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Report by Independent Actuary on the Application by the Association of British Insurers to the Genetics and Insurance Committee for Approval to use Genetic Test results for Insurance Risk Assessment – Use of Huntington's Disease Test in Life Insurance

1 *Introduction*

1.1 I have been asked by the Genetics and Insurance Committee (GAIC) of the Department of Health to give an independent actuarial report on the actuarial aspects of the Application by the Association of British Insurers (ABI) for approval to use genetic tests for Huntington's Disease (HD) in life insurance. I have been supplied with a copy of the application by the ABI, and also copies of all the references listed therein.

1.2 The main actuarial evidence is presented in the Section 8 of the Application, but additional actuarial or demographic evidence is presented in other Sections of the Application. I comment on these as well.

2 *Overall comments*

2.1 I understand that the GAIC needs to be satisfied only that the extra mortality risk for an applicant for life insurance who has had a genetic test and has been found to be "positive" for HD is more than +50%. There is no doubt that this is the case for many applicants. There is therefore a *prima facie* case for allowing the use of genetic tests for life insurance underwriting.

2.2 It is also the case that, when an applicant has had a genetic test and has been found to be "negative", that applicant can be assessed on normal underwriting criteria, ignoring the possibility of the applicant's ever contracting HD. The use of genetic tests for life insurance underwriting can only be beneficial to this group.

2.3 However, the evidence presented by the ABI in support of their case is, in detail, very unsatisfactory, and, in my opinion, it would give a quite wrong message if the GAIC were to approve the detailed underwriting criteria that have been presented.

2.4 The only actuarial evidence presented by the ABI with their Application is a paper published by Swiss Re Life and Health, entitled *Huntington's Chorea*. It is attributed by the ABI to "Christopher Smith of Swiss Re", but his name does not appear on the document. This paper has not been independently peer reviewed; and has not been published in a peer-reviewed journal. According to the ABI it has been "validated by Bill Baker, Alan Hester and Paula Stapleton (also of Swiss Re)". Such validation by colleagues of the author is not independent peer review.

2.5 In my view, if the Swiss Re paper were to be presented to a reputable journal for publication, it would not be accepted without very substantial revision and considerable

reworking. I have not carried out a full refereeing job on this paper; however, I shall indicate below some of the problems with it, and with the data on which it has been based.

2.6 In spite of its faults, the Swiss Re paper is a very useful step in the right direction. It is one of the first attempts to put together an integrated model for a genetically inherited disease, and it is in principle on the right lines.

3 *The Swiss Re paper*

3.1 The paper by Smith of Swiss Re proposes a model for individuals known to be positive (I ignore those parts of the paper that deal with the situation where the individual has not had a genetic test). The model displayed in Figure 4 of the paper is a sensible one, but it has a major flaw. Individuals with the HD gene start at a given starting age in an asymptomatic state, and may move out of that state to a symptomatic state, or may die. The transition intensities for these moves depend only on age (within one model, which is for those of a certain sex and inheritance). For those who are symptomatic the only transition is to death, and the transition intensities depend only on duration in the symptomatic state. The flaw in Smith's implementation of the model is that the intensities of death for the symptomatic should depend on *both age and duration*. This adds no complexity to the implementation of the model, because as one tracks individuals of a given starting age, one knows their age at every point. But to not allow for this creates an inconsistency, as I describe in Section 5 of this Report.

3.2 In order to parameterise the model Smith needs three sets of transition intensities:

(a) normal mortality of the asymptomatic (by age)
(b) incidence rates for the onset of HD (by age)
(c) mortality rates for the symptomatic (by duration, and desirably also by age)

These transition intensities may be different for Males and Females, and different for those with affected Fathers and affected Mothers.

3.3 For (a), the normal mortality of the asymptomatic, Smith uses Dutch mortality tables, GBM85/90 and GBV85/90 for males and females. I do not have ready access to these tables, and I have used the latest UK tables for assured lives, AM92 and AF92 (ultimate) for males and females. One might hope that this makes little difference, but in fact the underlying mortality table seems to make a lot of difference to the extra premiums calculated, as I discuss in Section 6.

