



# **What is the Nature of Evidence?**

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## What is the Nature of “Evidence”?

### 1.1 Introduction

The collection of information and gathering of data, with its subsequent interpretation to support or disprove a hypothesis ought to be an activity on which all interested parties can agree. Yet experience tells us otherwise. Groups and individuals often seem to look at what is ostensibly a common set of circumstances and draw different conclusions, each claiming sincerely that the facts support their case.

In the context of the debate about genetics and insurance this is an important issue because the debate about whether or not genetic information could and/or should be admissible when determining insurability and the premium to be applied is a common source of controversy, with “pros” and “antis” claiming that evidence supports their position.

This workshop aimed to try and set out the criteria with which three of the key stakeholders in this debate – physicians, consumers and insurers – use to determine what constitutes the evidence they need in order to act. The views expressed by the speakers and by participants in the subsequent discussions are their own and should not be taken as representing the opinions or policies of any institution or organisation with which they might be associated.

### 1.2 A Public Health Perspective

For Public health physicians, data is collected to enable them to quantify the risks associated with a particular disease, and the links between exposure to the disease causing incidents and the outcomes. Conclusions are based on calculations of probability built on the observation of disease in populations. Inevitably this takes place in the context of complex systems, with (in most cases) multiple relationships between determinants and the disease itself. Some of these determinants will be genetic, and some are environmental. Measuring the exposure of an individual or population to these, and creating an association between that exposure and the disease is difficult, particularly when preventative measures can be taken, but where peoples’ compliance with these measures may not be complete, nor the measures themselves totally effective.

The methods used to try and quantify the relationship between exposure and disease include:

- The case control study (which compares the likelihood of a particular exposure (odds) between individuals with (cases) and without (controls) a particular disease).
- The cohort study (which obtains information over time from a study population, and calculates the incidence of disease in individuals exposed to a given risk factor compared with those not exposed).

In both of these it is possible to bias the outcomes in a number of ways:

- By selection of cases or controls
- Through observer bias about the disease, risk or exposure
- As a result of differences in re-call
- Through publication bias (positive results are more readily published than negative ones)

The evidence itself can be hard to gather, particularly when effects are slow to emerge. Whilst the link between smoking and lung cancer is widely accepted today, it took huge studies to establish this, carried out over many years. Yet this is a relatively simple



measure of exposure to a specific risk, with a well-defined outcome. Most systems are much more complex, making it very difficult to establish significant causal links.

Nor is “risk” itself a simple concept. In some circumstances it is the relative risk (the ratio of disease in those “at risk” to those “not at risk”) that is needed, whilst in others it is the absolute risk – the percentage chance of getting a disease in some stated time period or by a specific point – that is needed.

Common diseases have both genetic and environmental risk factors. In order to evaluate the genetic component use is made of the family history and gene association studies to establish the relative risk. Combining relative risk data with other data (e.g. age specific disease incidence and mortality), relative risk can then be converted to an absolute one. Such work has been carried out in Cambridge in the context of breast/ovarian cancer family history and colorectal cancer. There are further plans to develop this in a major project funded by the Association of British Insurers (ABI) to be carried out in the Public Health Genetics Unit (PHGU) to look at family history and a range of common complex diseases.

However, moving from a general picture to the more specific – to establish the risk of developing common complex disease associated with a specific mutation, for example, is often not practical. Screening for mutations is complex, and specific mutations may be rare in a given population, creating a necessity for large studies. Concentrating attention on those with a family history speeds up the process, but also introduces potential for error and/or bias. Studies are often reporting results based on small numbers and rare events, so estimates of risk will have wide confidence limits, making specific predictions difficult – especially when seeking to transfer inferences to other contexts.

Inevitably much epidemiological data is historical. As knowledge of preventative measures develops so the risk can be reduced by intervention. Thus, for example in families with a history of colon cancer a 3 yearly colonoscopy can reduce the risk to individuals by 74% by virtue of the fact that it creates the possibility of early intervention before the cancer develops.

Genetic epidemiology is seeking to develop evidence about the relationships between genes and disease by asking population specific questions about:

- The prevalence of gene variants
- The size of the disease risk associated with them
- The contribution to the risk of gene:gene and gene:environment interaction
- The impact of genetic testing and the validity and utility of the data derived from them.

