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HUMAN GENETICS AND FINANCIAL SERVICES

A DISCUSSION MEETING WITH SUPPORTING PAPERS

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ABSTRACT OF THE DISCUSSION

HELD BY THE FACULTY OF ACTUARIES

The President (Mr P. H. Grace, F.F.A.): I welcome guests and visitors to this sessional meeting, in particular: Professor Cairns Aitken, Chairman of the Insurance Group of the Human Genetics Advisory Commission; Professor W. G. Hill, Fellow of the Royal Society of Edinburgh, Professor of Animal Genetics and Head of the Division of Biological Sciences at the University of Edinburgh; Professor Proust Proudfoot, O.B.E., Fellow of the Royal Society of Edinburgh, recently retired as General Secretary of the Royal Society of Edinburgh; Professor John Fincham, Fellow of the Royal Society of Edinburgh, Emeritus Professor of Genetics, University of Edinburgh; Professor David Finney, Fellow of the Royal Society of Edinburgh, Emeritus Professor of Statistics of Edinburgh University; and Professor David Porteous, MRC Human Genetic Unit at the Western General Hospital.

This meeting takes the form of a panel discussion, chaired by Professor Wilkie.

Professor A. D. Wilkie, F.F.A., F.I.A. (introducing the discussion)**:** We will be discussing the following topics:

— genetically inherited diseases;
— the implications of recent discoveries in genetics;
— the statistical evidence available;
— the financial consequences for insurance, life, health and PHI; and
— the practical and ethical issues of using genetic information for underwriting, taking into account the interests of proposers, insurance and society.

It is important that we cover the first four to give us an adequate background on which to base our judgements, before we discuss the last topic.

I start by asking the panellists to introduce themselves.

Mr D. J. Le Grys, F.I.A.: I spent many years working for a reinsurance company, from which I have now retired, but to which I am still a consultant. Currently I spend a considerable amount of time on the problems associated with continuing care for elderly people.

Dr A. F. Wright (a visitor)**:** I am trained in genetics and medicine, and am a clinical scientist at the MRC Human Genetics Unit in Edinburgh, and an honorary consultant geneticist at the Western General Hospital.

Dr P. Wilkie (a visitor)**:** I was first introduced to this subject some 25 years ago, when I was asked to carry out a project on the acceptability of having a national genetic register. We were 25 years ahead of our time, and the issues that we raised then are the issues that are under discussion here. I continued to work in the area, and did my Ph.D. in genetic counselling and the ethical and psychological issues thereof.

Dr A. S. Macdonald, F.F.A.: I am a member of staff in the Department of Actuarial Mathematics and Statistics at Heriot-Watt University. My interest is the application of mathematical models to insurance problems, in this case mortality modelling.

Professor Wilkie: Before we discuss genetically-inherited disease, it is helpful to remind you about the features of genetic inheritance, in relation to what we might call simple Mendelian inheritance, which seems to obey simple probability laws, and then about the more complex polygenic inheritance.

First Dr Wilkie will explain basic Mendelian inheritance.

Dr Wilkie: Heredity was studied first in the 19th century by scientists such as Mendel, Galton and Weissman, in different ways.

Gregor Mendel was a monk, a botanist and the son of a farmer. He discovered the mathematical law governing dominant and recessive hybrids, although the application of this discovery belongs to the 20th century.

Mendel fertilised tall plants with pollen from short plants. He noted that a uniformally tall generation of plants was produced. When a second generation was grown from these plants, some of the shortness characteristics of the first generation returned in the ratio of three tall plants to one short one. He concluded that each of these characteristics must be determined by two distinct factors, which acted as physical particles transmitted from one generation to another. One of these was inherited from the male and the other from the female. In addition, Mendel concluded that one of these factors dominated the other. For the first time an explanation for heredity had been found.

It was not until some many years later, in the 20th century, that these applications have been used. To put it into perspective, 35 years later, in 1908, Ottenbirg and Epstein demonstrated that blood groups were inherited in Mendelian fashion, and in 1911 Wilson assigned, for the first time, the gene for colour blindness to the X chromosome.

One hundred years ago, a special dye was added to a cell at a critical point in its formation, and the thread-like structures of protein took up the dye and stained them, making them easier to see. These were called chromosomes from the Greek — 'chroma' meaning colour, and 'soma' meaning body.

There are 46 chromosomes, arranged in pairs, in each cell, except for the sperm and the ova, which have 23 each. One chromosome from each pair comes from the male and the other from the female. Strictly there are 44 autosomes and two sex chromosomes. It was only in 1956 that humans were shown to have 46 chromosomes in every cell. Previously, it had been thought that we had 48, as have chimpanzees and gorillas.

Chromosome disorders are often serious, and occur because of too few chromosomes, too many, a defective structure, deleted chromosomes or broken chromosomes.

There are two chromosomes in each cell called the sex chromosomes, since they carry the message that determines which sex the individual will be. Each parent passes one sex chromosome to the foetus. The two female sex chromosomes are denoted as XX, and the two male sex chromosomes as XY. Thus, when the female contributes an X and the male an X, the child is a female. When a Y chromosome is passed by the male the child is male, and there is thus a 50-50 chance of having a male or a female child, a familiar fact.

There can be problems too, of course, with sex chromosomes. There can be too many or too few, as in Turner's syndrome, where a female child has only one X chromosome.

Genetic transmission of Mendelian type is determined by a gene on the autosome, and is said to be inherited in an autosomal fashion. It may be autosomal dominant, which is denoted as AD in shorthand, or autosomal recessive, which is denoted as AR. A genetic condition determined by a gene

on one of the sex chromosomes is said to be sex linked and may be sex linked recessive (XR) or sex linked dominant (XD), but I shall not discuss this last condition.

In autosomal dominant inheritance, each child of an affected person has a 50-50 chance that he or she has inherited the gene, and equally a 50-50 chance that he or she has not. Occasionally in a pedigree for autosomal dominant inheritance there is no past family tree. The patient will say, "No, my parents are alive and well". There may be quite simple explanations for this. The patient may be adopted or the patient may not be the child of those parents. The patient may or may not be aware of this. Other explanations for a lack of family history are a parent having died without the child knowing the cause of death, or dying before the disease manifested, or it may be a new mutation, a sport, which we are all familiar with if we are gardeners.

Common autosomal dominant diseases are Huntington's chorea, adult polycystic kidney disease, polyposis coli and retinal blastoma of the eye. Some autosomal dominant diseases are recognisable at birth, like retinal blastoma, but others have variable age of onset, like adult polycystic kidney disease and Huntington's chorea; and some are variable in expression, that is that they may be either more or less severe.

For autosomal recessive inheritance, the condition is only present when the gene is present in a double dose — that is, the person must inherit the affected gene from both parents, the male and the female. Thus, the affected person is homozyous for the condition. In this situation both parents are usually healthy, in that they do not normally manifest any of the symptoms of the condition for which they carry the gene.

In a family tree of autosomal recessive inheritance, such as cystic fibrosis, there are seldom previously affected individuals. That has been the past pattern. However, people with, for example, cystic fibrosis, do live much longer now and do have children. They are able to because of the good treatment that is now available for cystic fibrosis. All children of an affected person will be obligate carriers for cystic fibrosis. Each child of a carrier couple has a 50-50 chance of being a carrier; a one-in-four chance of being unaffected; and a one-in-four chance of being affected.

Considering a sex linked recessive inheritance, some disorders, such as haemophilia, which is the well known one, are carried on the X chromosome. A female with the gene for haemophilia on one of her two X chromosomes has another X chromosome to counter the effect. She is known as a carrier of the illness. Sometimes she may be a manifesting carrier. That means that she has some of the symptoms of the illness. A female carrier of haemophilia has a 50-50 chance of having a carrier daughter, and when a female carrier is carrying a male child, a 50-50 chance of having an affected son. Thus, there is a one-in-four chance of having an affected son; a one-in-four chance of having a carrier daughter; a one in four chance of having a non-affected son; and a one-in-four chance of having a non-carrier daughter. For a male affected by an XR disorder, all his daughters will be carriers — what are called obligate carriers — and his sons will be unaffected.