3.4 For (b), the incidence rates for the onset of HD, Smith assumes the hazard rates for a normal distribution (based on his investigation of work by Newcombe (1981) ["A life table for onset of Huntington's chorea", *Annals of Human Genetics*, **45**, 375-385. This paper is not in the list of references supplied by the ABI to GAIC, but fortunately I have access to a copy of it. The other papers referred to by Smith have also not been supplied.] with the parameters quoted by Roos *et al* (1991) for Roos's whole group. This makes two assumptions which I question. A normal distribution is unusual in mortality statistics, and it has some inconsistent features, like a range which is infinite in both directions. This point is rather technical and I have put my investigations about this into Appendix A. However, Smith's use of Roos's whole group, without question, seems to me to be flawed. I discuss this in Section 4.

3.5 For (c), mortality rates for the symptomatic, Smith again uses data derived from Roos *et al* (1993). For each subgroup, Roos quotes three points on the survival curve, for 80%, 50% and 20%. Smith assumes that again a normal distribution will fit, and assumes that the mortality rates depend only on duration of sickness, and not on age attained. This produces an inconsistency at high ages, because the mortality rate for an individual whose symptoms appear at a high age is immediately *lower* than the mortality rate for one of the same age according to the base mortality. For the base mortality tables that I have used this occurs in the 50s of age for both males and females. It means that the extra premiums for those with the HD gene who are still asymptomatic at high ages become *negative*. This seems to me to be obviously inconsistent. I discuss this further in Section 6.

3.6 A further technical criticism that I have of the Smith paper is that he uses a discrete model with one-year steps, rather than a continuous model. In my view it is preferable to define a continuous model, with transitions determined by differential equations. These are easy to write down and to understand. They then require numerical solution, but this can be done with any desired step size, to give solutions with as much numerical accuracy as desired. However, in this case the transition intensities do not vary rapidly, either by age and duration, and I do not think that different numerical methods make a very great difference to the results, though they do make a difference.

4 *Roos's incidence rates*

4.1 Roos et al (1991) investigated over 1,000 individuals affected with HD in the Netherlands. They recorded the age of onset (AO) for each person. They also categorised the individuals into four groups, by sex and by lineage:

Female with affected Mother (FAM)
Female with affected Father (FAF)
Male with affected Mother (MAM)
Male with affected Father (MAF)

Note the inconsistent meaning of F and M, initially Female and Male, terminally Father and Mother!

4.2 They then calculated the mean and standard deviation of the age of onset for each group, separately for all cases and then for those born before 1925. From these data it is possible to calculate the means and standard deviations of those born after 1925, too. I show the full data in Table 1. Roos's original values are shown with one decimal place, my calculations with two.

Table 1: Roos's Incidence Data: Age at Onset of HD

		number	**mean**	**s.d.**
Whole data	FAM	250	41.8	10.5
	FAF	255	39.2	11.9
	MAM	257	39.7	11.4
	MAF	258	37.2	14.0
	All	1,020	39.5	12.1
Pre-1925	FAM	168	44.8	10.2
	FAF	159	42.4	10.9
	MAM	163	42.5	11.0
	MAF	142	42.6	13.5
	All	632	43.1	11.4
Post-1925	FAM	82	35.65	8.22
	FAF	96	33.90	11.64
	MAM	94	34.84	10.46
	MAF	116	30.59	11.60
	All	388	33.51	10.85

4.3 Smith provides no statistical testing of this data. Roos investigates differences between the means, concluding that there are significant differences between the groups for the whole data, but not for the pre-1925 data. However, it is clear that there are significant differences between the means of the pre-1925 data and the post-1925 data.

4.4 Neither Smith nor Roos investigates the differences between the standard deviations. But it is clear that Males with an affected Father (MAF) have higher standard deviations (14.0 and 13.5) than the other groups in the whole data and in the pre-1925 data, but not in the post-1925 data. Pairwise F-tests of variance ratios show that these differences are very significant, whereas the other three groups, in the whole data and in the pre-1925 data, are not significantly different from one another.

4.5 However, in the post-1925 data Females with an affected Mother (FAM) have a lower standard deviation (8.22) than the other groups, and this difference is significant, whereas the standard deviations of other three groups are not significantly different.

4.6 Roos's methodology, of basing calculations on the observed age at onset of those whose HD has commenced, is flawed, because those younger positive individuals that have not yet shown symptoms are excluded; but when they develop symptoms, they will contribute higher ages at onset than their present age. It is analogous with calculating the ages at death of those in the general population born in say 1970 who have died before the year 2000; if they have died by 2000 they have necessarily died at an age of 30 or less, so the mean age at death must be a lot less than 30; but most of those born in 1970 have not yet died, and can be expected to live much longer than 30 years.

