Genetics and Insurance

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Genetics – Some Basic Facts

Genetics is today a vast subject, but it is necessary to know only a small part of it to appreciate its impact on insurance. In this short summary, we ignore all complications; see [32, 35], for a full account, or [8, 9], for introductions aimed at insurance.

Most cells in the human body have a *nucleus* that contains 23 pairs of *chromosomes*. One pair (the X and Y chromosomes) determines sex; women have two X chromosomes, men have an X and a Y chromosome. The other 22 pairs are homologous. Because every cell is descended from the fertilized egg by a process of binary cell division in which the chromosomes are duplicated, the chromosomes in every cell ought to be identical. *Mutations* arise when the duplicating process makes errors, or when chromosomes are damaged, hence genetic disorders may arise.

Chromosomes are simply very long sequences of DNA, arranged in the famous double helix. A *gene* is a region of DNA at a particular *locus* on a chromosome, whose DNA sequence encodes a *protein* or other molecule. Genes can be regulated to produce more or less of their gene product as required by the body. A mutated gene has an altered DNA sequence so it produces a slightly different protein or other product. If this causes disease, it is usually eliminated from the gene pool by selective pressure, hence genetic disorders are relatively rare. However, many mutations are harmless, so different varieties of the same gene called *alleles* may be common, leading to different physical characteristics (such as blue and brown eyes) called the *phenotype*, but not necessarily to disease.

Sperm and eggs each contain just 23 chromosomes, one of each type. When they fuse at conception, the fertilized egg has a full complement of chromosomes, hence two copies of each gene (other than those on the X and Y chromosomes). Sometimes different alleles of a single gene cause an unambiguous variation in the fully developed person. The simplest example is a gene with two alleles, and this is the basis of *Mendel's laws* of inheritance, first published in 1865. For example, if we denote the alleles A and a, then the possible *genotypes* are AA, Aa, and aa. The distribution of genotypes of any person's parents depends on the distribution of the A and a alleles in the population. Assuming that each parent passes on either of their alleles to any child with probability 1/2, simple **combinatorics** gives the probability distribution of the genotypes of the children of given parents. The distribution of the childrens' phenotypes depends on whether one of the alleles is dominant or recessive. A dominant allele overrules a recessive allele, so if A is dominant and a is recessive, genotypes AA and Aa will display the A phenotype, but only aa genotypes will display the a phenotype. Simple combinatorics again will give the distribution of phenotypes; these are Mendel's laws.

Simple one-to-one relationships between genotype and phenotype are exceptional. The *penetrance* of a given genotype is the probability that the associated phenotype will appear. The phenotype may be present at birth (eye color for example) or it may only appear later (development of an inherited cancer for example). In the latter case, penetrance is a function of age. In the case of disease-causing mutations, the burden of disease results from the frequency of the mutations in the population, their penetrances, and the possibilities, or otherwise, of treatment.

Developments in Human Genetics

Human genetics has for a long time played a part in insurance underwriting, though it has only recently attracted much attention. Some diseases run strongly in families, with a pattern of inheritance that conforms to Mendel's laws; these are the *single-gene* disorders, in which a defect in just one of the 30 000 or so human genes will cause disease. A few of these genes cause severe disease and premature death, but with onset deferred until middle age, typically after having had children; this is why these mutations are able to persist in the population. Examples are Huntington's disease (HD), early-onset Alzheimer's disease (EOAD), adult polycystic kidney disease (APKD), and familial breast cancer (BC). When a family history of such a disorder is disclosed on an insurance proposal form, the decision has often been to charge a very high extra premium or to decline the proposal.

Quite different from the single-gene disorders are the *multifactorial* disorders, in which several genes, influenced by the environment, confer a predisposition to a disease. The majority of the genetic influences on common diseases like cancer or coronary

heart disease (CHD) are of this type. Underwriters have often used the proposer's parents' ages at death and causes of death as risk factors, for example, for CHD, but without ever knowing how much of the risk within a family might be genetic and how much the result of shared environment. Not all familial risk is genetic by any means.

