Position on spectrum (population attributable risk)

On a scale from zero (100% preconceptional) to 100 (100% postconceptional), ischaemic stroke is about 63-83.

Potential for reducing burden of diseases

- Environmental and lifestyle risk factors.
Stop smoking - health protection: increase taxation, extend advertising/sponsorship bans.
Encourage exercise - safe cycling to work and school; easy access to cheap, pleasant facilities.
Stimulate fruit and veg consumption.
Reduce salt in convenience foods.
- Drug therapy – increased coverage of current therapy
 - anti-hypertensives
 - lipid lowering agents
 - warfarin
 - aspirin
 - genetically targetted conventional therapy
 - genetic therapy
- Invasive procedures – access to valvular surgery and carotid endarterectomy

Haemorrhagic Stroke

A condition, often fatal, whereby bleeding into the brain causes death of neurons responsible for speech, purposeful movement, intellectual functioning etc.

Key points:

- Haemorrhagic stroke comprises about 10% of stroke in the UK. It does not share the genetic causes

of blood lipid abnormalities with IHD and ischaemic stroke. It looks similar clinically because the resultant brain damage causes similar patterns of disability in movement, speech etc.

- The major risk factor for “primary” haemorrhagic stroke is high blood pressure. “Secondary” haemorrhagic stroke is mainly due to brain tumours, or abnormalities of the blood.
- At one year after first ever haemorrhagic stroke, approx 65% of people will have died, 10% will be alive and dependent, and 25% alive and independent.
- Any genetic influence is via any genetic influence on high blood pressure

Causation:

The major risk factor for “primary” haemorrhagic stroke is high blood pressure (PAR: 68% (Lindholm & Lithman, 1985)).

Women oral contraceptive users are at increased relative risk (1.5) of death from stroke, but this is largely theoretical as stroke is very, very rare in premenopausal women, and the relative risk has fallen away by ten years after stopping using oral contraceptives (Beral et al, 1999).

- Known genes predisposing to high blood pressure

A rare autosomal recessive abnormality in the region encoding the enzyme aldosterone-synthase.

A rare autosomal recessive abnormality (Liddle’s syndrome) acting to increase the amount of salt the kidney takes back into the body from part-processed urine.

The M235T variant of the angiotensinogen gene, which affects blood pressure control, and salt and water balance (Corvol et al, 1997).

An autosomal dominant gene for high urinary kallikrein excretion (kallikrein is involved in blood clotting mechanisms, and also in controlling the size of small blood vessels) is probably protective against high blood pressure. About 28% of the Utah population have at least one copy of this gene. (Berry et al, 1989)

- Likely genetic risk factors

Other susceptibility genes must be involved (Corvol et al)

Risk of haemorrhagic stroke tends to be associated with the ApoE 3/4 genotype, while 2/3 tends to be protective (Basun et al, 1996)

- Known environmental and lifestyle risk factors

Low birth weight (PAR for hypertension \leq 5%) (Holland et al, 1993)

Obesity (BMI >30 kg/m², PAR for hypertension \leq 12%) (Holland et al, 1993)

Obesity: Blood pressure increases linearly with BMI; magnitude of the relationship greater in whites than blacks, young than old. PAR for hypertension \leq 33% (MacMahon et al, 1987)

Obesity interacts with heredity in production of hypertension (Pollini G et al). The joint effect of overweight and familial predisposing factors on the occurrence of hypertension in an industrial population. (The Pavia Study, 1987)

Heavy alcohol consumption (>2 drinks a day) (PAR for hypertension = 6-8% in those < 50 , and 5-7% in those aged > 50 years old). (Moore et al, 1990)

- Likely environmental and lifestyle risk factors

Non-steroidal anti-inflammatory drugs usage may be an independent risk factor for hypertension in

elderly people (Johnson et al, 1993)

Exposure to environmental lead (Schwarz, 1991)

Chronic moderate salt intake eg adding salt to food, eating salty processed foods

Smoking

- Position on spectrum (population attributable risk)

On a scale from zero (100% preconceptional) to 100 (100% postconceptional), haemorrhagic stroke is about 67-77.