4.7 Rather than attempting to fit a single statistical distribution to the ages of onset (or death) it is much better to use the "life table method" and to estimate the hazard rates directly, as was done by Newcombe. Roos *et al* are aware of the problem, however, which is why they have separated out their pre-1925 data, on the assumption that all the onsets of HD that were going to happen to this population have in fact happened by the time of their investigation. This is, however, second best to using a better method in the first place.

4.8 For these reasons I would be suspicious of including Roos's post-1925 data at all, and I would prefer to have used only the pre-1925 data. Smith, however, has used the whole data, but without any explanation of why he has chosen this. The ABI (page 19 of their Application) states that he has used the pre-1925 data, but this is not what Smith says in his paper.

4.9 However, there is the problem of the high standard deviation in the pre-1925 data for Males with an affected Father (MAF). Other studies quoted by Roos have identified cases of juvenile HD, with onset as early as age 2. In Roos's data a comfortable majority of cases with AO<20 are among Males (38 out of 58 or 66%: note that the headings "M" and "F" under "A" in Roos's Table 3, page 518, must be reversed) and a majority of them had an affected Father (74%). Roos does not say how many of them were in his MAF group, but there must have been more than among the other groups. A number of outliers like this could produce the higher standard deviation that he records. The problem then with using the assumption of a normal distribution, as Smith does, is that it assumes a symmetry which may not be justified. In effect he assumes that for every juvenile HD case among MAFs there is a corresponding case with an extremely late age of onset. There is no evidence for this. Indeed in Roos's data for those with AO>50, only 47% were Males and 50% had an affected Father.

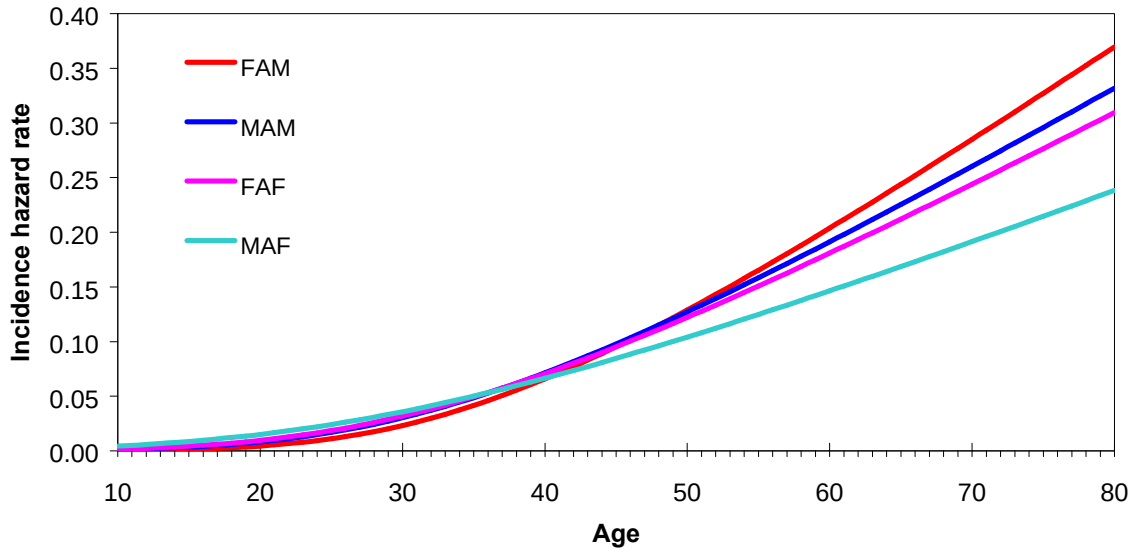
4.10 It seems to me much more plausible (and one would need access to Roos's detailed data to confirm this) that the high standard deviation is generated from only young AO outliers, and that the distribution is somewhat skewed, rather than being symmetrical. Roos remarks on page 561 that the AO distributions were symmetrical, but he may mean only broadly symmetrical; he is justifying the use of a particular statistical test. Of course the young outliers would also reduce the mean, and the mean of the pre-1925 MAFs is 42.6, not out of line with the other groups, so there must be *some* corresponding older AO cases; but extreme outliers affect the standard deviation more strongly than they affect the mean. In fact if one assumed, arbitrarily, that the 142 cases included 8 with an age of onset of 8 years, and omitted these 8 cases, the mean of the rest would alter from 42.6 to 44.67 and the standard deviation from 13.5 to 10.81. The mean would be similar to that of FAMs and the standard deviation would be intermediate among the other groups. 8 cases of such very juvenile HD may be too many, but the point should nevertheless have been considered

4.11 I would therefore have relied much more on the FAM, FAF and MAM data than on the MAF data, and I would have used the same incidence rates for all groups because there seems to be no significant difference between them. The parameters of the pre-1925 data for these groups, aggregated, are: number of cases 490; mean 43.26 years, standard deviation 10.74 years.