Beginning in the early 1990s, geneticists began to locate and to sequence the genes responsible for major single-gene disorders. This work has tended to show that their apparent simplicity, when all that could be observed was their Mendelian mode of inheritance, is not usually reflected in the underlying genetic mutations. Thus, HD was found to be caused by an expanding segment of DNA of variable length; two major genes were found to be responsible for most familial BC, and each of those to have many hundreds of different disease-causing mutations; APKD was found to have two forms and so on. Single genes have also been found to be associated with several diseases; thus, the discovery that an allele of the APOE gene was associated with heart disease gave rise to suggestions of genetic screening, which were stopped dead when it was also discovered to be associated with Alzheimer's disease (AD), which is currently untreatable.

The sequencing of major disease-causing genes meant that DNA-based genetic tests would become available, which would be able to distinguish with high reliability between people who did and did not carry deleterious mutations, and among those who did, possibly even the prognosis given a particular mutation. In the absence of such tests, all that could be known is the probability that a person had inherited a mutation, given their family history. For example, HD is dominantly inherited, meaning that only one of the two copies of the huntingtin gene (one from each parent) need be mutated for HD to result. But HD is very rare, so the probability that anyone's parents have more than one mutated huntingtin gene between them is negligible, even in a family affected by HD. Mendel's laws then lead to the conclusion that any child of a parent who carries a mutation will inherit it with probability 1/2, and without a genetic test, the only way to tell is to await the onset of symptoms. Other forms of family history, for example, an affected grandparent but unaffected parent, lead to more elaborate probabilities [31]. As an at-risk person ages and remains free of symptoms, the probability that they do carry a mutation is reduced by their very survival free of symptoms. For example, let $p(x)$ be the probability that a carrier of a HD mutation is free of symptoms at age x. Then the probability that a child of an affected parent who is healthy at age x is a carrier is $1/(1 + p(x))$. This may be reflected in underwriting guidelines, for example, in respect of HD [5] recommended declinature below age 21, then, extra premiums decreasing with age until standard rates at ages 56 and over. A DNA-based genetic test resolves this uncertainty, which could result in the offer of standard rates to a confirmed noncarrier, but probably outright declinature of a confirmed carrier. Thus, the insurance implications of genetic tests were clear from an early stage.

Research into multifactorial disorders lags far behind that of single-gene disorders. The helpful factors of Mendelian inheritance and severely elevated risk are generally absent, so multifactorial genotypes are hard to find and the resulting risks are hard to measure. Very large-scale studies will be needed to make progress, for example, in the United Kingdom the Biobank project aims to recruit a prospective sample of 500 000 people aged 45–69, to obtain DNA samples from all of them and to follow them up for many years. Even such a huge sample may not allow the detection of genetic associations with relative risks lower than about 1.5 or 2 times normal [37].

The differences between the single-gene disorders and multifactorial disorders are many. As far as insurance is concerned, the subset of single-gene disorders that matters includes those that are rare, Mendelian, highly penetrant, severe and often untreatable, or treatable only by surgery. Multifactorial disorders are common, non-Mendelian, are likely mostly to have modest penetrance and to confer modest extra risks, and may be amenable to medication or change in lifestyle. It is not entirely clear why the great concerns over genetics and insurance, which have been driven by single-gene disorders, should carry over to multifactorial disorders with equal strength.

Responses to Genetics and Insurance Issues

Public concerns center on privacy and the inappropriate use of genetic information, often naming insurers and employers as those most eager to make mischief.

Potential difficulties with privacy go beyond the usual need to treat personal medical information confidentially, because information may be requested

about a proposer's relatives without their being aware of it, and any genetic information gained about the proposer may also be informative about their relatives. However, the actuarial dimension of this question is limited and we will not discuss privacy further.

Inappropriate use of genetic information means, to many people, using it in the underwriting of insurance contracts. The principles involved are no different from those surrounding the use of sex or disability in underwriting (except perhaps that the privacy of persons other than the proposer may be invaded), but genetics seems to stimulate unusually strong fears and emotions. Many governments have responded by imposing, or agreeing with their insurance industries, moratoria on the use of genetic information, usually up to some agreed limit beyond which existing genetic test results may be used. There is general agreement that insurers need not and should not ever ask someone to be tested, so only existing test results are in question.