So, for example, genetic tests are assessed for their analytic validity (how accurately does the test pick out a given DNA sequence variant) and for their clinical validity (how reliably does the result of a test predict future clinical outcomes). Again there is the prospect of bias creeping in. Initially the lifetime risk of breast cancer resulting from a mutation in the BRCA 1 gene was thought to be about 85% due to the population chosen for study being a highly selected one. In the more general population, further research has shown that the population risk is between 36-56%. Although less than was first thought, this is still a substantial figure.

To conclude, from a public health perspective there is still a long way to go before we have a reliable body of evidence about risk. In particular, genetic epidemiology is a relatively young science, leading one to advocate caution when seeking to apply findings derived from populations to specific individuals. On the other hand risks do not go away, and in some instances a “ball park figure” may be sufficient to indicate a need for action, and



greater accuracy may be an expensive luxury. This consideration may apply when transferring public health derived data to other contexts such as insurance; where decisions will be influenced by social, political and other factors in addition to strictly clinical ones.

### 1.3 An Insurer's Perspective

The underwriting process has three points of entry for "evidence":

- When setting the underlying pricing of a product
- When compiling the manuals
- When assessing an individual application for cover

External pressures – including legislation such as the Disability Discrimination Act and competition from other companies require insurers to make evidence based decisions, when pricing for morbidity or mortality. Some of this comes from existing insurance data, such as that generated by the Continuing Mortality Investigation Bureau (useful for Life Cover), whilst other types of policy such as Critical Illness may rely on other sources such as published epidemiological data. This raw data is then adjusted to allow for various factors important to the company – such as the degree of uncertainty in the data, and the nature of the insurance contract on offer (i.e. are terms/rates guaranteed or periodically revisable).

Too much complexity increases costs, so insurers are generally seeking evidence that will enable them to structure pricing in broad categories rather than differentiate precisely between small variations in predicted outcomes.

Product manuals for underwriters are compiled from medical research and epidemiological data re-expressed for insurance needs. Because the research from which this data is derived was not carried out with insurance in mind the extent to which it is applicable may be an issue. For example the population base may not be comparable with those in the group at which a particular type of policy is targeted, and the results will almost certainly be expressed with clinical rather than insurance uses in mind. The best data, unsurprisingly, is available for the most common diseases – which also happen to be the sorts of risk which most people want to insure against. For rarer events the data available will probably be less comprehensive and may have serious gaps. In all cases there is a risk of bias arising by neglecting the biases inherent in the research from which the inferences are drawn such as the selection of the original research subjects.

For any given risk factor the insurers' objective will be to try and define (broadly) the extra risk of a claim arising averaged out across a group of individuals who share the same risk factor. This is a group, not an individual estimate, and the final figure may be modified by the presence or absence of other specified factors affecting those deemed to be in the relevant group or sub-set of the population.

When an individual application for cover is received the decision as to whether to accept, impose an additional loading, or reject the application will draw on information from a variety of sources. The first of these is the responses made to questions on the application form. This may trigger a request for further information from the applicant's GP, or it may require a special medical examination to be arranged. In rare cases (usually when high value policies are being arranged) further information may be sought from hospital consultants or from test results. Under the terms of present moratorium genetic test results, where known to the applicant, are not requested (except for Huntington's Disease when life cover is in excess of £500,000 is being sought). The information from the sources is then brought together with the data in the insurer's manual in an attempt to define and quantify the extra risk the applicant represents, and then to convert that to an underwriting decision.



Clearly this is not an exact science, and there is potentially scope for adjustments to be made if people are able to provide additional information that will modify the general principle applied. There may also be inconsistencies in the data arising from different sources as recollections of events and dates may vary, creating a need to check in order to establish the facts as accurately as possible, and reflect these in the subsequent insurance decision.

#### **1.4 A Public and Consumers' Perspective**

The need to consider access to and the cost of insurance for aspects of health and welfare protection is becoming more important to people as the state gradually withdraws from or reduces the value of a range of welfare benefits. If consumers are to protect themselves against risks in a society which is becoming more individualistic then they will increasingly have to turn to insurance as the route by which this is achieved. Whilst the implications for individuals now may not be huge, given the continued existence of a range of social security benefits and the availability of the NHS funded from taxes, the implications of policy creep by Government means that the future impact of current decisions may be substantial. In the absence of clear policy statements to the contrary, many consumers do not trust that the state will be there for them in the future, and are fearful that developments in insurance practice may close off the option of taking out cover against eventualities such as poor health or premature death.