Prevalence

Age	Male	Female
25-44	0	0
45-64	4	2
65-74	8	4
75-84	3	5
85+	18	14

Potential for reducing burden of disease

- Environmental and lifestyle risk factors

Obese people should reduce weight, and subsequently maintain weight loss (MacMahon et al, 1987)

Vigorous exercise protects against hypertension, partly by reducing obesity (Paffenbarger et al, 1983)

Physiotherapy, speech therapy and occupational therapy to address specific problems after stroke.

- Drug therapy

2.2, 2.4, 2.5 for treatment of hypertension to avoid haemorrhagic stroke

- Invasive interventions

Neurosurgical opinion on clot evacuation

Prevalence

- Prevalence rates of cerebrovascular disease per 10,000 m or f

Age	Male	Female
16-24	0	0
25-44	0	0
45-64	41	18
65-74	142	91

75-84	286	224
85+	427	420

- Prevalance rates of transient cerebral ischaemia per 10,000 m or f

Age	Male	Female
16-24	0	1
25-44	1	2
45-64	24	21
65-74	125	81
75-84	283	205
85+	380	301

TIA is a specific risk marker (rather than a risk factor) for stroke; 22% of people who have a stroke have previously had a TIA (Hankey, 1997).

Prevalence “essential” hypertension per 10,000 men or women

Age	Male	Female
16-24	9	10
25-44	99	95
45-64	743	849
65-74	1,458	1,757
75-84	1,108	1,584
85+	493	703

- Secular trends: stroke incidence and mortality have been falling in Western Europe and similar countries for most of this century, eg Davies et al, 1988.

Potential for reducing burden of disease

- Environmental and lifestyle risk factors
- Drug therapy – increased coverage of current therapy (British National Formulary section references will be given; this is published twice a year by the BMA and Royal Pharmaceutical Society of GB)
 - genetically targetted conventional therapy
 - genetic therapy
- Invasive interventions

5.8 Manic depression

Manic depression, also called bipolar affective disorder: a mental disorder with alternating periods of elation and depression.

Key points:

- Family, twin and adoption studies support an effect of genetic susceptibility, but to date no susceptibility genes have been conclusively identified.
- Information that is available supports the view that some psychiatric disease has a molecular basis, so that in the medium term we can reasonably hope for effective drugs whose design is tailored to the underlying pathogenesis.

Causation:

- Known genes

None

Likely genetic risk factors

Risch and Botstein summed up the problems of genetic research in manic depression (Risch and Botstein, 1996). At least 14 possible loci of susceptibility genes have been suggested. None of the 14 has been convincingly, or at least, consistently, replicated, although some regions have been implicated more than once.

- Known environmental and lifestyle risk factors

Stressful events

- Likely environmental and lifestyle risk factors

None

- Position on spectrum (population attributable risk)

On a scale from zero (100% preconceptual) to 100 (100% postconceptual), manic depression is about 40-50.

Incidence

Annual incidence: estimates vary between 1.0-1.5 per 10,000 men, 1.0-3.0 per 10,000 women, making it much rarer than depression (10-20 per 10,000 men and 30-60 per 10,000 women (Oxford Textbook)

Potential for reducing burden of disease

- Environmental and lifestyle risk factors

Psychological management

- Drug therapy
- Antimanic drugs - benzodiazepines, antipsychotic drugs, lithium or carbamazepine (BNF 4.2.3), antidepressant drugs (BNF 4.3).
- Genetically targeted conventional therapy: none yet
- Genetic therapy: none yet
- Invasive procedures
Electroconvulsive therapy for severe depression.

5.9 Multiple sclerosis

A condition in which the “insulation” is lost from around nerve fibres, and they cease to function. People with multiple sclerosis have difficulty with mobility, self care, and ultimately speech and swallowing. They also often have visual problems, and may endure urinary incontinence. It comes and goes in severity, and patients have “plateaux” of months or years of stable disease.

Key Points

- A condition which must result from an interplay of genetic and environmental factors.
- We do not currently understand enough to prevent it, or to treat it well.