The United Kingdom and Australia are of particular interest, because their governments have tried to obtain evidence to form the basis of their responses to genetics and insurance. In the United Kingdom, the Human Genetics Commission (HGC) advises the government [19, 20], and was instrumental in deciding the form of the moratorium (since 2001, genetic test results may not be used to underwrite **life insurance** policies of up to £500 000, or other forms of insurance up to £300 000). The industry body, the Association of British Insurers (ABI) introduced a code of practice [1] and appointed a genetics adviser, who drew up a list of eight (later seven) late-onset, dominantly inherited disorders of potential importance to insurers. The Genetics and Insurance Committee (GAIC), under the Department of Health, has the task of assessing the reliability and actuarial relevance of particular genetic tests, for use with policies that exceed the ceilings in the moratorium. In 2000, GAIC approved the use of the test for HD in underwriting life insurance, but following reports that were very critical of the industry [18, 19], the policy has been reformed and the basis of that decision may be reconsidered. In Australia, the Australian Law Reform Commission (ALRC) has produced the most thorough examination of the subject to date [2–4]. It recommends that a Human Genetics Commission in Australia (HGCA) should be set up, and this would approach the regulation of the use of genetic information in a manner quite similar to the GAIC process. It remains to be seen if these interesting and evidence-based approaches to the subject will be followed by other countries; see [7, 25] for more details.

In the course of the whole genetics debate, the question of what exactly is genetic information [40] has been raised. The narrowest definition would include only information obtained by the direct examination of DNA [1], while the broadest would include any information relating to any condition that might be in any way genetic in origin. Differing views have been reflected in the moratoria in different countries, for example, that in Sweden covers family history as well as genetic tests, while that in the United Kingdom does not (though the HGC indicated that it would revisit this in 2004).

Actuarial Modeling

Most actuarial modeling has concentrated on single-gene disorders, because it necessarily relies on genetic epidemiology to parameterize any models, and that is where the epidemiology is most advanced. We can identify two broad approaches.

- A top-down approach treats whole classes of genetic disorder as if they were homogeneous. This avoids the need to model individual disorders in detail, which in the case of multifactorial disorders may be impossible just now anyway. If, under extremely adverse assumptions, either extra premiums or the costs of **adverse selection** are small, this is a useful general conclusion; see [22–24] for examples. In the long run, this approach is limited.
- A bottom-up approach involves detailed modeling of individual disorders, and estimating the overall premium increases or costs of adverse selection by aggregation. Examples include models of BC and ovarian cancer [21, 28, 29, 36, 39], HD [14, 15, 34], EOAD [11–13], APKD [16] and AD [26, 27, 33, 38].

Multiple-state models are well suited to modeling single-gene disorders because these naturally divide the population into a reasonably small number of subpopulations.

Figure 1 shows a model that includes all the features needed to represent genetics and insurance