4.12 Roos *et al* were writing before the influence of the number of CAG repeats was known, since many of their cases had already died, it would not have been possible to test the number of CAG repeats. I discuss the work of Brinkman *et al* (1997) in Section 7.

4.13 That the incidence rates for the different groups (FAM, etc) are considerably different can be seen from Figure 1, which shows the rates for the four groups, from the whole data, using Smith's normal distribution assumption. [If this is printed in black and white, the lines at the right hand end of the graph are in the sequence indicated.] One can see that at higher ages, the rates for MAF are considerably lower than the rates for the other groups. This is a consequence of the higher standard deviation assumed.

Figure 1: Roos: whole data: inception hazard rates



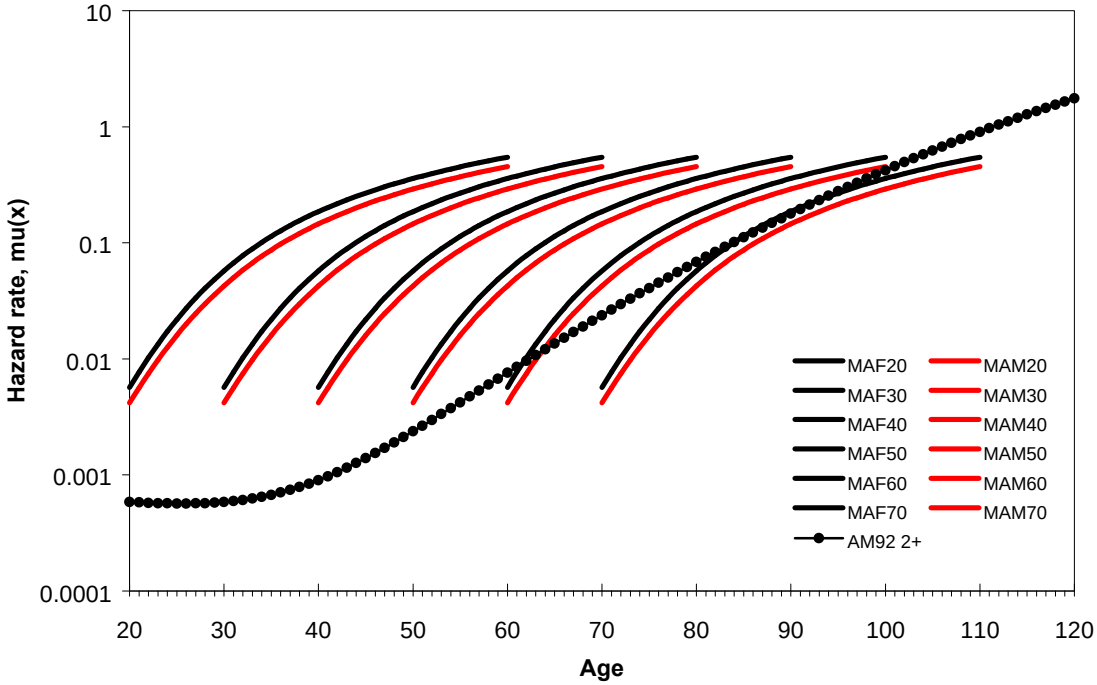
5 *Roos's survival rates*

5.1 In a second paper, Roos *et al* (1993) investigated the survival rates of their population after the onset of HD. This time they did use the life table method, and they quote the ages at which 80%, 50% and 20% had survived, subdivided, first, by age of onset (<20, 20-34, 35-49, □50), and then by sex and lineage (FAM, FAF, MAM, MAF). They concluded that survival was much the same, regardless of AO, but that sex and lineage were important, with MAF cases having shorter durations than the others.

5.2 Smith assumes that survival is independent of age of onset, and fits normal distributions that match as closely as possible the three points of the survival functions quoted by Roos. A minor problem of using normal distributions is the range of the duration of survival, which is necessarily positive. To use a mean of 15.06 and a standard deviation of 6.98 (as for MAFs) implies that 1.5% of cases had a negative duration of illness (!), not a wholly trivial proportion.