Causation:

- Known genes
None yet
- Likely genetic risk factors
Genes involved in the immune response.
Possibly, genes specifying the structure of myelin
- Known environmental and lifestyle risk factors
Childhood north of the tropic of Cancer or south of the tropic of Capricorn.
- Likely environmental and lifestyle risk factors
Viral infection in late childhood/adolescence ?specific virus: measles, mumps, rubella and Epstein-Barr virus are all candidates
- Position on spectrum (population attributable risk)

On a scale from zero (100% preconceptual) to 100 (100% postconceptual), multiple sclerosis is about 52-58.

Prevalence

Age	Male	Female
-----	------	--------

16-24	1	2
25-44	6	14
45-64	11	20
65-74	6	11
75-84	5	1
85+	0	0

Potential for reducing burden of disease

- Environmental and lifestyle risk factors

For prevention, none known (although MMR immunization in early childhood may be protective).

Physiotherapy and OT treatment and aids reduce the burden for people with the disease

- Drug therapy – increased coverage of current therapy

Corticosteroids

Beta-interferon may be indicated

Symptomatic treatment of complications

genetically targeted conventional therapy

None yet

genetic therapy

None yet

- Invasive interventions

None applicable.

5.10 Osteoarthritis

A disease of cartilage and bone affecting joints, and causing pain and stiffness.

Key points:

- A very common condition in which it seems likely that a number of genes will be shown to be involved, together with lifestyle factors.

- It is likely that it will be divided into a number of separate diseases by genetic pathology.

Causation:

- Known genes

None currently

- Likely genetic risk factors

Family history, and concordance patterns in twins suggests polygenetic effects.

Some forms of premature OA appear to be inherited. (Oddis, 1996). Type II collagen gene implicated (Oxford Textbook)

- Known environmental and lifestyle risk factors

Use of abnormal (eg congenitally dislocated hip) or injured joints

Repetitive minor trauma to a joint, and joint hypermobility

Fracture involving a joint

Being overweight (especially relevant to knee OA)

Female sex (especially relevant to knee OA)

(Hip OA has equal sex incidence, little or no link to obesity, and an association with farming)

- Likely environmental and lifestyle risk factors

- Position on spectrum (population attributable risk)

On a scale from zero (100% preconceptual) to 100 (100% postconceptual), osteoarthritis is about 53-75.

Prevalence

“Osteoarthrosis and allied disorders”

Age	Male	Female
16-24	11	9
25-44	55	82
45-64	466	654
65-74	818	1217
75-84	1017	1581
85+	1022	1584

Geography

Near and Far Eastern, Chinese and Japanese populations have a low incidence of hip disease, and sub-Saharan Africans have a high rate of knee disease but little hand disease. It is not known whether these effects are environmental or genetic.

Potential for reducing burden of disease

- Environmental and lifestyle risk factors

Avoid joint misuse

Avoid obesity

Maintenance of quadriceps strength

Heel raisers, knee support splints, correct length walking stick etc

- Drug therapy – increased coverage of current therapy

Analgesics 4.7

Non-steroidal anti-inflammatory drugs 10.1.1 (cave side effects in this elderly population)

genetically targeted conventional therapy

None currently

genetic therapy

None currently

- Invasive interventions

Total hip replacement

Total knee replacement

5.11 Osteoporosis

Osteoporosis: a condition in which bone structure and calcium content is not maintained, leading to bone weakness. Characteristically, patients' vertebrae collapse into wedge-shapes giving them curvature of the spine in the chest ('dowager's hump'); they are also vulnerable to breaking bones in falls, usually the wrist or femur.

Key Points

- It is likely that osteoporosis is a complex disease which will be revealed to have specific genetic as well as lifestyle components.

Disease name and brief description

A condition of decreased bone density and increased bone fragility. Those affected are likely to suffer fractures of the forearm, vertebrae and neck of femur when minimal forces have been involved.

Causation:

- Known genes

None known currently

- Likely genetic risk factors

Peak bone mass (reached at approximately age 30) is partly genetically determined; race, collagen gene mutations and general family history are involved.

- Known environmental and lifestyle risk factors

Disuse atrophy ie exercise protects against bone loss.

Being underweight

Low calcium intake - affects both peak bone mass, and bone loss.

Sex hormone exposure; women are protected by oestrogen so hysterectomy, early natural or surgically induced menopause and episodes of amenorrhoea in early life.