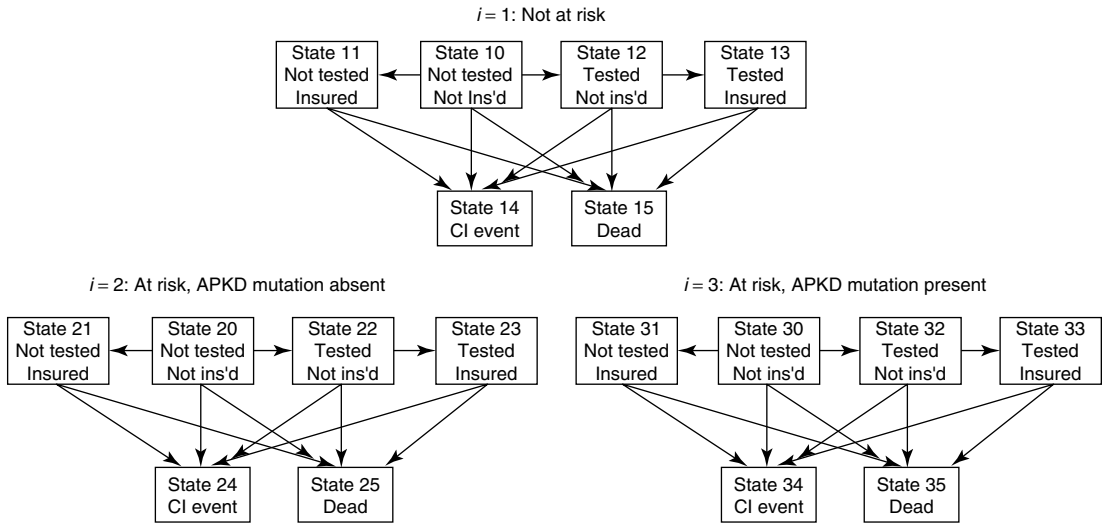

Figure 1 A Markov model of critical illness insurance allowing for family history of APKD and genetic testing. Source: Gutiérrez & Macdonald [16]

problems, using **critical illness** (CI) insurance and APKD as an example. APKD is rare (about 1 per 1000 persons), dominantly inherited and has no cause except mutations in the APKD1 or APKD2 (or possibly other) genes. Therefore, at birth, 0.1% of persons have an APKD mutation, 0.1% are born into families affected by APKD but do not carry a mutation, and 99.8% are born into families unaffected by APKD and are not at risk. This determines the initial distribution of the population in the starting states 10, 20, and 30. In these states, a person has not yet bought insurance, nor have they had a genetic test. They may then buy insurance without being tested (move to the left) or be tested and then possibly buy insurance (move to the right). Clearly, their decision to buy insurance may be influenced by the result of a test, and adverse selection may arise. At any time, a person can suffer a 'CI event' – an illness that triggers a claim, which would include kidney failure caused by APKD – or can die. All the transition intensities in this model may be functions of age, so it is Markov (*see* **Markov Chains and Markov Processes**), and computationally straightforward. Life insurance can be modeled similarly but often survival after onset of a genetic illness is age- and duration-dependent, and a semi-Markov model results.

As well as adverse selection, this model captures the market size (through the rate of insurance purchase), the prevalence of genetic testing, and the frequency of mutations, all of which influence the cost of adverse selection. It is also possible to group states into underwriting classes, within each of which the same premiums are charged, and thereby to represent underwriting based on family history, or under any form of moratorium. And, just by inspecting the expected present values (EPVs) of unit benefits and unit **annuities** conditional on presence in an insured state, the extra premiums that might be charged if insurers could use genetic information can be found (a simpler multiple decrement model would also suffice for this).

Parameterizing such a model is challenging. Intensities relating to morbidity and mortality can be estimated in the usual way, relying on the medical literature for rates of onset of the genetic disorder. Intensities relating to insurance purchase can plausibly be based on market statistics or overall market size. The rate of genetic testing is very difficult to estimate. Testing is still fairly recent, so there is no long-term experience. The take-up of testing varies a lot with the severity of the disorder and the availability of treatment, so that even after nearly 10 years of HD tests, only 10 to 20% of at-risk persons have been tested [30].

Once the intensities in the model have all been fixed or estimated, we proceed by solving Kolmogorov's forward equations (*see* **Markov Chains and Markov Processes**) for occupancy probabilities,

or Thiele's equations (*see* **Life Insurance Mathematics**) for EPVs of insurance cash flows [17]. With μ_x^{jk}, the transition intensity between distinct states j and k, and ${}_tp_x^{jk}$, the probability that a person in state j at age x will be in state k at age $x+t$ (the occupancy probability), Kolmogorov's equations are:

$$\frac{\partial}{\partial t}{}_tp_x^{jk} = \sum_{l\neq k} {}_tp_x^{jl}\mu_{x+t}^{lk} - \sum_{l\neq k} {}_tp_x^{jk}\mu_{x+t}^{kl}. \quad (1)$$