5.3 The problem here is that at high ages of onset, the mortality rates, which depend only on duration from AO, fall below the mortality rates of the general population. This can be seen from Figure 2, which shows data only for Males (Females would be similar). It is on a logarithmic vertical scale, which brings out the features better. The continuous line shows the mortality rates, □(*x*), for AM92 Durations 2+, which is the most recent standard table for male assured lives in the UK published by the Continuous Mortality Investigation Bureau. It is almost straight on a logarithmic scale, for higher ages, as is normal for all population or insurance mortality tables. The sequences of curved lines show the mortality rates for MAF and MAM for decennial ages of onset, from 20 to 70. MAF is the higher.

Figure 2. Roos/Smith: Males: mortality rates, and AM92 2+



5.4 At young ages, the mortality rates of those with HD are far higher than those of the "normal" lives. For inceptions at age 20, the rates start at duration 0 between 7 and 10 times normal; they rise by age 40 to over 200 times normal for MAF, 160 times for MAM. However, for inceptions at age 70, the MAM rates are below the normal ones at all ages, sometimes well below. This is unrealistic. Even for inceptions at age 60 the rates for HD are below normal for the first few ages.

5.5 It is clearly necessary to adjust the mortality rates of the affected so that they vary by age as well as by duration. One method would be simply to add the normal rates to the HD rates. This would make very little difference at young ages, and be more realistic at older ages. It is a pity that Roos *et al* did not analyse their data as compared with some Dutch population mortality; but since their data stretches over more than a century, it would perhaps have been difficult either to decide on one base or to use a varying, calendar-year-dependent base.

6 *Results*

6.1 I have calculated percentage extra premiums (PEPs) for term assurance, and show them in Tables 2M and 2F. These can be compared with the figures in Table A.2.1 of Smith's paper. I have used the same incidence rates as Smith, the same rates of mortality for those affected, and the same interest rate (3½%). I have used a British mortality table for the underlying mortality, instead of a Dutch one. I have done the calculations using the continuous model, with steps of 1/12 of a year, and I have calculated true monthly premiums (i.e. with the same frequency as the calculation steps; this is not an essential requirement; one can calculate premiums with any frequency less than the calculation step). Smith does not state whether his premiums are annually in advance; I assume that they are, but they might be single premiums.

6.2 I have also calculated premiums using annual steps and annual premiums. This makes a noticeable difference, the PEPs being 10% or so lower than with monthly calculations.

6.3 What is calculated is the value of 100 × (HD Premium / Normal Premium – 1), where HD Premium and Normal Premium are calculated allowing only for the risk of death, and with no allowance for expenses, commission, or safety margins. I assume that Smith has done the same.

6.4 My calculations are **not warranted to be correct**. They have been done fairly quickly, and have not been checked by an independent calculator. But I believe them to be correct.

6.5 Smith stops his Tables at term 30, entry age 50, and terminal age 70. I have gone further, showing values for terms up to 50, entry ages up to 70 and terminal age up to 80. The numbers in my tables are quite a bit different from Smith's, but they do show the same pattern, with the PEPs first rising with increasing age and term, and then falling. Smith generally does not show long enough terms to register the feature of the PEP falling with increased term for the same entry age, but I do. Note that this does *not* mean that the HD Premium falls. It rises with increasing age and increasing term throughout; but so does the Normal Premium, and at higher ages it rises faster then the HD Premium so the PEP falls.

6.6 Even from Smith's table one can see that different assumptions make a big difference to the PEPs. For entry age 20, term 10 (which I shall denote (20,10)), his values range from +11% for MAMs to +233% for MAFs. For entry age 20, term 30 (20,30), which show the highest values in his tables, his values range from +727% for MAMs to +1212% for FAFs. My corresponding values range for (20,10) from +105% for MAMs to +237% for MAFs, and for (20,30) from +863% for MAMs to +1323% for FAFs.

6.7 Smith (page 17) states that sensitivity testing showed that the mortality table used affects the premiums to some extent. My calculations show that it probably affects the PEPs to a considerable extent. British population mortality rates in the 20s of age are particularly low, as compared with many other countries, so I would expect the rates in AM92 and AF92 to be much less than those of the Dutch tables that Smith has used. Thus the Normal Premiums might be very much lower; so the PEP could be very much higher, as indeed I show (for MAM (20,10) +105% instead of +11%). It might be better to show the actual amount of the HD Premium, rather than the extra relative to a changing base.

6.8 By going up to high ages at entry I show the negative values of the PEPs that result from the assumption that the mortality of the affected does not vary by age.