There is haemophilia in the family of Queen Victoria. She passed the trait on to at least three of her children, and it was carried to other European royal families by marriage.

Professor Wilkie: I now ask Dr Wright to explain something about polygenic inheritance and the genome project.

Dr Wright: Mendel was very lucky, because only one in three visible traits in peas are inherited in a simple Mendelian fashion. If he had studied two thirds of them, he would not have discovered these laws. In fact, the majority of disorders with a genetic predisposition are not inherited in a simple Mendelian fashion — in other words, they are not attributable to one single gene.

We have seen how, with a Mendelian trait, the relationship between gene and what we call phenotype, in other words the trait or disorder that is related to that gene, is a relatively simple one — almost a one-to-one relationship. However, this is not the case with what is called oligogenic inheritance. Polygenic inheritance has been mentioned, and polygenic implies many genes with individually small effects, but there seems to be increasing evidence, at least with regard to genetic disorders in man and in other animals, that much of the biological variation can be attributed to a smaller number of genes of intermediate effect (oligogenic), often on a background of genes with

small effects as well. So, oligogenic inheritance, meaning due to a handful of genes, is the favoured term here.

These are really multifactorial traits, since they are determined, not just by genes, but by combinations of genes interacting with other genes and with environmental factors. The key point here is that interactions between the genes and between genes and non-genetic or environmental factors, are crucial, and complicate the interpretation of inheritance.

Genetic disorders are familial, but that is not helpful, because almost all disorders in man are familial to some degree. If you have an affected relative, then you are more likely to suffer from that disease than a person who has no affected relative, all other things being equal. This applies to tuberculosis, even to measles, to diabetes, and to disorders that have environmental — in some cases major environmental — components. In other words, genes affect virtually everything. So, what multifactorial inheritance tries to do is to quantify the extent of the genetic role. We know that genes are involved in these common or multifactorial disorders, through family studies, by looking at the resemblance between relatives. If there is an increased number of affected individuals among relatives, then it is more likely, but by no means proof, that there may be a genetic component. There may be a common environmental component, of course, and twin studies help to sort that out. Looking at the incidence of a disease or trait in identical twins and non-identical twins can help to dissociate the genetic from the environmental components. Adoption studies are another way of looking at this.

More recently, what has happened with the genome project is that, with increasingly powerful molecular tools for identifying genes, specific genes have been identified in common disorders. These genes are shown to have effects in these disorders, although these effects are not always straightforward.

The oligogenic or multifactorial models can deal either with continuously varying traits, like cholesterol level, or with discrete traits, such as a disease. To illustrate how models have been used that conveniently describe and predict the behaviour of such groups of genes, imagine that you have a single gene with two different variants, at what we call a genetic locus. You have, as Dr Wilkie said, a 1:2:1 ratio, as predicted by a simple Mendelian model. When you have variants at two genes, the number of genotypes increases, and you get a distribution which is slightly more continuous. With three genes the genotypes add up, and this is only considering additive interactions between genes. Very quickly, a continuous distribution is obtained. For so-called discrete or qualitative traits, such as a disease which is present or absent, this can be dealt with by assuming a continuously varying distribution of liability — both genetic and environmental — with the extremes of high liability and low liability, and a threshold. Anybody with a liability beyond the threshold would be affected for that trait or disease. There can be multiple thresholds, which are used to model diseases where there is a sex difference. If females are the less affected sex, then they may have a higher threshold than the males.

One property of this model is that, if you take the population beyond the threshold, and look at its liability distribution, then it differs from the general population. This can also be seen in the first degree relatives of somebody with a liability beyond the threshold in the general population — their liability is shifted to the right, so that they have an increased liability for the disease or trait. With diabetes, for example, 6% of first degree relatives are affected compared with only 0.4% in the general population. This can be modelled in this sort of way. For second degree relatives, the mean liability will have shifted back towards the general population; for third degree relatives it will be getting quite close to the general population.

Another prediction from this model, which is observed with multifactorial inheritance, is illustrated when you look at the incidence in affected individuals compared with the general population, you see how it falls off in their first, second and third degree relatives. Under a simple, Mendelian, genetic model, monozygotic or identical co-twins, who are genetically identical, should all be affected. First degree relatives share half their genes, so 50% of them should be affected; second degree, 25%; third degree $12\frac{1}{2}\%$. It is a linear decrease as the relationship to the affected individual declines.

With multifactorial inheritance, the decline is of an exponential nature, which is predicted by the normal distribution curve. Here, for example, under multifactorial inheritance, 50% of identical co-twins might be affected, in other words there is a non-genetic component, otherwise they would all

be affected, but for first degree relatives it has dropped away much more sharply, from 50% to 10%. The fall off is even more steep for second degree relatives. This presumably reflects interactive components between genes and environment, and between genes and other genes, many of which are not simply additive.

The model also predicts that the risks in these types of disorder are not uniform. There are higher risks of developing the illness for relatives compared with the general population if the disorder is more severe. For example, if you have multiple tumours instead of one, or if the disorder itself is more severe — cleft lip and palate as opposed to just cleft lip — or if there is earlier onset; and, of course, this last one is crucial, if there are more affected relatives, then the risk is higher. The less commonly affected sex is presumed to have a higher liability, so the risk to their relatives will be higher. Finally, if the population prevalence is low, the risk for relatives compared with the general population is obviously higher than if the population prevalence is high.

The next problem is that common multifactorial disorders are causally heterogeneous. There is almost certainly a genetic-environmental continuum. There may be a small proportion of cases — it may be very small — where there are causal factors in affected individuals that are due to major gene effects (Mendelian disorder). There may be a larger number where there is a combination of weaker genes interacting with the environment, and at the other extreme there will be individuals who are affected because of non-genetic or environmental causes only.

This heterogeneity makes things very complicated. One gene can cause several different diseases, and one disease can be caused by many different genes. So, with different affected individuals, one may have predisposing genes 1 and 3 plus some environmental factors; another may have genes 2, 3 and 5, and so on. The unpredictability of the different interactive components is another problem.

To give a few examples of this type of inheritance, starting with cancer, Sir David Weatherall, one of Britain's leading geneticists, wrote in 1985: "It is well established that the genetic contribution to the common cancers is relatively low". Since then there has been a wide coverage in the press and scientific journals about the discovery of genes for breast cancer and colon cancer. It now appears that somewhere between 5% and 10% of all breast cancer is due to susceptibility genes which confer a roughly 90% lifetime risk. These are Mendelian genes, although less than 100% of gene carriers are affected.

The two commonest breast cancer genes are BRCA1 and BRCA2, and there are probably at least one or two other ones. These are relatively common disease genes. It is estimated that about one in 200 of the population carry one of these susceptibility genes. The point should not be lost that the great majority of breast cancers are not, to our present knowledge, caused by heritable variation in such genes. They may be due to combinations of minor genes and damage to cells with age, which is not heritable. Cancers increase exponentially with age, and most forms of cancer result from genetic damage to cells which is not heritable. Nevertheless, it is now known that a small, but significant, proportion of breast cancer has a major genetic component.

Colo-rectal cancer is very similar — about 5% of new cases of this cancer are caused by major gene effects. It has been estimated that about 50% of colo-rectal cancer has a hereditary component, but these figures have to be taken somewhat cautiously, because there is a tendency to overestimate the genetic component, partly because it is a fashionable view, and partly as a means of increasing funding. Nevertheless, it is the case that, for the *familial* colo-rectal cancers — these are defined by having at least three affected relatives in two generations, and an onset in one member under the age of 50 years — about 50% have been found to have mutations in so-called mismatch repair genes, which confer a high life-time risk of cancer.