(Note that we omit the i denoting genotype g_i for brevity here.) We can add insurance cash flows to the model, with the convention that positive cash flows are received by the insurer. If a continuous payment is made at rate b_x^j per annum while in state j at age x, or a lump sum of b_x^{jk} is made on transition from state j to state k at age x, Thiele's equations for the statewise prospective reserves ${}_tV_x^j$, at force of interest δ, at age $x+t$ are

$$\frac{\partial}{\partial t}{}_tV_x^j = \delta\ {}_tV_x^j + b_{x+t}^j - \sum_{k\neq j}\mu_{x+t}^{jk}\left(b_{x+t}^{jk} + {}_tV_x^k - {}_tV_x^j\right). \quad (2)$$

These must be solved numerically.

The conclusions from such models, applied to single-gene disorders, are consistent. We give an example, for HD and life insurance, based on [14, 15]. The age at onset of HD is inversely related to the number of times the trinucleotide CAG (cytosine-adenine-guanine) is repeated in a certain region of the huntingtin gene on chromosome 4. Brinkman et al. [6] estimated the age-related penetrance for 40 to 50 CAG repeats, by Kaplan–Meier methods (*see* **Survival Analysis**); these are shown in Figures 2 and 3. Also shown, as smooth curves, are modeled penetrance functions from [15]. Brinkman's study [6] is, in fact, an unusually good and clear basis for the fitted model, since the actual numbers in the graphs were tabulated; many genetical studies merely give penetrances in the form of point estimates at a few ages or graphs of Kaplan–Meier estimates, but we must acknowledge that actuarial models are relatively demanding of the data. On the basis of this model, and a conventional analysis of survival after onset of HD [10], premium rates for life insurance of various ages and terms are shown in Table 1 (expressed as a percentage of the standard rate that would be paid by a healthy applicant). Note that these are specimens only, based on the mortality of the population of England and Wales as expressed in the English Life Table No. 15; an **insurance company** might take account of the lower mortality typical of insured persons, which would result in higher premiums than in Table 1. This table shows the following features:

- Premiums increase rapidly with the number of CAG repeats. Nevertheless, if there were fewer than about 45 repeats, terms could be offered within normal underwriting limits (in the UK, cover would usually be declined if the premium exceeded about 500% of the standard rate).
- The premiums vary greatly with age and term, suggesting the need for a model that takes account of the heterogeneity of HD mutations. Note that many other single-gene disorders could be as heterogeneous, but few have such a simple underlying cause of heterogeneity as the length of a trinucleotide repeat.

As mentioned above, the take-up of genetic testing for HD is quite low, so many applicants may present a family history of HD, and in some jurisdictions this can be used in underwriting. Table 2 shows premiums (as percentages of standard) in respect of applicants who have an affected parent or sibling. Note that these need the distribution of CAG repeat length at birth among HD mutation carriers, see [15], another complicating feature of any heterogeneous disorder.

- The premium rates based on family history decrease to negligible levels by age 50, consistent with [5], because most HD mutations are so highly penetrant that anyone who is free of symptoms at age 50 is unlikely to be a carrier.
- Comparing Table 2 with Table 1, we see that premiums based on a small number of CAG repeats can sometimes be lower than those based on family history, because the latter are in a loose sense averaged over all CAG repeat lengths. This raises the prospect of a person with (say) 40 or 41 CAG repeats requesting a premium based on that information, even though it derives from an adverse genetic test result that could not be used under most moratoria. Again, this may be a recurring feature of heterogeneous genetic disorders.