Smoking and more than moderate alcohol intake.

Falling (risk factors for this: poor balance, declining muscle strength, hypothermia, medication, alcohol and environmental factors)

- Likely environmental and lifestyle risk factors (status)

- Position on spectrum (population attributable risk)

On a scale from zero (100% preconceptual) to 100 (100% postconceptual), osteoporosis is about 70.

Prevalence

“Other disorders of bone and cartilage”

Age	Male	Female
45-64	16	57
65-74	23	95
75-84	15	127
85+	24	136

Potential for reducing burden of disease

- Environmental and lifestyle risk factors
 - Exercise to maintain bone density, muscle strength and balance
 - Avoiding smoking
 - Measures to reduce the severity of falls that do happen, eg hip protectors
- Drug therapy – increased coverage of current therapy
 - Hormone replacement therapy 6.4.1
 - Bisphosphonates are the subject of a current NHS R&D call for proposals
 - genetically targeted conventional therapy
 - None currently
 - genetic therapy
 - None currently
- Invasive interventions
 - Total hip replacement following hip fracture
 - Pinning following hip fracture

5.12 Parkinson’s disease

“Progressive disease of the nervous system with tremor and muscular rigidity”.

Key Points

- A disease with a genetic element where occupational medicine has given specific clues regarding the interaction of industrial chemicals with genetics, and quite a good understanding of the biochemistry of how symptoms are produced.
- We should know how to ameliorate or avoid disease as understanding develops.

Causation:

- Known genes (identity, nature and magnitude of influence)

Autosomal recessive juvenile parkinsonism (ARJP) maps to a specific region on chromosome 6. Deletions and point mutations are both pathological (Lucking et al, 1998)

- Likely genetic risk factors (chromosomal areas being worked on, likely role)

Some families with members with necropsy-proven Parkinson's disease (PD) show a highly penetrant, autosomal dominant pattern of inheritance. The gene for alpha synuclein (a brain protein the function of which is unknown) is implicated in these (Polymeropoulos MH et al, 1997) (Kruger et al, 1998).

Family history is also significant (3 or 4 fold risk) in families without a clearcut pattern of inheritance, and no change in alpha synuclein. (Golbe 1998)

One form (GSTP1) of the gene coding for glutathione transferases (enzymes that destroy toxins) is found significantly more often in patients than in controls, when both groups had previously had exposure to pesticides. (Menegon et al, 1998)

- Known environmental and lifestyle risk factors

Some drugs produce the same effect as a side effect by blocking the receptors which in the natural disease are lost with cell death in a specific area of the brain. These drugs include the phenothiazines and butyrophenones which are groups of anti-psychotic drugs (see BNF section 4.2.1), and reserpine (which was, but is no longer, used in Britain to treat high blood pressure).

- Likely environmental and lifestyle risk factors (status)

Unidentified environmental toxins; any which were metabolized in the brain to produce MPP+ (1-methyl-4-phenyl-pyridinium) would be regarded with particular suspicion. Some pesticides and herbicides share characteristics with MPP+ and its precursor molecules, and people exposed to them have a 3 or 4 fold increased risk for PD. (Golbe, 1998)

Extensive studies have failed to identify any viral agent responsible for Parkinson's disease, and attempts to suggest that all cases are due to residual effects of encephalitis lethargica have been discredited.

- Position on spectrum (population attributable risk)

On a scale from zero (100% preconceptual) to 100 (100% postconceptual), Parkinson's disease is about 75-90.

Prevalence

Rates per 10,000 in each age and sex group

Age	Male	Female
25-44	1	1
45-64	14	9

65-74	64	51
75-84	149	91
85+	155	128

- Geographic/secular trends

Occurs worldwide in all ethnic groups (perhaps slightly reduced frequency in China and Africa). No social class effect.

Potential for reducing burden of disease

- Environmental and lifestyle risk factors

As general good practice, farmers, horticulturalists etc should seek to minimise exposure for themselves and others to pesticides and herbicides; specific constituents have not yet been clearly linked to the disease.

- Drug therapy –

- increased coverage of current therapy

See BNF section 4.9)

- genetically targetted conventional therapy

None yet

- genetic therapy

None yet

- Invasive interventions

Neurosurgical procedures for those no longer benefitting from levodopa.