6.9 In spite of all the sensitivity problems that I have described, it is clear:

- first, that an HD positive individual may carry a very high mortality risk, much higher than the +50% extra mortality laid down by GAIC;
- secondly, that for some entry ages and terms the extra premium would be less than the +400% or so that is commonly considered "uninsurable";
- thirdly, it would be the case, though I have not carried out explicit calculations, that the extra premiums for endowment assurances, for some entry ages and terms, would be quite low (as a proportion of the endowment assurance premium).

6.10 However, it also seems to me clear that the tables of proportionate extra premiums (and extra mortality; I have not checked these, but the pattern must be broadly the same as for

proportionate extra premiums) are so dependent on the assumptions made that Smith's tables should not be assumed to be correct, and I would recommend that GAIC does not make any decision that would give them credibility for commercial use.

Table 2M: Term assurance percentage extra premiums, Males

Male with affected Father

	Term								
	10	15	20	25	30	35	40	45	50
20	237	515	847	1118	1239	1195	1032	821	620
25	319	650	976	1158	1146	996	792	595	437
30	379	694	932	992	896	724	548	402	296
35	361	597	731	722	614	477	353	260	x
40	279	428	495	467	385	293	217	x	
45	181	268	301	278	225	170			
50	100	148	166	151	121				
55	42	68	78	71					
60	4	16	22						
65	–21	–16							
70	–37								

Male with affected Mother

	Term								
	10	15	20	25	30	35	40	45	50
20	105	260	481	709	863	895	814	670	515
25	186	409	667	853	902	823	675	516	381
30	255	496	709	802	759	635	490	362	266
35	267	462	596	617	545	433	324	239	
40	217	346	419	412	350	271	202		
45	142	219	257	246	205	157			
50	74	116	137	131	108				
55	23	45	58	56					
60	–11	–1	7						
65	–34	–30							
70	–49								

Table 2F: Term assurance percentage extra premiums, Females

Female with affected Father

	Term								
	10	15	20	25	30	35	40	45	50
20	217	494	843	1149	1323	1340	1230	1046	839
25	246	544	883	1134	1221	1157	1001	810	627
30	260	542	830	1004	1019	914	754	590	447
35	235	469	689	796	772	665	530	405	
40	185	362	517	578	541	450	350		
45	128	252	355	387	353	286			
50	76	157	223	240	213				
55	33	83	124	133					
60	–1	29	54						
65	–25	–10							
70	–42								

Female with affected Mother

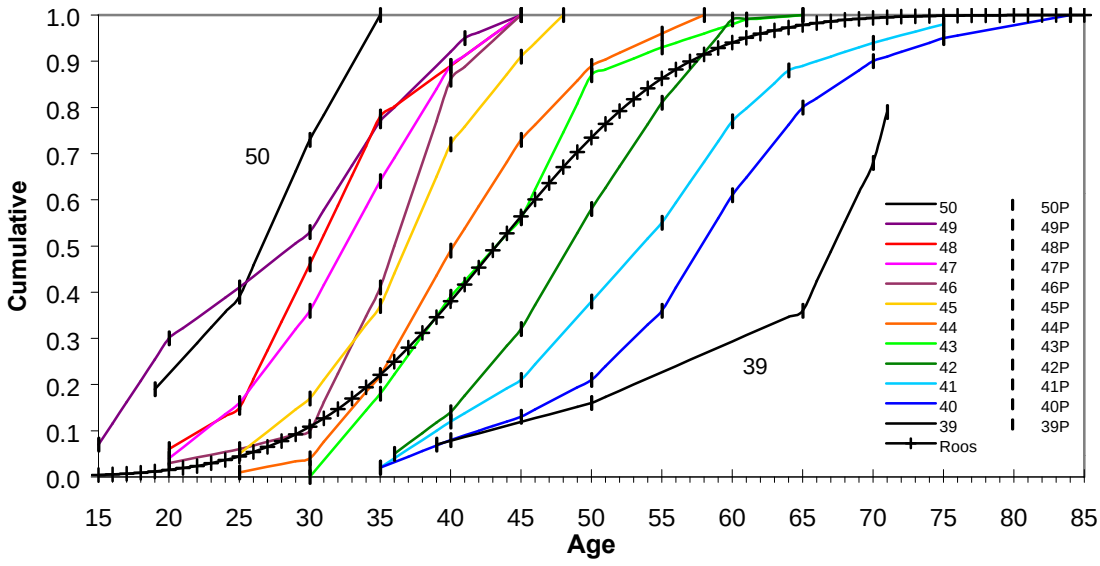
	Term								
	10	15	20	25	30	35	40	45	50
20	186	391	650	897	1067	1122	1065	928	757
25	243	496	774	988	1080	1044	920	754	588
30	301	563	810	956	969	876	728	572	435
35	304	535	724	806	773	664	531	407	
40	263	440	571	609	560	464	361		
45	197	322	406	419	374	301			
50	129	210	262	265	230				
55	70	120	151	151					
60	24	53	71						
65	–10	5							
70	–34								