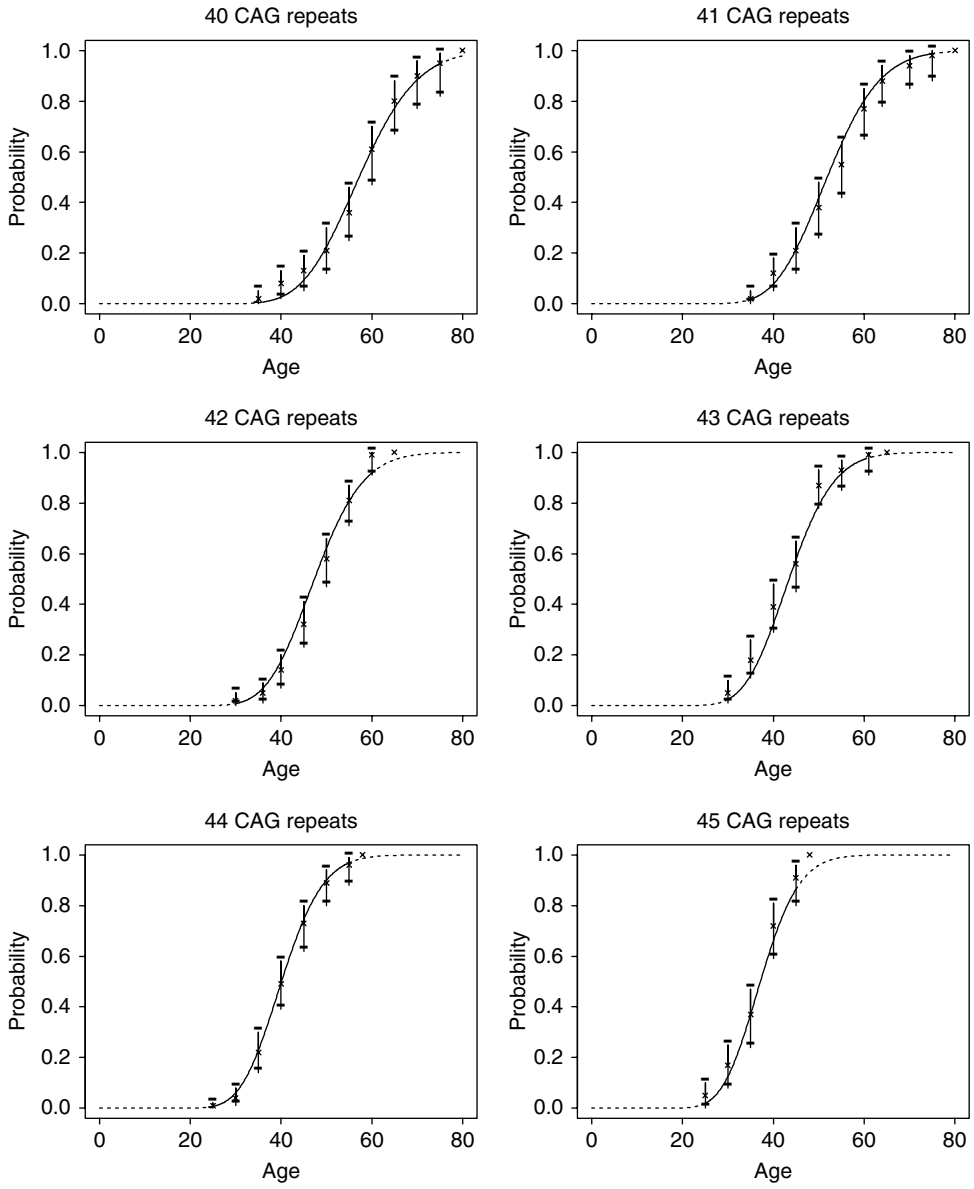

Figure 2 Penetrance estimates of onset of HD with 40 to 45 CAG repeats (crosses) and 95% confidence intervals, from Gutiérrez & Macdonald [15], based on data from Brinkman et al. [6]. Also shown are fitted penetrance curves

The cost of adverse selection under any given moratorium depends on the mutation frequencies, the size of the market for any particular type of insurance, the rate at which genetic testing takes place, how people will react to learning that they carry a more or less serious mutation, and the precise form of the moratorium, as well as the mutation penetrance. The cost can conveniently be expressed as the percentage premium increase that would be needed to recover it. In the case of HD and probably every other single-gene disorder, the rarity of mutations is the most important factor in any but a very small market, and even quite extreme adverse selection would be unlikely to require premium increases of more than