5.13 Rheumatoid arthritis

A chronic progressive disease causing inflammation & stiffening of the joints.

Key points:

- A fairly common disease which affects people in young adult life and therefore causes many years of disability. Its drug treatment is not particularly targeted or effective, and tends itself to have serious side effects. So, an insight from genetics could be particularly valuable.

- It appears that certain HLA types confer susceptibility to rheumatoid arthritis.

Causation:

- Known genes

Major histocompatibility complex, chromosome 6

It appears that certain HLA types confer susceptibility to rheumatoid arthritis by binding to HSP 73 which is similar to E. coli HSP 70 and has homologies at the important binding sites (Auger et al,

1996).

- Likely genetic risk factors

- Known environmental and lifestyle risk factors

Female sex

Winter:summer onset 2:1

- Likely environmental and lifestyle risk factors

Ubiquitous infectious organism - Gram-ve bacteria/rubella/parvovirus/ atypical mycobacteria/mycoplasma?

- Position on spectrum (population attributable risk)

On a scale from zero (100% preconceptional) to 100 (100% postconceptional), rheumatoid arthritis is about 45-60.

Prevalence

- Prevalence rates per 10,000 men or women

Age	Male	Female
0-4	1	1
5-15	1	5
16-24	2	9
25-44	12	29
45-64	48	96
65-74	71	144
75-84	52	131
85+	18	89

- Secular/geographic trends

Worldwide prevalence generally consistent at 1% (cave rural sub-Saharan Africa (low) and Amerindians (high))

Dearth of evidence for antiquity - a “new” disease

Confined to humans - unknown in other species

Potential for reducing burden of disease

- Environmental and lifestyle risk factors

Self care joint protection

Muscle stretching and strengthening exercises

Suitable footwear

Home adaptation

“Grip gadgets” and others to give mechanical advantage
Wheelchairs +/- motor.

- Drug therapy -
 - increased coverage of current therapy BNF 10.1.1, 10.1.2, 10.1.3.
- Simple analgesics for pain
Second line drugs - gold, sulphasalazine etc
Third line drugs - azathioprine, cyclophosphamide etc
- genetically targetted conventional therapy
 - genetic therapy
- Invasive prodecures
- Repair of ruptured tendons, synovectomy, arthodesis
Hip, knee, elbow and shoulder replacement (not wrist or ankle yet)

5.14 Schizophrenia

“A mental disease marked by disconnection between thought, feelings and actions, often with delusions and withdrawal from social relationships”.

Key points:

- A moderately common (1% of population) disease with a peak of incidence in young adults.
- Family, twin and adoption studies support an effect of genetic susceptibility, but to date no susceptibility genes have been conclusively identified.
- Information that is available supports the view that some psychiatric disease has a molecular basis, so that in the medium term we can reasonably hope for effective drugs whose design is tailored to the underlying pathogenesis.
- Following concerns about care in the community, the balance of public provision between community psychiatric and institutional care is currently under review. It must be remembered that some ‘long-term residential care’ for people with schizophrenia happens within the prison service, where cases may not actually be recognised and therefore appropriate treatment not given.

Causation:

- Known genes
- Likely genetic risk factors

The gene for 5-hydroxytryptamine type 2a (5-HTA2a) receptor, or a locus in linkage disequilibrium with it. Genotypes 1/1, 1/2, and 2/2 have been assigned. There is a significant excess (relative risk 1.7 (CI: 1.22-2.36) of allele 2 amongst people with schizophrenia. Allele 2 is common in the population: the population attributable risk is estimated at 35% (Williams et al, 1996).

- Known environmental risk factors

Stressful life events

Physical illness

- Likely environmental and lifestyle risk factors

Pre-natal abnormality of brain development in temporal lobes/parahippocampal areas,? marker for infective episode? ?genetic effect?

- Position on spectrum (population attributable risk)

On a scale from zero (100% preconceptual) to 100 (100% postconceptual), schizophrenia is about 40-65.