7 *Brinkman's Paper*

7.1 Smith makes no reference to the paper by Brinkman *et al* (1997), though the ABI does refer to this. Brinkman calculates cumulative distributions for groups with CAG repeats from 39 to 50 inclusive. He also gives numerical values for selected ages. I have plotted these in Figure 3. The black diamonds show Brinkman's data; the intermediate lines (possibly in colour) show my linear interpolation between these points. The line for 39 CAG repeats is at the right of the diagram, and that for 50 CAG repeats is at the left. The cumulative lines for intermediate numbers of CAG repeats hardly overlap, showing that the age of onset is lower, the more CAG repeats there are. The lines do not start at zero, because Brinkman's data does not, and not all go up to unity for the same reason.

7.2 I also show one line (in an already too cluttered diagram) based on Roos's data. For this I have taken his pre-1925 data, using FAM, FAF and MAF only, as described in 4.10 above, with mean 43.26 years and standard deviation 10.74 years, and then using a normal distribution. This curve runs right across the others, and can be thought of as sort of amalgam of Brinkman's curves.

Figure 3: Brinkman: Cumulative distributions of age of onset for CAG repeats from 39 to 50



7.3 Brinkman does not analyse his data by sex or by lineage, as does Roos. He presumably knows at least the sex of his cases. However, his numbers are already getting rather small (the maximum number of cases with any one number of CAG repeats is 129 for 42 repeats), so he may have considered that this would subdivide his data too much. Nevertheless, full analytical life table analysis, allowing for several different factors, would have meant that all the information could have been used.

7.4 Brinkman does not show a cumulative distribution for those with CAG repeats greater than 50, though he has 65 cases, 60 with ages of onset between 4 and 35, and 5 aged between 16 and 23 still asymptomatic. A distribution comparable with the others could easily have been constructed. It would reach full penetrance by age 35, as does the curve for 50 CAG repeats.

7.5 Brinkman also does not show a cumulative distribution for those with CAG repeats under 39, though for CAG repeats 36-38 he has in total 32 cases, 7 with age of onset between 35 and 84, and 25 asymptomatic aged between 9 and 85. He could have grouped these together, even if the numbers for any one number of CAG repeats was small. He does use the data for 39 CAG repeats with only 8 cases with observed ages of onset.

7.6 Using Brinkman's data for incidence would give a much finer analysis than Smith's. If insurance companies are going to take the results of a genetic test into account, in my view they should be using the latest information at all times, to the best of their ability and knowledge. The finer analysis would reduce extra premiums for those individuals with a low number of CAG repeats, and increase them for those with a high number. Some individuals would move from the uninsurable category to insurable at an extra premium, while others would remain even more uninsurable. On balance this is a benefit to both the applicants for insurance and the insurance companies.

7.7 Brinkman does not provide an analysis of survival rates according to CAG repeat. Smith makes a good point when he uses Roos's survival data combined with Roos's incidence data, because onset may be defined differently in different studies. Mixing data from different studies would require care, but should not be rejected as impossible. However, none of the papers in the references available to me provide a full analysis of survival subdivided by number of CAG repeats, on the same lines as Brinkman has done for incidence. Both Brandt *et al* (1996) and Illarioshkin *et al* (1994) consider the progression of the disease according to the number of CAG repeats, but do not progress as far as death. Of course it takes time before those whose CAG repeats have been tested do die. One cannot work, as Roos could, on past demographic records, because one cannot (normally) perform a genetic test on those that are already dead.

7.8 Brinkman makes two odd statements. On page 1204 he states that "There were no individuals with a CAG repeat length >41 who remained asymptomatic at >56 years of age." "56" should probably be "65", as can be seen from Table 1. Then on pages 1204 and 1205 he states that "there were no instances of nonpenetrance with a CAG length >41 repeats". He must mean, "by a high age". He has many asymptomatic cases with high numbers of CAG repeats, but they are all still below the highest age at which onset has occurred for the particular number of CAG repeats, so his cumulative tables reach 1.