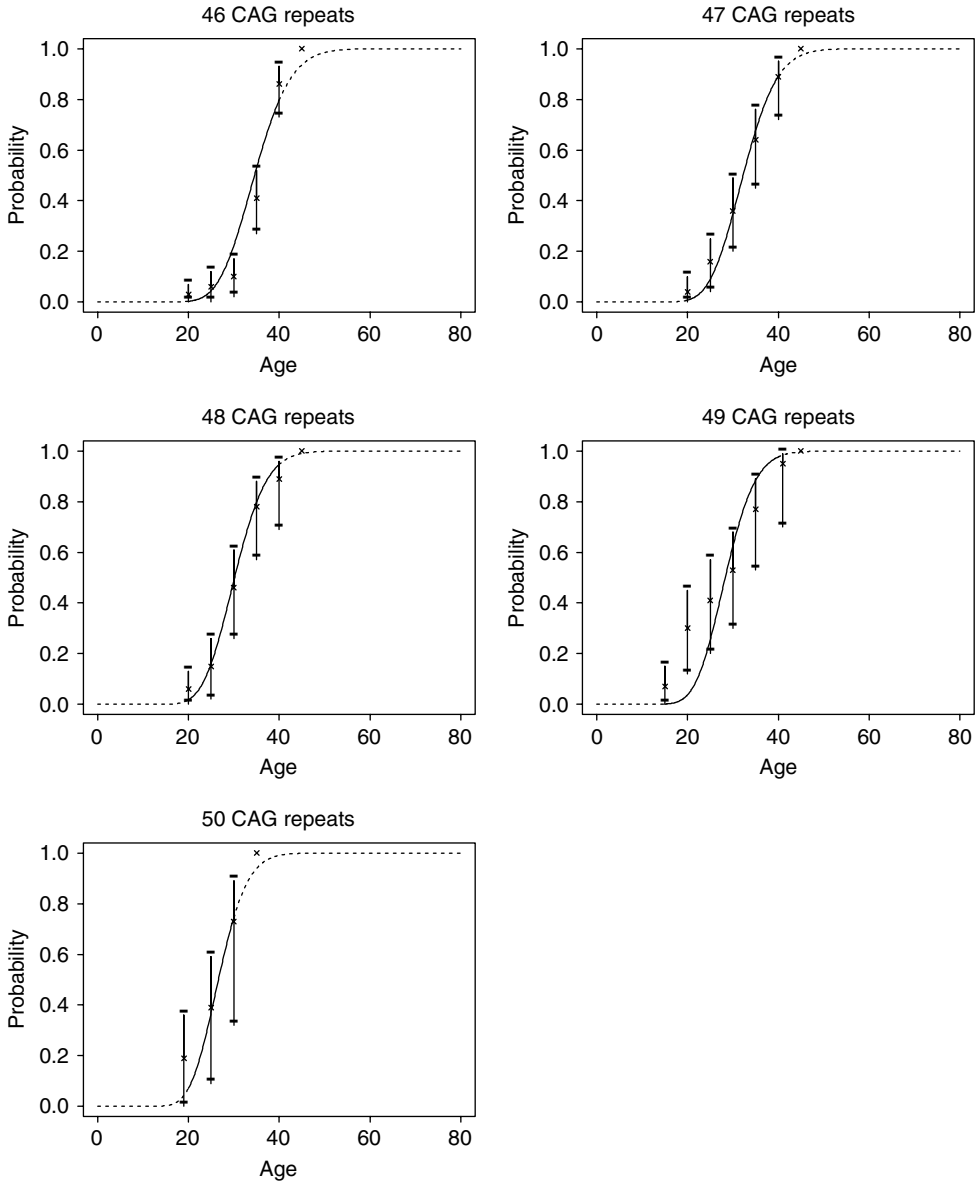

Figure 3 Penetrance estimates of onset of HD with 46 to 50 CAG repeats (crosses) and 95% confidence intervals, from Gutiérrez & Macdonald [15], based on data from Brinkman et al. [6]. Also shown are fitted penetrance curves

a fraction of 1%, if the use of family history was still allowed. Higher costs are possible if family history may not be used, and the cost for critical illness insurance could be considerably greater than for life insurance. References [13, 15, 16, 22–24, 36] suggest that, taking all genetic disorders together, premium increases of 10% would be a conservative upper limit for the cost of adverse selection in life insurance.