Prevalence

Prevalence rates per 10,000 men or women

Age	Male	Female
16-24	8	3
25-44	19	9
45-64	22	21
65-74	10	15
75-84	3	12
85+	12	6

Potential for reducing burden of disease

- Environmental and lifestyle risk factors

None

- Drug therapy

- Anti-psychotic drugs, often intra-muscular rather than oral (BNF 4.2). Increased coverage of current therapy is desirable eg awareness in Prison Service staff

- Genetically targetted conventional therapy: none yet

- Genetic therapy: none yet

- Invasive procedures

None.

6. Appendices

6.1 Abbreviations and acronyms used within the document

ABI	Association of British Insurers
AD	Alzheimer's disease
ACE	Angiotensin converting enzyme
ACGT	Advisory Committee on Genetic Testing
ApoA	Apolipoprotein A
ApoE	Apolipoprotein E
BRCA 1 &2	Genes conferring increased risk of breast cancer
CAD	Coronary Artery Disease
DNA	Deoxyribonucleic acid
GAIC	Genetics and Insurance Committee
HGAC	Human Genetics Advisory Commission
HLA	Human leucocyte antigen
IDDM	Insulin dependent diabetes mellitus
LDL	Low density lipoprotein
MODY	Maturity onset diabetes of the young
NIDDM	Non-insulin dependent diabetes mellitus
OR	Odds ratio
PAR	Population attributable risk
PKU	Phenylketonuria
TIA	Transient ischaemic attack
VLDL	Very low density lipoprotein

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6.3 Tables

Table A: Examples of genetically simple and complex diseases: coronary artery disease

Table 1: Prevalence of ApoE genotype in population at age 60

Table 2: Estimated expected lifetime costs at age 60, with low overall mortality and high mortality while institutionalised (equivalent to single premium costs).

Table 3: Estimated expected lifetime costs at age 60, with high overall mortality (100% of AM80 and AF80), that is, more of the population are supposed to die prematurely.

Table 4: Estimated expected lifetime costs at age 60, with low additional mortality risk while institutionalised.

Table 5: Estimated expected lifetime costs at age 60, with relative risks given by the odds ratios at age 60 in Farrer et al (1997).

6.4 Figures

Figure 1: Projected age distribution, United Kingdom, 1996-2036

Figure 2: Actual and projected dependency ratios, United Kingdom, 1971-2036

Figure 3: A model of Alzheimer's disease

Figure 4: Odds ratio (OR) relative to ApoE genotype e3/e3 (e3/e4 and e4/e4)

Figure 5: Odds ratio (OR) relative to ApoE genotype e3/e3 (e2/e4 and e2/e3)

Figure 6: AD costs depending on level of relative risk

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6.5 Useful Addresses

Association of British Insurers (ABI)

51 Gresham Street
London EC2V 7HQ
Tel: 0171 600 3333
Fax: 0171 696 8999
Web: <http://www.abi.org.uk>

British Society for Human Genetics
Clinical Genetics Unit
Birmingham Women's Hospital
Edgbaston
Birmingham B15 2TG
Tel: 0121 627 2630
Web: <http://www.bham.ac.uk/bshg>

Genetics and Insurance Committee (GAIC)
Department of Health
Room 401, Wellington House
133-155 Waterloo Road
London SE1 8UG
Tel: 0171 972 4017
Fax: 0171 972 4196
E-mail: mstraugh@doh.gov.uk
Web: <http://www.dh.gov.uk/Home/fs/en/genetics.htm>
(Also contact point for Advisory Committee on Genetic Testing (ACGT), Gene Therapy Advisory Committee (GTAC) and Human Genetics Commission (HGC)).

Human Genetics Advisory Commission (HGAC), Secretariat
Office of Science and Technology
Albany House
94-98 Petty France
London SW1H 9ST
Tel: 0171 271 2131
Fax: 0171 271 2028
E-mail: mileva.novkovic@osct.dti.gov.uk
Web: <http://www.dti.gov.uk/hgac>
(To merge with HGA, December 1999).