Another example of this type of inheritance is Alzheimer's disease. Here you have a different situation. A very small proportion of Alzheimer's disease, which is, of course, a very common disease, is due to major genes. Three particular major genes have been found, but these account for only about 5% of Alzheimer patients. However, the apolipoprotein E (ApoE) gene shows three common variants in the general population. One of these, (ApoE $\varepsilon 4$), confers a very significantly increased risk of Alzheimer's disease. We are talking about 25% of the population with an 'at risk' genotype. Also, 2% of the population have two $\varepsilon 4$ genes, with the highest risk of Alzheimer's disease. Now we are talking about common variants in the population which lead to increased disease risk.

For example, an affected individual with the $\varepsilon 4/\varepsilon 4$ genotype develops the disease 15 years before somebody with the common genotype.

In my last example, ischaemic heart disease, which is, of course, a major killer, it has been estimated that about 2% of cases are due to major gene effects. Familial hypercholesterolaemia and familial combined hyperlipidaemia are both relatively common — one in 500 and one in 200 respectively. At least seven other genes have been found with minor effects on susceptibility. Interactions between these genes and between genes and environmental factors, such as smoking or alcohol, have already been demonstrated. So, in most cases of a common disorder, we are dealing with very complex interactions, although a small proportion may have identifiable susceptibility genes of significant effect.

Professor Wilkie: What are the implications of recent discoveries in genetics? What can medicine offer to those who have particular genetic features?

Dr Wright: You can make a more precise diagnosis. As I said, one disease is often due to very many different genes, so you can define the particular genetic cause of the disease. In addition to that, because you can have different types of mutation or change within the same gene, you can often predict what the patient's outlook is more precisely.

You can give patients more accurate assessments of the risks; both in terms of their own prognosis or outlook, but also for their relatives. In some cases you can define the prognosis very precisely. As an example, today I saw somebody who was given a particular genetic diagnosis, and, because he had a specific change in the gene, it was possible to predict that he will be affected between the ages of 20 and 30. The uncertainty is being narrowed to quite a considerable degree.

With Huntington's disease, if you give somebody a positive genetic diagnosis, all you can say is that somewhen between the ages of 40 and 60 they are likely to develop the disease. However, the new genetics is refining clinical predictions. You can also give more explanation as to what is the cause and what is likely to happen.

In some cases there is a treatment, but only in a small proportion of cases. If somebody is diagnosed with one of a number of metabolic disorders, you can put them onto a diet free of a particular nutrient, and they will develop and function normally. In other cases, like polycystic kidney disease, you can put someone into a programme to monitor one of the symptoms of their disease, like high blood pressure, and ensure that they do not develop complications arising from that. In other words, you can ameliorate the disease. In other cases, a modification of lifestyle is required. There are certain genetic disorders in which, if the individual smokes, he or she does not just have the usual risks associated with smoking, but a very substantially increased risk of, say, emphysema, as in α_1-antitrypsin deficiency, for example. If patients have another type of genetic disorder, then you can tell them to avoid sun exposure, because it will increase the risk of skin cancer, and so on.

As far as preventative treatment is concerned, with breast cancer, those who are diagnosed as having a mutation in one of the breast cancer genes will be advised to see a surgeon, and they will then discuss whether or not to have the breast removed. In the case of patients with mutations in the major genes causing colon cancer, they will, in many cases, either have regular screening or have a preventative colectomy.

So, there are treatments for some genetic conditions, but, in many cases, these have yet to be developed.

Dr Wilkie: Those are the prophylactic treatments to which Dr Wright was referring. There may also be prenatal diagnosis in some cases, but that may not be acceptable to the people concerned. They may not wish to take the advice, tests or treatment, particularly if it cannot be done in the first trimester of pregnancy.

In the case of Huntington's chorea, for example, to which Dr Wright has already referred, there really is only treatment of the symptoms of the illness as it occurs. There is not really very much that can be done. What one needs is quality of care, which is even more difficult to find.

Professor Wilkie: So, summarising, you suggest that there are no cures for genetically inherited

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diseases, because people have it in their cells. There may well be treatments, but sometimes not even those. Certainly good advice can be given, and forecasting and assistance with the genetic counselling aspects when people are thinking whether or not to have children.

The genome project, as I understand it, is intended to map all the different genes in the whole structure, but it is, presumably, an enormous job to do that for any one person, and why do we start looking at either the family tree or the genetic structure of somebody other than for research purposes?

Dr Wright: From our point of view, we look because patients want to know a diagnosis; they want to know a prognosis; they want to know if there is any treatment; and they want to know what is going to happen to their children.

Thus, the general reason for seeking genetic advice is because patients ask these questions. The genome project, so far, is not very helpful from this point of view, because it is limited by technological difficulties in screening genes, but we are probably on the verge of a time when it will become possible to screen much larger numbers of genes more easily than at present. There was a recent paper suggesting that you could screen, very rapidly and efficiently, over 100 different genes and look for specific changes in those genes. So, probably within the next few years, it will become possible to screen very large numbers of individuals.

With an increasingly health-conscious population, the tendency will be for people to want to have their genes screened purely out of interest in their own health, possibly even large numbers of genes that confer increased risk of disease. I think that this is going to become possible, but there are obvious dangers to this, particularly when, if abnormalities are found, there may be nothing useful that can be done.

Professor Wilkie: In the first instance, people come to see you because either they know that the particular disease that they are concerned with runs in the family or that their general practitioner has spotted that there is a genetic component to it. You do not really get people coming in off the street saying: "Am I a carrier of such and such a disease?".

Dr Wright: Very occasionally somebody asks whether they are a carrier for cystic fibrosis, or something that is relatively common.

Dr Wilkie: We women and our parents have always been aware of 'genetic factors', but not expressed formally in a family tree. All of us know if we have got some 'problem' in the family.

I have a squint, and our son has a squint, and I can trace the squints all the way back through the generations, through photographs of uncorrected squints, so I knew that there was this problem in the family.

It may be that, if it was a more suspicious problem, a more complicated problem, then people would come eventually to geneticists. So, it is formalising what has always been done in society.

Mr Le Grys: I want to make the point that there is an increasing number of genetic tests which identify that people have a predisposition to certain diseases. The ones that principally interest us for life assurance are cancers and heart disease. There is no certainty that a person will develop the disease, but he or she is at increased risk in the future. It is likely that the ability to quantify and forecast will improve steadily.

I think that having knowledge of your own genetic profile is essentially good, because it gives a person the opportunity, at an earlier stage, to change his or her lifestyle, to take some kind of preventative action. Maybe there is some therapy, not necessarily gene therapy, that is available, but there may be medical treatment or surgical treatment which can be applied at an earlier stage.

So, I would see a knowledge of one's genetic profile improving the public's health, and leading to reductions in mortality of the population.

Dr Wright: I fully agree. One of the dangers of linking genetic testing with insurance loading is if this will deter people from having these tests, many of which are likely to be highly beneficial to them.

Dr Macdonald: The traditional practice of life insurers offering ordinary rates to such a very wide range of people (a figure of 95% of applicants is often quoted) is important. The ordinary rates group, almost by definition, will contain people who are going to die of the most common causes of death, which are those for which genetic markers might, in due course, be identified, but only a predisposition, a slight adjustment to the probabilities of death, will be identified.

Much attention has been given to the more severe genetically-related illnesses, such as Huntington's disease, not surprisingly, because these have been the first ones for which specific genetic markers have been identified. That is a separate, relatively small, problem, and one which falls outside the issues related to what is currently the ordinary rates class. If that problem can be dealt with separately, *there is no reason, necessarily, to believe that identification of predispositions arising from* multifactorial disorders is going to lead to an overall worsening of the insured mortality experience.