The suggestion that insurers should have access to genetic data is particularly worrying to those who fear that this will impact disproportionately on the vulnerable, effectively pricing them out of the market and undermining the notion of social solidarity that has been an essential feature of the welfare state over the last fifty years.

The perceived likelihood of this scenario is the subject of often-heated debate, much of which seems to be based on assumption rather than hard evidence. It is the absence of evidence that is resulting in a vacuum in public policy making, and an inability to anticipate the consequences of this in terms of consumer behaviour and a willingness or otherwise to participate in the market.

In order to address consumers' concerns and to provide the evidence that will allow this vacuum to be filled appropriately, research is needed to establish a clearer understanding of the predictive value of genetic data – especially with regard to their use in respect of common complex disorders.

Research into the impact of the use of genetic data on consumer behaviour in the real world will also help illuminate decision-making. It often seems to be assumed that consumers act in rational ways, but this is not a valid model. Indeed experience would lead one to doubt the ability of many individuals to understand and process information in ways that lead to rational outcomes.

Thirdly, there needs to be an assessment of the likelihood of significant adverse selection against insurers and of its potential impact for companies and for other consumers of a one sided access to genetic information.

The application of a precautionary principle would impose a duty of care on those who would propose changes (i.e. allowing those who seek the disclosure of genetic test results



to demonstrate that they will be of benefit to society, not just used as a tool to protect insurers profit margins).

## 1.5 Discussion

A central question that has to be addressed when considering evidence in relation to insurance is the issue of where is it legitimate to draw the line between that which could or should be shared, and that which is either not relevant or private. It is possible to argue (and many insurers do) that more information has become available to them, so they have become more socially inclusive, developing products targeted at particular sectors of the population. As a converse, there is the fear that if access to information is denied, so insurers may become more cautious, either putting up prices to compensate for uncertainty, or withdrawing from sectors of the market altogether.

Perceived threats to the ability of a solidarity driven social insurance model to meet consumers needs also need to be examined critically. It is clear that medical and demographic changes are putting social welfare and pension systems under pressure throughout Western Europe, but there may be other relevant contributory factors (such as poor gate keeping) which also contribute to the pressures such systems are currently experiencing.

The assumed massive predictive power that it is claimed genetic data will have in the future also needs to be assessed and evaluated thoroughly if public policy about the role it will have to play in insurance is to be rational and fair. In the meantime thought should be given as to the value and the validity of the evidence available now as a guide to the future and as a factor in present day consumer and industry behaviour. There is a spectrum in the feasibility of making reliable predictions as to the effect of any given genetic make-up on life expectancy. Today, most genetic data operates at the extremes – especially at the “adverse” end of the continuum where highly penetrant genes of large effect (such as the one for Huntington’s Disease) has given rise to the fear that a large genetic underclass of uninsurable’s will be created. Even if this were to be a biologically feasible scenario, it might well be open to modification in practice by the operation of social and political considerations and the application of consumer pressure.

Our understanding of risk is generally poor. The use we make of our perceptions of what are the potential consequences of a given risk and what we might do to avoid or ameliorate these is equally poorly understood.

As medical research advances, and as new evidence about the possible preventability of certain diseases (or at least some of their adverse symptoms and consequences emerge) so insurers will need to develop new ways of factoring these into their calculations. The development of agreed templates as a vehicle for establishing the general prognosis for a given condition prevailing at the time of an individuals application for cover, and of the possible options open to reduce the risk might be a way of creating an agreed corpus of understanding as to how some genetic conditions are likely to affect health and life expectancy and how, as a result, the relationship between an individual and the general population may play out.