Outstanding Issues

Molecular genetics is racing ahead of epidemiology, and it may be some time before we have an accurate

Table 1 Level net premium for level life insurance cover for persons with a known HD mutation, with 40 to 50 CAG repeats, as a percentage of the premium for standard risks

			Premium as percentage of standard										
			Number of CAG repeats										
Sex of applicant	Age at entry (years)	Policy term (years)	40 %	41 %	42 %	43 %	44 %	45 %	46 %	47 %	48 %	49 %	50 %
Female	20	10	100	100	100	102	105	114	132	166	219	293	387
		20	101	105	117	147	209	315	475	690	951	1242	1545
		30	112	138	192	288	432	624	853	1107	1371	1631	1877
		40	141	192	272	381	513	664	825	990	1154	1310	1456
	30	10	101	106	117	139	175	225	285	349	414	477	535
		20	116	146	208	307	438	588	741	885	1014	1125	1220
		30	147	206	294	408	535	662	780	884	972	1044	1104
	40	10	106	114	126	141	158	174	190	205	219	231	242
		20	142	181	229	279	326	366	401	430	454	474	491
	50	10	108	114	120	126	132	137	142	147	151	155	158
Male	20	10	100	100	100	101	102	105	111	123	142	169	203
		20	101	102	108	121	148	196	269	367	487	621	760
		30	106	118	146	195	270	369	490	624	764	902	1032
		40	119	144	186	244	316	399	488	581	672	760	842
	30	10	101	103	108	120	139	165	196	230	264	298	329
		20	109	126	161	219	295	384	475	561	638	705	762
		30	124	155	205	270	344	419	490	552	604	648	684
	40	10	103	107	113	121	130	138	147	155	163	170	176
		20	120	140	165	192	218	241	261	278	292	304	314
	50	10	102	104	106	108	109	111	113	114	116	117	119

Table 2 Level net premiums for level life insurance cover as percentage of the level premium for standard risks, for persons with a family history of HD (affected parent or sibling)

Age at entry (years)	Policy term (years)	Females (%)	Males (%)
20	10	114	105
	20	211	150
	30	297	202
	40	293	203
30	10	122	112
	20	187	151
	30	208	160
40	10	107	103
	20	130	115
50	10	102	101

picture of the financial impact of all the genetic knowledge that is emerging from the laboratory. Bodies like GAIC have a difficult task to perform, as politicians and others demand answers before the evidence base is properly in place. Almost by default, genetics seems to be leading the way towards 'evidence-based underwriting'.

- At what point in the spectrum of genetic disorders, from highly penetrant single-gene disorders to complex multifactorial disorders, should normal underwriting be allowed? Is genetic information so exceptional that nothing with the slightest genetical content should be accessible to insurers?
- There is often evidence that a rare mutation may be highly penetrant, but its rarity prevents the reliable estimation of relative risks. Amyloid precursor protein (APP) mutations associated with EOAD is an example (from the ABI's list). How should this be handled within the framework of evidence-based underwriting?
- Heterogeneity leads to two problems. The first is the obvious statistical one, that sample sizes quickly become too small to be useful. Occasionally, as with HD, there is structure underlying the heterogeneity that offers a basis for a model, but that may be unusual. The second problem is that if family history may be used in underwriting,

premiums on that basis can exceed premiums based on the less severe mutations, creating pressure for the use of adverse test results when that would be to the applicant's advantage.

- The impact of multifactorial disorders on insurance is as yet largely unexplored, but we can expect that many of the discoveries that will be made in the future will concern them.

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(*See also* **Markov Chains and Markov Processes**; **Survival Analysis**)

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