Mr C. G. Lewin, F.I.A.: To what extent is there a risk, in the present state of the art, that people will be given advice which, in the end, turns out to be incorrect, particularly about having a short expectation of life, which could actually spoil their life? Is that a significant risk, or is it a very slight risk, in the present state of knowledge?

Dr Wright: I think that it is a real consideration. Much of the data, for example on Alzheimer's disease, was not obtained in whole population epidemiological studies, so it would be premature to rush out and start screening. The next door laboratory to us was doing the ApoE screening, and some people were tempted to go next door to find out their genotype, and, possibly, to conclude falsely that they were going to develop Alzheimer's disease by the age of 60. It is well established that this gene has a significant effect in lowering your age of onset of the disease, but it is certainly much more complicated than was at first appreciated. There are strong interactions with cardiovascular status, and the situation is not straightforward.

So, if large scale population studies are carried out, then one could, perhaps, accurately conclude certain things about mortality or morbidity. However, at present there is a danger that people will look at the rather focused, and often small-scale, studies that have been carried out, many of which are appropriate to one small population, but not necessarily to another, and draw false conclusions.

Dr Wilkie: *Could I just say that individual testing with this problematic situation must always be* offered good counselling, so that the person concerned can cope with the information, and not go off and jump off the Forth Bridge.

Mr Le Grys: That point is important. We need to develop the language that people can understand. I have seen a report from a geneticist that says: "You have a 90% chance of getting this cancer by the age of 90". That sounds absolutely dreadful. If you then turn it round and ask: "What will the insurance people say?" the answer will be: "You have a +75% addition to your normal mortality". That does not mean very much, either, to the ordinary person.

Perhaps actuaries and geneticists should find a way, so that we can simply explain the extra risk in terms that people can understand.

Professor Wilkie: Concerning the third topic on our schedule, the statistical evidence; the press seems to assume that geneticists and actuaries have enormous amounts of information, and can pinpoint exactly that such and such a gene is going to produce exactly, say, 59.7% increased mortality for somebody.

In reality, in what sort of areas do we have good statistics, and how can we get more?

Mr Le Grys: What statistical evidence have we got? The answer is very little indeed. Our information on genetics and its implications for mortality come from the geneticists, it is obtained from medical and research papers.

From an actuary's point of view, the information is from very small populations indeed. We do not have the type of statistics that actuaries love, where the 'exposed to risk' is in hundreds of thousands

and the statistics have been collected over a 20-year period. That type of statistics does not exist for genetics, and all that can be done is to pick up on medical trials and the published results, recognising that the statistics are from very small samples, and therefore the variation between the reality in the long run and the results at the moment might be quite large.

Again, I make a plea for actuaries and geneticists to get a better understanding of the risks. It will enable insurers to underwrite more scientifically, and for the geneticists to get a better appreciation of the shape and the extent of the risk.

Dr Macdonald: The question of the standard of evidence that is required to substantiate an underwriting decision is an interesting one. At the moment, in the United Kingdom we have three categories of risk factors:

(1) There are those that are unregulated, such as age and occupation and, within limits, medical history, where there is no great push for stricter regulation, and insurers are pretty much allowed to follow customary practices.

(2) A second category was introduced by the Sex Discrimination Act, which allowed discrimination, although in a very contentious area, provided that it could be justified in some actuarial way, which was left open to the courts to interpret. Since then there has been one major test case, which was won by the insurer.

(3) The most interesting category, and I think more relevant for genetic factors, is the recent Disability Discrimination Act. That allows the insurer to discriminate on the grounds of some disability if the discrimination is based on relevant information, is based on reasonable sources of information, and is reasonable, having regard to any other relevant factors.

This third category seems to be the crucial one when considering multifactorial disorders, where there are very strong interactions among a variety of genes, and lifestyle, and the environment. The question that I want to address with a small numerical example is whether we could pinpoint relatively small additional risks, such as might be associated with multifactorial disorders, and meet a criterion such as that in the Disability Discrimination Act.

For this numerical example, I have simulated some random samples of a lifetime, from a known distribution, which is given by exponential mortality or a constant hazard (which is not a realistic model of human lifetime, but I am making things as simple as possible). Any complications that we might add would make the job more difficult, and the answers obtained, even from this oversimplified model, cast some doubt on how reliably a small difference in mortality could be pinpointed.

Suppose that we have two populations with proportional hazards — in other words, one force of mortality is a constant multiple of the other force of mortality — and that we have no censoring. That means that every life observed is observed until he or she dies (which never happens in reality). Suppose, also, that there are no covariates, which means that interactions with other factors, such as the presence of other genes, lifestyle, smoking, diet, and so on, do not have to be considered. We assume a normal hazard of 0.04, which corresponds to forces of mortality in, perhaps, early old age, and in the second population assume that there is an additional hazard or additional force of mortality of 25%. Thus, the total is 0.05. Then the statistician's task is to identify that additional hazard, although without of knowing the real answer in advance. Moreover, we suppose that, for underwriting purposes, it is not sufficient just to say that there is a difference, but we have to say how big that difference is, since a financial consequence will ensue. The first line in the table shows an estimated 95% confidence interval for the additional hazard, given different numbers of lives in the samples.

Sample number	Number in each group		
	100	1,000	10,000
	%	%	%
1	12-95	19-41	21-28
2	−24-33	17-39	21-28
3	8-89	11-33	22-29

With 100 lives in each group, the confidence interval is 12% to 95%. A question to consider, and

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I do not know the answer — possibly only a lawyer could tell us — is whether or not we could defend an additional premium of 20%, 30%, 40%, somewhere in the middle, or 45% or 50%. If we increase the number of lives in each group to 1,000 or 10,000, then, as we would expect, the results are considerably better. However, in the case of the multifactorial disorders that we are considering, as has already been said several times, samples are rather small, and we do not get to carry out whole population surveys.

Matters are worse because these confidence intervals are estimated from the data themselves, without knowledge of where the real answer is. Were we to repeat the experiment with a different set of lives, we would expect to get a different answer. The second and third lines in the table show the results of repeating the experiments another two times with independent samples of lives. With the smaller sample there is a great deal of doubt, even about how much uncertainty there is in the location of the additional mortality.

In this example, as I said before, I missed out all the complicating factors, such as censoring and covariates, which certainly will complicate a real statistical investigation. It is open to question whether we could defend underwriting decisions for relatively small additional differences in mortality, if we were required to adhere to a standard such as that in the Disability Discrimination Act.

If insurance companies move towards preferred lives underwriting, it raises questions about many more areas of underwriting than just those that are raised by genetic testing.

Professor Wilkie: To summarise, either you would need very high extra mortality to be identified or you would need a very large sample.

Dr Macdonald: Yes, the doubt about the location of the additional mortality does not depend very much on what the additional mortality is, it depends on the sample size. If the true additional mortality were 100% or 200%, the smaller samples would be sufficiently far away from zero that you could identify its existence. The problem arises when you try to identify relatively small differences in mortality from quite small samples.

Professor Wilkie: As Dr Macdonald said, the Disability Discrimination Act (Services and Premises Regulations) 1996 is now in force. The salient features are that insurers may discriminate on the grounds of disability if "less favourable treatment is ... based upon information (for example, actuarial or statistical data or a medical report) which is relevant to the assessment of the risk to be insured and is from a source on which it is reasonable to rely; and" is "reasonable having regard to the information relied upon and any other relevant factors".

Note that the Act does not apply to people who have only a propensity to become disabled in future, but to people who are currently disabled in some way.

What do insurers do to justify their underwriting decisions for people who are currently disabled? Do life offices rely on the reinsurers' manuals? If so, what do the reinsurers do to justify the recommendations in their manuals?

Mr Le Grys: Reinsurers are able to defend the decisions that they put into their underwriting manuals, which are compiled with a great deal of effort. We have good statistical information, but not from the U.K. However, if you can say that American information is relevant, then we have much information. From America we have industry-wide statistics; the medical impairment studies, where they compare actual ratings with the actual amount of extra mortality. In addition, we have the very large epidemiological studies, like the Framlingham studies and the MRFIT studies. We also have medical studies and medical data, which help us with some of the more specific and less common diseases and impairments.