For example, in people with a genetic predisposition to colon cancer, the disease is about 80% preventable if regular monitoring and early intervention is available. A template might be a way in which the general risk/ expected survival at the time of application was juxtaposed with evidence of the applicant’s compliance with the surveillance regime



deemed to be appropriate, and the potential size of the risk reduction that this represents. Such a development would potentially enable insurers to offer cover to some people they currently decline, and lead to greater levels of public trust in insurers. It would also result in better compliance with legislation such as the Disability Discrimination Act as an increasingly medically sophisticated public becomes more prepared to challenge insurers' decisions. Patient groups and their advisers may have a useful role to play in helping to develop formulations about prognosis that are as clear and unambiguous as possible, especially in the case of rare diseases where their expertise is likely to represent a significant proportion of the available understanding of the disease in question.

The use of standardised templates would also reduce the risk of a rush to judgement as they would represent the considered judgement of a range of relevant experts, not all of whom would otherwise be available to all insurers.

The medical information available to insurers currently arises from a limited range of sources. For example evidence of cause of death is often not available to companies so they may not know if a claim arises as a result of a condition which they may have noted, or for some other reason entirely. During the moratorium on genetic test results an aspect of evidence is closed off, and whilst it may be possible to infer from evidence about genetic testing in the general population, the similarity between the general population and the insurance buying population is not known; making it difficult, for example, to quantify the fears that have been expressed about adverse selection. Whilst there is clearly the potential for fraud, the risk is uncertain - as is the effectiveness of other measures such as the use of family history as a "gatekeeper".

The effect of evidence emerging about links between genetics and insurance on consumer behaviour is also unknown. If reliable genetic predictors were to be developed, would that, for example result in people deferring the purchase of cover until nearer the time they were likely to need it? Such a shift would eventually become apparent in terms of the impact on the profitability of certain types of policy, but without evidence, assumptions about the cause of any observed shift in consumer behaviour would have to remain unproven.

Life and critical illness policies are bulk products. In most scenarios there are a small number of "pots" into which applicants can be put, and whilst it is clearly possible to develop increasingly sophisticated ways of segmenting the population, there is a cost/ benefit trade off to be had from keeping things relatively simple and straightforward. Unfortunately the consequence of this is that underwriting does not operate beyond a certain distance from the mean. Most companies will use a range of categories such as "standard", "mild", "moderate", "severe" and "uninsurable" when calculating risk and consequent loading to premiums. In this way they reach the majority of their target population. Those excluded have to fall back on either the state or their own resources.

With the predicted explosion in the use of genetic data in medicine, there will be an inevitable increase in the number of people in possession of potentially pertinent (to an insurer) genetic data about themselves. Whilst this may prove to have little or no significance, many in the industry are worried that the incremental effect of large numbers of people changing their insurance buying behaviour slightly may have the same effect as a small number making major decisions. This, coupled with increasing social and political pressure not to discriminate in other areas (disability, gender etc) makes the future uncertain. The converse also holds good, with members of the public being fearful of any change in the behaviour of insurers reducing their opportunities to purchase affordable cover.



## 1.6 Conclusion

Even in the most researched areas of medicine, the evidence available to underpin decision-making is almost always incomplete. The complexity of common diseases, and the variety of factors, both genetic and environmental, that interact to cause and control these means that in practice the evidence base that informs the ability to forecast the probability of particular genetic factors leading to a life-threatening illness is often very partial. Applying this to contexts outside the clinical one is often difficult but in these other contexts the coarseness of the filter through which evidence is sieved prior to decisions being taken can mean that a reasonable estimate of a link between cause and effect is all that is needed.

“Risk” is a poorly understood concept. The word itself can be used in a variety of ways – to a clinician it might refer to the likelihood of a cancer re-occurring in a 5 year period, whilst to an insurer it might refer to the potential for a valid claim. The consumer may see it as something completely different to either of these! This highlights the importance of continued communication between the various stakeholder groups if decisions and policies are to be made that reflect both the interests of patients and consumers whilst providing legitimate protection for insurers against real risks of fraud.

The current moratorium on the use of genetic test results is almost half way through. If a decision is to be taken as to whether it should continue or end, and if so what should replace it then the nature of evidence on which such a decision should rest must be specified in order that this can be collected systematically and with due regard for issues such as rigour and independent scrutiny. Whatever decisions are taken in the short term about genetics and insurance, and whether or not the moratorium ends in 2006 or is continued for a further period, without attention to evidence, and its systematic collection and rigorous interpretation, then the debate will be dominated by supposition and hypothesis, generating heat rather than shedding light. This is not a sound basis for rational policy making.

### **Disclaimer:**

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