Medical Research Council (MRC)
20 Park Crescent
London W1N 4AL
Tel: 0171 636 5422
Fax: 0171 436 6179
Web: <http://www.mrc.ac.uk>

Nuffield Council on Bioethics
28 Bedford Square
London NW1 2BE
Tel: 0171 631 0566
Fax: 0171 637 1712
Web: <http://www.nuffieldfoundation.org>

Public Health Genetics Unit
Strangeways Research Laboratory
Worts Causeway
Cambridge CB1 4RN
Tel: 01223 740200
Fax: 01223 740200
E-mail: phgu@srl.cam.ac.uk
Web: <http://www.medinfo.cam.ac.uk/phgu>

UK Forum for Genetics and Insurance
Staple Inn Hall
High Holborn
London EW1V 7QJ
Tel: 0171 632 2136
Fax: 0171 632 2131
E-mail: ukfgi@actuaries.org.uk

The Wellcome Trust
183 Euston Road
London NW1 2BE
Tel: 0171 611 8888
Fax: 0171 611 8545
Web: <http://www.wellcome.ac.uk>

Genetic Interest Groups & Consortia

General

Genetic Interest Group
Unit 4D
Leroy House
436 Essex Road
London N1 3QP
Tel: 0171 704 3141
Fax: 0171 359 1447
E-mail: mail@gig.org.uk
Web: <http://www.gig.org.uk>

Alzheimer's Disease

United Kingdom Alzheimer's Disease Genetics Consortium
Institute of Psychiatry
London SE5 8AF
Tel: 0171 703 5411

Huntington's Disease

United Kingdom Huntington's Disease Genetics Consortium
Institute of Medical Genetics
University Hospital of Wales
Heath Park
Cardiff, CF14 4XW
Tel: 01222 747747
Fax: 01222 747603

Societies for Specific Conditions

Alzheimer's Disease

Alzheimer's Disease Society
Gordon House
10 Greencoat Place
London SW1P 1PH
Tel: 0171 306 0606
Tel: 0845 300 0336 (Helpline)
Fax: 0171 306 0808
Email: info@alzheimers.org

Cancers

CancerBACUP
Bath Place
Rivington Street
London EC2A 3JR
Tel: 0171 613 2121 (Info line)
Tel: 0808 8001234 (Info line)
Tel: 0171 696 9003 (Admin)
Tel: 01415531553 (Counselling, Glasgow office)

Cancer Care Society
Jane Scarth House
39 The Hundred
Romsey , Hants, SO51 8GE
Tel: 01794 830374
Fax: 01794 518133
E-mail: info@cancer-care-soc.demon.co.uk

CancerLink
11-21 Northdown Street
London N1 9BN
Tel: 0171 833 2818
Tel: 0800 132905 (Helpline)
Fax: 0171 833 4963
E-mail: cancerlink@cancerlink.org.uk

Cataract

Royal National Institute for the Blind
224 Great Portland Street
London W1N 6AA
Tel: 0171 388 1266
Fax: 0171 388 2034

Diabetes Mellitus

British Diabetic Association
Youth and Family Services
10 Queen Anne Street
London W1M 0BD
Tel: 0171 323 1531
Tel: 0171 636 6112 (Careline)
Fax: 0171 637 3644

Fragile X Syndrome

Fragile X Society
53 Winchelsea Lane
Hastings TN35 4LG
Tel: 01424 813147
Web: <http://www.fragilex.org.uk>

Huntington's Disease

Huntington's Disease Association
108 Battersea High Street
London SW11 3HP
Tel: 0171 223 7000

Fax: 0171 223 9489

Web: <http://www.had.org.uk>

Huntington's Disease Association of Northern Ireland
C/o Department of Medical Genetics
Floor A
Belfast City Hospital Trust
51 Lisburn Road
Belfast BT9 7AB
Tel: 01232 263555
Fax: 01232 236911

Scottish Huntington's Association
Thistle House
61 Main Road
Elderslie
Johnstone PA5 9BA
Tel: 01505 322245
Fax: 01505 382980

Ischaemic Heart Disease

British Heart Foundation
14 Fitzharding Street
London
W1H 4DH
Tel: 0171 935 0185
Tel: 0171 486 5860

Manic Depression

Manic Depression Fellowship
8-10 High Street
Kingston-upon-Thames
Surrey KT1 1EY
Tel: 0181 974 6550
Fax: 0181 974 6600