The reinsurers, themselves, undertake their own studies. My former office used to collect data on all impairments on every case that was underwritten by one of their underwriters, wherever they were in the world. That was the only way to get data in sufficient quantity. Unfortunately they are not homogeneous, because they are a mix of North American data with Scandinavian data with Japanese data, etc. This leads to some questions of its validity.

The only information that we have had, until recently, in the U.K., is from one very large life office, which has released its experience on impaired lives. Some useful work has been done at City University, among others, and researchers have compared the underwriting decisions of three reinsurance offices with the data coming from the large life office, and, fortunately, they found that it was a reasonable fit.

Reinsurers have never had to justify their underwriting standards, but I am confident that, for the majority of diseases and impairments, the reinsurers could justify them.

Professor Wilkie: You have evidence of the experience for people with existing impairments which are identified at the time of underwriting, and possibly rated up at the time, but not necessarily so.

Mr Le Grys: That is true. If you ask what is the basis for rating up cases where there is some genetic weakness, then we have to rely totally on reports from geneticists.

Professor Wilkie: Does the insurance industry get the statistics that it needs?

Dr Macdonald: I do not see what the insurance industry can do by way of generating the basic data, because that can only arise from medical and epidemiological studies. Therefore, we will have to continue to rely on those data, and if they are not available in the quantities that the large reinsurers have been able to collect in the case of major impairments in the past, then we have to accept the consequences for underwriting.

Professor Wilkie: It has been suggested that the ABI might ask the CMI Bureau to start gathering statistical evidence, not just by investigating life office data, but also by looking up the public medical papers and similar information. Is that a realistic possibility?

Mr C. G. Kirkwood, F.F.A.: I am Chairman of the CMI Bureau. We have had preliminary talks with the ABI as to what might happen, but it is at a very early stage yet.

Professor J. Fincham (a visitor)**:** There seems to be one question, and that is: how much DNA analysis is the insurance industry prepared to pay for? There is almost no limit to it. We hear about genetic profiles and about how many genes these cover. Potentially there are thousands, some of trivial importance, some of greater importance. You have to make a decision about where to draw the line.

Mr Le Grys: The insurance industry is unlikely to request that new genetic tests be performed. In fact, the insurance industry has given the undertaking that it would not request new tests, but the insurers do want to see, in some cases, the results of past genetic tests. Therefore, there is no great cost involvement from the insurance offices at this stage. However, like other investigations that insurance companies require, such as an ECG or a serum cholesterol measurement, etc., the offices pay for it. That practice has been established, and I would imagine that it would continue if insurers wanted some further work done on an existing genetic test.

Professor D. Porteous (a visitor)**:** What we have to recognise — and it stems from comments that Dr Macdonald made — is that we seek genetic information for very different purposes, depending what role we play. If you are a clinical geneticist, then you are collecting information for the benefit of your client; if you are a basic scientist, then you are collecting information as a way to better understand the disease; if you are a commercial buyer, a pharmaceutical industry representative, then you are collecting information with the aim of, perhaps, developing a new treatment; and if you are an insurer, then you are collecting the information to make actuarial risk calculations.

The point that Dr Macdonald's presentation made very clearly is that your industry needs very large numbers — much larger numbers than we, as researchers, require. It is sufficient for us to undertake a relatively small study that indicates, for example, the APoE $\varepsilon 4$ gene as being an important contributor to Alzheimer's disease, and to use that to help us understand the biological processes. This leads us, by an unravelling process, to new genes and new targets for drug discovery.

Ultimately, all genetic testing serves one common purpose that is to your advantage — that is to reduce risk, both to the individual and to the population as a whole. When you have that information to hand, you are in a better position than you were before you had that information to make lifestyle changes, to make reproductive decisions, to make personal decisions. So, apart from the vexed question of cherry picking, there are great difficulties in seeing how one can actually do anything useful, in an actuarial sense, with the data, and, perhaps, there is much unnecessary worry about the 95% of the population who, at the moment, get basic terms. There is a tremendous amount that we, as researchers, can do about individuals who are at risk.

Mr M. J. Breingan, F.F.A.: Suppose that the actuarial profession was giving evidence to some official committee on genetics, and was asked: "Can the profession sign off the assumptions underlying insurance companies' underwriting practices along the lines of the Disability Discrimination Act?" I think that the profession would have to say: "Sorry; the statistics do not allow us to provide such comfort." Therefore, although the insurance industry might like to develop a genetics underwriting policy based on such little data as are available, I question, on hearing the debate, whether the actuarial profession can support it in this attempt.

Mr P. D. Robertson, F.F.A.: Approximately how many genes are likely to have an effect on health?

Dr Wright: The list, from McKusick's catalogue of genetic disorders in man, contains about 4,000 genes. There are roughly 70,000 genes in man; those that are listed cause single gene, Mendelian types of disorders. The number is, however, very much larger if you move into the complex disorders or illnesses.

Mr Robertson: The reason for my asking that question is, if there are several thousand genes, then most of us are going to have some bad news in there.

Dr Wright: All of us.

Mr Robertson: Exactly; I do not know what number of genes will be faulty, but we also have the problem that we are also likely to have some fairly good genes. I cannot see how anyone is going to go through all those genes in order to underwrite, because, as soon as one increases the rating for some small factor, one would have to consider the 10,000 other genes not yet tested, any of which might show positive factors causing a reduction of premium.

The more I hear, the stronger my view grows that, as, I think, Professor John Bell said, life assurance is an irrelevance to the genetics debate.

Dr Wright: I agree that when you get into the more common genes, then the danger is that you will exclude a large number of your potential customers. That will be to the detriment of the industry, and there will be other people who have decreased risks. None of these are simple effects.

Professor W. G. Hill (a visitor)**:** There is also information available on relatives. The insurance industry asks questions about how old the grandparents or parents were when they died. One can put together the information on the survival of one's ancestors and other relatives to make predictions based solely on quantitative information, using essentially genetic and also, to some extent, environmental information, to compute the risks on individuals.

Insurance companies have chosen not to do this, or at least only to make exclusions, not to do a sum on every single individual, which they could do. We do it for dairy cattle; we make predictions on a sire-by-sire or a cow-by-cow basis, in terms of life expectancy in the herd, and breeders will be expected to use this information.

The situation is that specific DNA testing is going to add information to these basic data — sometimes the extra information will be useful; sometimes it is not going to add a great deal. The

question that the insurance industry has to address is how much does it wish to use this molecular genetic information; how much detail to go into in terms of making calculations and of changing the probabilities or the costs which attach to individuals?

The issue is whether there will be a situation of differential charging or whether the current position of putting individuals in the pool, except for exclusions, will continue.

Professor Wilkie: Professor Porteous mentioned reducing risk. Did he mean reducing uncertainty? I give an example. Earlier on, it was said that somebody with Huntington's disease has a 50% chance of passing on the gene. If one could do a genetic test, which I think is possible in the case of an individual aged 15 or 20, one of whose parents was affected, you could remove the uncertainty and find out whether the individual was affected. Is that what is meant by reducing risk?

Professor Porteous: It was not what I was meaning, but the relief of anxiety is a highly relevant reason for undertaking a test for a client. If you know that you are within a family at high risk of, say, breast cancer, and you are planning to start a family, then there is anxiety: am I going to pass it on?

However, that was not what I was meaning. What I was meaning is that, if you undertake a test, then there is nothing that happens other than to the personal advantage of the individual, either the relief of anxiety or to allow him or her to take action to counteract the predisposition. There are lifestyle changes, there is the question of taking a more appropriate form of treatment, all of which changes, not the genotype, but the probability of illness.

Taking a genetics test never increases the burden that will fall upon the insurance industry, assuming that everybody is taking out insurance for the normal purposes. There is, however, the vexed issue of whether there is a problem with the proposer having access to information that the insurer does not have.

Professor Wilkie: What are the financial consequences for life insurance?

Mr Le Grys: I do not think that the consequences for life assurance business are very great. I believe that widespread genetic testing will come in during the early decades of the next century. It will be beneficial, for the reasons that we discussed earlier: earlier diagnosis; people taking preventative action; there may be medical treatment; and, by then, there might be gene therapies as well. Population mortality, which has already been improving steadily by 1%-1.5% p.a., will continue to decrease, and may decrease even faster with the result of gene therapy.

That trend will happen with assured lives as well. On the other hand, people's buying habits may change. If you have been told that you have a predisposition to a certain disease, will that affect the way that you will buy life assurance? It probably will not be the critical decision, but surely it must have some influence on your decision as to whether or not you are going to buy life assurance, and how much?

I see people's buying habits changing, and, in time, ultimate mortality will include proportionately more of the less-fit lives and proportionately less of the fit lives. Although the assured lives mortality is slowly decreasing, there could be a change in buying habits which could reverse the direction. One cannot predict whether that means that assured lives mortality will decrease in line with population mortality, or whether it will go up relatively. My best guess, from looking at models, is that assured lives mortality will continue to decline, but it will do so more slowly in the future than it has done in the past. Population mortality and assured lives mortality will tend to come together over the next 20 to 30 years.

I do not think that this is particularly significant, and there will always be time to adjust, because these trends are not going to happen overnight. That is conditional upon three things:

(1) There is no adverse selection. By 'adverse selection' I mean that people who know that they have a predisposition to disease take out policies with very high sums assured.
(2) Underwriting practice will stay unchanged, and we will continue to operate with wide pools that have considerable cross-subsidy in them.
(3) The pools are not disturbed by the equivalent of cherry picking.

How do we prevent people who know that they have a poor genetic profile from taking very large amounts of insurance, and thereby selecting against the insurer? There must be some size limit, where the insurers say: "If you have had a past genetic test and you know the result, then the insurance company needs to know as well."

At the moment, insurers subscribe to the ABI code of practice, which says that we will not take any notice of genetic profiles or genetic tests for sums assured below £100,000. I disagree with that limit. There are some offices that say: "Never mind what the ABI says, at this stage we are not going to ask for a genetic test at all". That is more than slightly risky. If a person is proposing to your office for £10m, and he knew his genetic profile and the office did not, then I suggest that, if the office accepts the risk, then it is moving away from insurance and more into gambling. I would look for a sensible limit where the average person can get enough cover to insure his or her own house and to provide for the family. I think that that is somewhat higher than £100,000.

Dr Wilkie: Concerning changing buying habits, when HIV testing came out, over ten years ago, it was well known that certain people who suspected that they might be HIV positive got their insurance on day one and then got their test on day two or soon after.

Dr Wright: One thing I am not clear about is why, assuming that somebody is taking out an average life assurance policy, should genetic testing be any different from any number of other medical tests, many of which, as I understand it, are not currently used, cholesterol, renal function or blood pressure?

Mr Le Grys: I think, as far as the insurance industry is concerned, that we do not see a genetic test as being any different from any other type of medical test, and we would wish to treat genetic information in the same way as we treat any medical information, with the strictest confidence. There is no difference, in our opinion, between genetic information and other medical information.

Dr Wright: You are saying that, if somebody has had a genetic test, then you would want to know the result. If somebody has gone to their doctor and has a blood cholesterol analysis, you would not, as I understand it, at the present time, ask for that information, or, for that matter, for his or her blood pressure? It implies that there is a slightly different emphasis.

Mr Le Grys: If a small amount of insurance was proposed, then the insurer accepts the information on the proposal form. The insurer asks relevant questions on the proposal form, and these are meant to elicit whether the proposer has high cholesterol or not. Thereafter the insurer might ask the proposer's doctor.

It is an imperfect world, and you do not always get the information. For the 25% of proposers, where insurers ask for some medical information or for a report from the doctor, then the insurer expects that the report will state that the proposer has raised cholesterol levels. Where, in my opinion, insurance companies are naive, is that, having got the information, they do not do anything with it.

Dr Macdonald: My paper describes an effort to apply a simple mathematical model to the additional costs of adverse selection. The main aim of a modelling exercise such as this is to try to combine the additional mortality that might arise from genetic testing, about which we have very little data, with insurance buying behaviour, which, as Mr Le Grys mentioned, might change. We know even less about that, which, perhaps, does not do us credit as an industry.

Without adequate data, we can use a model to do two things. One is to put in some rather extreme assumptions and see if the answers suggest any bounds on the additional costs, which can then be judged to be reasonable or unreasonable. The other is to suggest what kind of data might be worth collecting in the future, and what kind of research ought to be carried out — in particular with respect to insurance buying behaviour (which is the one part that is specific to our industry).

There are two parts of my paper to which I would direct your attention. In ¶4.3.5 I have attempted to describe how extreme the assumptions are that underly the results, particularly with respect to the

adverse selection of the lives with genetic disabilities. I do not suggest that more extreme assumptions could not be made, but I think that these are already quite extreme.

Then, Section 8.1 describes the conclusions, where the figure of 10%, which has been quite widely quoted, is suggested as an order of magnitude. This is not meant to be an upper limit, rather it suggests that 10%, 20% or 30% might be more realistic than 100%, 200% or 300%. A crucial feature in arriving at that conclusion is the extent of the ordinary rates class and the amount of cross-subsidy which exists in the ordinary rates class.

Someone who suffers from one of the complicated, but not spectacularly severe, predispositions arising from the multifactorial disorders — assuming that they do not change their lifestyle in order to improve their expected mortality — on discovering that they suffer from such a predisposition, is going to buy insurance in the ordinary rates class that they could have obtained anyway, because only at the margins would someone be shifted out of the ordinary rates class if they have been identified as having one of these predispositions. However, the conclusion certainly does not hold for other forms of insurance. Life insurance is relatively simple compared with critical illness, long-term care or disability insurance, and it would be dangerous to assume that we could extrapolate conclusions from life insurance to these other forms of insurance.

Professor Wilkie: Now, considering other forms of insurance; what about critical illness?

Mr Le Grys: This is a growing class of business, and I think that the effect of genetic testing and the widespread knowledge of genetic profiles will have much more effect on critical illness insurance than on life assurance:

(1) There is no continuing trend towards lower inception rates for diagnosis of disease. Depending on the available health services, diagnosis of the disease could happen earlier. Widespread genetic testing could make diagnosis even earlier. That is very good news for the public, but it is pretty bad news for the insurance companies, because they are going to pay more claims and earlier.

(2) I think that adverse selection on critical illness will be more severe than it is on life assurance. Under critical illness, insurers are going to pay a large sum on diagnosis of disease. The person is still alive; often he will recover; and he may have many years ahead in reasonable health in which he can spend his money.

My belief is that buying habits could change much more significantly for critical illness than for life assurance. However, I do not advocate requesting the results of genetic tests on every critical illness policy; there has to be a practical limit.

One aim of the insurance industry is to make the process of buying insurance simple, easy and acceptable to the proposer. I would expect insurers to continue that concept, and to try to get the majority of cases insured with the least amount of red tape and examination. I think that premium rates under critical illness policies will have to go up, rather than down, in the future.

Guaranteeing critical illness rates for the next 10, 20, 30 years is probably unwise, but even more unwise if widespread genetic testing is going to come. I see the industry being embarrassed in the next century by some of their critical illness products, and offices will have to reshape their policies so that they do not pay very large windfalls on diagnosis of a relatively minor disease or impairment.

The impact of genetic testing will be more severe on critical illness than on life assurance.