Multiple Sclerosis

Multiple Sclerosis Resource Centre
4a Chapel Hill
Stansted
Essex CM24 8AG
Tel: 01279 817101
Fax: 01279 647179

Multiple Sclerosis Society
25 Effie Road
Fulham
London SW6 1EE
Tel: 0171 610 7171
Tel: 0808 800 8000 (Helpline)
Fax: 0171 736 9861

Osteoarthritis/ Rheumatoid Arthritis

Arthritis Research Campaign
Copeman House

St Mary's Court
St Mary's Gate
Chesterfield
Derbs, S41 7TD
Tel: 01246 558033
Tel: 01246 558007

Osteoporosis

The National Osteoporosis Society
PO Box 10
Radstock
Bath BA3 3YB
Tel: 01761 471771
Tel: 01761 472721 (Helpline)
Fax: 01761 471104

Parkinson's Disease

Parkinson's Disease Society
215 Vauxhall Bridge Road
London SW1V 1EJ
Tel: 0171 931 8080
Tel: 0171 233 5373
(Helpline, Mon-Fri 9.30 – 5.30)

Schizophrenia

National Schizophrenia Fellowship
28 Castle Street
Kingston-upon-Thames
Surrey KT1 1SS
Tel: 0181 547 3937
Tel: 0181 547 3862 - Advice Service)

Stroke

Stroke Association
Stroke House
123/7 Whitecross Street
London EC1Y 8JJ
Tel: 0171 566 0300
Fax: 0171 490 2686
Web: <http://www.stroke.org.uk>

6.6 CCC and its members

The Continuing Care Conference (CCC), a unique coalition of commercial, charitable and public service organisations, was established in 1992. Current members are listed below. Its purpose is to ensure that the public and private funding and provision for the long-term care needs of older people meets their reasonable expectations and preserves dignity in old age for all.

In 1998, as part of its ongoing programme, CCC established a study group on genetic tests and long-term care, chaired first by John Castagno, and then by Dr Virginia Warren, Consultant in Public Health Medicine, BUPA. The work group that produced this report was formed under the auspices of

the study group.

Continuing Care Conference: Current Members

Abbey National plc
Age Concern England
Anchor Trust
Association of Directors of Social Services (ADSS)
Assurance Medical Society
AXA Sun Life
Bacon & Woodrow
Barnet Directorate of Community Services
BUPA
Care and Repair (England)
Care Choices Ltd
City of Bradford Metropolitan Council
City of Sunderland Social Services Dept
CGU
Counsel and Care
Dirk Bloemers
Eagle Star Life Assurance Company Ltd
East Sussex Social Services Department
Eastern Health & Social Services Board
Eli Lilly
ERC Frankona
Friends Provident
General & Cologne Life Re UK Limited
Grace Consulting
Halifax Financial Services Limited
Hannover Re
Help the Aged
Homeowners Friendly Society
Housing 21
IFA Association
IFACare
Independent Healthcare Association
Institute of Actuaries
J Rothschild Assurance Holdings plc
Jewish Care
Laing & Buisson
Local Government Association
Long-term Healthcare Consultancy Services
Metropolitan Borough of Stockport
Metropolitan Borough of Wigan
Munich Reinsurance Company
NatWest Life
Norton Waverley Ltd
Norwich Union
Nursing Home Fees Agency
PPP lifetime care plc
Prudential UK
Quality Care & Nursing Home Advice Service (CNHS)
RB Kensington & Chelsea
Registered Nursing Homes Association
Research into Ageing
Retirement Strategies Ltd
SAGA Services Ltd
Salvation Army
Scottish Provident Institution

Scottish Widows
Shropshire County Council
Skandia Life Group
SmithKline Beecham Pharmaceuticals
Social Care Association
Solihull Social Services
Standard Life Assurance Company
Stalwart Assurance Co Ltd
Swiss Re Life and Health
Tameside Social Services
The Health Quality Service
The Relatives' and Residents' Association
Teachers' Benevolent Fund
United Kingdom Home Care Association
Warwickshire Assoc of Nursing Homes
Western Health & Social Services Board

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Please note that some of the illustrations in this report (Figures 2, 5 and 6) are not available in this version of this report.