Dr Wright: One thing that is clear is that genetic tests are most powerful at predicting early onset of multifactorial conditions, and are probably most relevant in this area. At the same time, these are the conditions where people would benefit most from having a genetic diagnosis.

Dr Wilkie: What sort of groups of people take out critical illness policies?

Mr Le Grys: These are much the same as those who take out life assurance. Critical illness insurance is often combined with life assurance. The experience for some offices, so far, is that, if a person

takes out critical illness insurance in conjunction with life assurance in a combined package, the critical illness experience seems to be lower than on stand-alone critical illness policies.

Mr D. L. Grimshaw, F.I.A.: I disagree with part of what Mr Le Grys has just said.

I am a member of an Institute of Actuaries group that is monitoring critical illness experience in the U.K., and our results are due to be published soon. Experience, so far, appears to be better on stand-alone policies than on acceleration. I do not understand it; I will not attempt to explain it; but that is what is happening.

Also, when discussing critical illness insurance, it is important to look at what diseases are actually being covered. My understanding of the current state of play on genetics is that with heart disease we are a long way from being able to predict people's predisposition to disease using genetic tests, and therefore, perhaps, for males, critical illness is still viable, and will continue to be so, because heart attack and stroke are probably the two main conditions. For females the position is rather different, because cancer makes up over 75% of current claims. Therefore, we have a real problem there, particularly on guaranteed rates.

Mr Le Grys: Could I just qualify my remarks? For one major reassurer the experience of stand-alone critical illness policies is worse. That might just be a function because they are taking the surplus risks, and they may be different from the ordinary cases.

Mr J. F. Buchanan, F.F.A.: The discussion does not seem to have covered what is involved in taking a genetic test. I would be interested to know whether you would have a genetic test and obtain the results for all faulty genes or would you be tested for the condition of a specific gene.

Dr Wright: No; for example, for Huntington's disease or breast cancer, these groups are generally identified because of the family history. At the present time, you have to come along for an initial counselling session, and then usually one or two follow-up counselling sessions, to discuss the full implications of having a presymptomatic test. In the case of Huntington's disease, you have to see a psychiatrist beforehand, to make sure that you are able to cope with potentially bad news, then the test is carried out, and there is extensive follow up afterwards.

So, it is very different from the idea of having a battery of genes tested. This may be closer to what is happening in the United States of America, where there are many private companies and the same rules do not apply. There are guidelines that are laid down for clinical geneticists in this country for applying these sorts of test, but that does not apply, necessarily, in other countries.

Professor Porteous: Following on from what Mr Buchanan asked, at the present time we are talking about a very limited number of tests. In relation to the position in the U.S.A. and commercial testing, we should anticipate a problem here too. There are commercial testers in the U.K., at present offering a limited number of tests, but the capacity to offer tests for a large and growing number of disorders will increase dramatically.

To assume that the status quo will remain would be a grave mistake. The pace of gene discovery, the genome project and the ability to define highly accurate genotyping across the whole genome will mean that it will be possible to do very large numbers of tests on very small samples very quickly. That will come in the next two to five years.

One has to anticipate dramatic change in this regard, and my suspicion is that, for a large majority of these conditions, the genetic counsellor will be by-passed, and it will be the GP that will be taking a blood sample and making the test. The question then will be: how is the test interpreted, both by the GP and by the insurers?

At present, the techniques that we use for genetic testing are highly accurate and do require sequencing on the DNA. We now have techniques, the so called 'DNA on a chip' techniques, in which you do not have to know the nature of the mutation, you can infer the mutation as a result of the test. This type of technology is going to be with us within the next two to three years. For example, today you can buy a chip from a company on the west coast of the U.S.A. which has the

entire sequence of the HIV genome on it. You can then take a blood sample from an individual and apply it to that chip, and determine whether or not that person has the HIV genome present in the blood sample, and, if so, what its mutational status is.

Likewise for the mitochondrial genome. You can infer the sequence of an individual's mitochondrial genome, which essentially is identifying him or her as an individual, because of the variation in that sequence. The same will follow for the cystic fibrosis gene and for the breast cancer susceptibility genes. So, rather than having to define a test for an individual, you will be using a method that will allow you to infer a mutational status.

Going back to Mr Robertson's question, today we are talking about a very limited number of tests; but there is a possibility of running highly parallel tests that would tell you the result of your mutational status for 1,000 genes — certainly 100 — good and bad.

Professor C. Aitken (a visitor)**:** The human genome project is certainly one of the most exciting areas of science that man has ever been involved in. It is like splitting the atom, and developments are happening at an incredible speed. Within a decade the human genome project will have answered many of the questions for the understanding of genetic science.

Frequently it is asked: what is its application? We do not yet know its application, because we do not yet understand the science. However, the speed at which the science is developing suggests that the implications are as major as of any science development that has ever occurred.

Let me put some figures to it. Billions of pounds and dollars of research money are being spent on genetic science, at the present time, by governments throughout the world and by industry. The pharmaceutical industry is pouring money into this area. In Edinburgh there are about 5,000 academic biologists, many hundreds of whom are geneticists. Thus, a very large expenditure is going on within our own city on this topic, and this is happening in many cities throughout the world.

Considering insurance, my understanding is that, so far, our state of knowledge about genetics is relatively irrelevant for life assurance in normal affairs, and some large companies have already indicated that to be so.

When we consider critical illness and permanent health insurance, in the context of what will happen within the next decade about the human genome project, greater problems arise. The whole area of social welfare is also to be reviewed, not just in this country and not just by the arrival of our new Government, but worldwide. The implications of having to look after people in their older years is now being appreciated worldwide. The implication for health insurance in the U.S.A. is enormous. There are also major implications for personal pensions.

The changes within our lifetimes — even for some of us who are retired — particularly those that will occur in the next decade, both in the insurance industry and in genetic science development, are major. What would be discussed if this meeting were held in 10 years' time would be very different from what we are now discussing. There will be very major changes, both in how the population insures for the difficulties that genetic knowledge in all its ramifications may lead to as the years go by, and in the benefits that will surely arise from better knowledge of the biological sciences.

Mr D. B. Keir, F.F.A.: I wish to consider the model that Dr Macdonald developed in his paper. This modelling is essentially about human behaviour. That is what much of this discussion has been about — the reaction of human beings to the knowledge that they obtain after having had tests, and how their insurance buying behaviour is going to change.

I do not think that we should underestimate the ability of human beings to select against insurance companies, and I mention, by analogy, my understanding of what happened with mortgage-related endowments. My understanding of the situation, not first-hand knowledge, because I was abroad at the time, is that the insurance industry offered to provide life insurance cover to people who took out mortgages, with little or no medical evidence, expecting that the effect on their mortality would be very small. The outcome was not just 10% to 20% extra mortality, but hundreds of percentage points extra mortality in the early years.

Thus, I remind you that human behaviour is such that people will select against insurance companies if they can gain financially from so doing. I believe that they will do exactly the same

once we have an environment where genetic testing is quite normal, quite cheap and commonplace, and there is much more information about people's future mortality, and their future likelihood of sickness is known.

Mr Le Grys: Concerning the public's ability to adverse selection, even if they have not got the ability to select against insurance companies, then their brokers and their agents certainly have. That was a major part of the problems with mortgage-related life assurance, where there was no underwriting. Brokers had drawers full of cases that had been declined, and then they could say to these clients: "I can get you insurance now. All you have to do is to take a mortgage". This adverse selection was part of the problem with mortgage-related business.

So, irrespective of what the public is doing, there is a vested interest group for whom earning commission is a high priority.

Mr Robertson: As a way of demonstrating non-anti-selection, French experience at age 40 gives a rate that is twice that of the rate in the U.K. At age 80, ours is 40% higher than theirs. There are two reasons for quoting these figures. First of all, people who think that everything is genetically determined will have to think again. The second reason is that the two countries in Europe with the highest propensity to buy insurance are the two with the lowest mortality rates, and these are Holland and the U.K. It appears that people are trying to get a good deal rather than trying to get a large amount of cover because they know that they are going to die. I am not entirely convinced that everyone is out to anti-select.

Correcting what Mr Le Grys said earlier, no company in the U.K., as far as I am aware, has said that it will not pay any attention to genetic tests 'ever'. One or two have said 'for the foreseeable future', but to use the word 'ever' would be something of an exaggeration.

Professor Wilkie: I now ask the panellists to give their final remarks.

Mr Le Grys: Genetic science is developing very rapidly, and will affect all of our lives in the future. It will certainly affect insurance companies. It will affect the way that we do business, and I suspect that it will affect the products that we sell in the future, and the ways in which we sell them. It will certainly change the way that we underwrite. At present, we underwrite by looking at a person's medical history and by considering what is wrong with him or her at today's date, and, as a secondary question, ask if there is anything that is likely to affect his or her mortality experience in the future.

I suspect that, in 20 years' time, we will be looking at genetic profiles and considering what impairment each proposer has a predisposition for, and also how far has he or she advanced along the road towards that predisposition. It will be a reverse of the way that we currently underwrite individual cases.

There are distinct possibilities for anti-selection, which we will have to guard against. The area that is worrying me at the moment is long-term care insurance, despite it being only in its infancy in this country. Currently the average stay in a nursing home is two years. However, if someone is diagnosed as having Alzheimer's disease, then he or she could stay in a nursing home for 5, 10, or even 15 years. If that is so, then the cost of that claim could be enormous. If people who have a predisposition to Alzheimer's disease or their children or their relations take out policies, then it could have a major impact on the claims outgo of the insurance industry.

I have tried to research how long people stay in nursing homes if they have Alzheimer's disease, and it only appears to be about 50% longer than for stays for other causes. I suspect that this is because their families look after them until such a stage when they cannot cope any longer. It is at this stage that people go into nursing homes.

My fear is that, once there is an insurance policy which will pay from the early stages of Alzheimer's disease, we will find more claims for nursing care, starting earlier in life, and with much longer claim periods.

This is another indication that the whole way we do business will change in the early decades of the next century.

Dr Wright: As far as the simple genetic disorders, the Mendelian disorders, are concerned, these are relatively rare, but some have substantially raised risks. Coronary artery disease was mentioned earlier. Here are some of the commonest genetic disorders in man: familial hypercholesterolaemia and familial combined hyperlipidaemia have frequencies of 1 in 500 and 1 in 200 respectively. The gene(s) for the second one has not yet been found. Sooner or later it will be found, and these tests will be applied. In the case of the first disease, the probability is that 50% of gene carriers will have severe coronary artery disease by the age of 50; 75% by the age of 60. These genes confer substantially increased risks.

Genetic tests are clearly very relevant to this group of disorders. I suppose that they are still quite a small group numerically, provided that the overall pool is large. It is perfectly reasonable and justifiable for insurance companies to see the results of genetic tests that have been carried out, provided that they are treated in the same way as other medical tests. I think that it is completely wrong if patients are required to have genetic tests, unless they are taking out unusually large policies.

In the case of complex diseases, I think that most of the information comes from family history. Alzheimer's disease may be an exception to this. Many of these disorders, with single gene components and a very substantially increased risk, such as breast cancer or colon cancer, occur in patients who have quite extensive family histories of the disorder, with three or more affected individuals, often with early onset of the disease.

You already have that information. I do not know whether you use it all, but if that information is used correctly, it will identify most of these subgroups. For the complex diseases, there may be a smaller number of tests that are going to be directly relevant.

With regard to trying not to discourage patients from having tests that are likely to be beneficial, confidentiality has not been mentioned. That is obviously extremely important. People are worried that information will get back to employers. This is even more of a concern in the U.S.A. than in this country.

It is clearly in everybody's interest, including the insurance companies' interest, that people do have the tests that are going to improve their health prospects.

Dr Macdonald: Apart from Professor Aitken, no-one has mentioned the huge problems looming over us of shifting provision for long-term care and health insurance from the state to the private sector, which seems to be being pursued across the globe, almost regardless of the political complexion of the parties in power.

Possibly the combination of unlimited competition on price and the limited liability of the owners of insurance companies is not the soundest combination upon which to base that shift. An idea that might be worth reinventing in a different form is with-profits participation in this form of insurance; when you face a wholly unknown future, the pricing can be carried out in retrospect, provided that the market is such that you cannot be exposed to unfair or unsound competition from competitors.

Dr Wilkie: I do have a wish list.

The first item concerns risk. Actuaries, the insurance industry and geneticists are all very familiar with probability theory and risk, but they are very poor at explaining that to the public. We did a small study in Glasgow, where we asked a group of about 100 patients what they understood by a 50-50 chance of inheriting a serious illness: was it a small risk; a medium risk; or a large risk? Something like 85% of them said that it was a medium risk. We went back and asked them what a large risk was. They said 90% to 100%. There is a degree of logic about it, but the public do need to be educated.

My second point is about the benefits and the disadvantages and limitations of genetics. We have heard about all the good things that genetics can do; but we still have limited knowledge in the genetics field.

Thirdly, I would like to see a much tighter control of confidentiality in insurance companies. I do not know what you think that confidentiality means. It is a word that is banded around in many places, including in the medical world, where I work. When HIV hit Glasgow Royal Infirmary's haemophilia population, everything was to be done in the strictest of confidence. People's test results

were to be highly confidential. We decided to ask a group of people, consultants, nurses, social workers, ward sisters, and the patients, what they thought that confidentiality meant. The consultant thought that a handful — perhaps two handfuls — of people would know, and the social worker thought that it would be one handful. The ward sister was much more realistic, because she knew that there were her deputies and those who were on duty at night. In fact, the patients were much nearer the reality of what confidentiality meant. Something like 90 people knew their HIV status when it was all added up. We have to define what we mean by confidentiality. I do not know to what extent family histories in an insurance company are anonymised. If you go to the Black Isle, in the north of Scotland, and you give a certain name, then everybody knows if you have a particular illness, because that is well known in that particular part of the world. The duties and the ethics of people working in insurance in terms of confidentiality may be different from other groups of people.

I also believe that companies should have to justify their decisions. When they make a decision either not to take on somebody or to uprate him or her, then the person should know and understand the decision.

Replying to Professor Porteous, as a researcher, I think that there is a responsibility for researchers to collect good epidemiological data of multifactorial diseases over time. We have to do it with drugs, so I would like to see it done for multifactorial genetic illness.

The President (Mr P. H. Grace, F.F.A.): When we run Sessional Meetings in the form of a panel discussion, it seems certain that, not only do we have a good turn out and many contributors, but we also manage to overrun.

It is unfortunate that we have not had an opportunity to comment on some of Dr Wilkie's closing remarks. Perhaps we will have a discussion on underwriting standards and confidentiality at a later date.

Commenting on one point which has not been mentioned in the discussion, a leading reinsurer has carried out some market research on the subject: 'How we live now'. It looked at marital status, cohabitation and a whole host of things, including one section on genetics. Many of us are very sceptical as to the public attitude on the use of genetic tests. A question was put to a sample of about 1,200 people of various ages, various occupations, etc.: "Do you think that the use of genetic technology to see how likely it is that people will develop diseases is a good medical development?"

In his paper Professor Wilkie put forward some arguments against this particular development. However, in the sample, it is surprising that over 90% of the young people believed that it was good. For the population overall, all age groups, it was over 80% who believed that the developments were good and in the public interest. It is a message to the industry, if the use of genetic information is a deterrent, we run the risk of antagonising a large proportion of the population.

I thank Professor Wilkie for chairing the panel so excellently — even if he did not manage to give us time on that last topic. I should also like you to join with me in thanking the panellists for their input into what has been a very informative and instructive discussion.