7.9 A final observation on Brinkman's paper: the "curves" shown in his Figure 1 should be step functions, with a step at each age of onset. Instead they are shown as series of straight

lines, or even as a series of convex curves. However, this is mitigated by the numerical values shown in his Table 3, which is what I have used.

8 *Section 8 of the ABI application*

8.1 I now make a few further observations on Section 8 of the ABI application. Most of the matter has already been covered in my remarks on Smith's paper.

8.2 On page 17 the ABI quotes the current underwriting recommendations of four large reinsurance companies. It does not identify the source of this information. Is it the companies themselves?

8.3 On page 19 the ABI states that Smith "follows Roos's advice and uses the data for people born before 1925". This is not in accordance with Smith's own statement, on page 18 of his paper, that he has used "onset distributions from Roos's whole group".

8.4 In the tables on pages 22 and 23 the ABI quotes percentage extra mortality, extracted from Smith's Table A.2.2, whereas I have looked at the percentage extra premium, as does Smith in Table A.2.1. The former is consistently a bit higher than the latter, but the shapes are the same, and arguments drawn from one can apply to the other.

8.5 On page 24 the ABI observes that "Smith's model does not differentiate the extra mortality suffered by people with different levels of CAG repeats. However, for showing that, on average, there is a significant impact on mortality for someone with a positive test, this additional piece of modelling is not necessary." This is of course correct, but one hardly even needed Smith's model to know that those who carried the HD had a very high risk for life assurance, and it is, in my view, not satisfactory for the insurance industry to rest on its laurels and say that Smith's work is all that needs to be done.

9 *Other parts of the ABI application*

9.1 While I have been specifically asked to review the actuarial evidence in Section 8 of the ABI application, I have also read through the rest of it. Just as the ABI does not seem to appreciate that Smith's paper is not a peer-reviewed one, and is therefore inadmissible as reliable evidence, so also do they make many statements that may or may not be correct, but for which they have provided no supporting evidence.

9.2 On page 4: "The prevalence of HD is around 6.5-8.5 per 100,00 of the indigenous UK population." No evidence is adduced for this. The studies in South Wales and in Northern Ireland show 7.61, and later 8.5, per 100,000 and 6.4 per 100,000 respectively. It is not clear whether these results can be transferred to the whole UK. The best that can be said is that, if the South Wales and Northern Ireland results could be applied across the whole of the UK, then there would be around 6.4 to 8.5 cases of HD per 100,000 population.

9.3 On page 5: "… we calculate that at least 5,000 people with a family history and at 50% risk who have not yet had pre-symptomatic tests are in the relevant age groups". No explanation is given as to how "we" have calculated this. It is not clear what the relevant age

groups are, nor what were the ages of the "almost 2000 people [who] had had pres-symptomatic testing for HD in the UK". My own calculations would go as follows:

> Assume 6.5 to 8.5 HD cases per 100,000 population. Assume a UK population of 55,000,000 (the exact figure could be ascertained). This would give 3,575 to 4,675 persons affected with HD in the UK. Is this reasonable? What confirmatory evidence could be found? How many members does the Huntington's Chorea Association or other patient associations have? Then the paper by Morrison *et al* (1995) suggests (page 529) that there might be about 2.5 times as many non-symptomatic heterozygotes in the population as there are already affected (at least that is what I think this paper means, but is seems rather obscure). This would give about 9,000 to 11,700 non-symptomatic carriers of the HD gene in the UK, or a total of 12,500 to 16,650 carriers of the gene. There would be at least as many non-carrier children of an affected parent; first, because the chance of inheriting the gene is 50%; then "at least", because their mortality would be normal, as compared with the much heavier mortality of those affected. One could use the methodology of Smith's model to estimate a multiplier, or use the following "back of the envelope" approach. Assume that those affected with HD die at an average age of 60, and those not affected die at an average age of 80. Then there will be 80/60 times as many of the latter as of the former. This would give 17,000 to 22,000 negatives in the UK, all of whom would have been "at risk" in the absence of a genetic test. Adding these to the unaffected heterozygotes gives 29,000 to 38,000 "at risk" in the UK. This seems a very large number, but HD is one of the commoner genetically inherited diseases. Many of these "at risk" are children, and many are older, but it seems to me difficult to get the numbers back down to 5,000.

On this basis the ABI is understating its case.

9.4 Further the ABI assumes that approximately 50% of the at risk would turn out to be negative. But because some of the heterozygotes would already have developed symptoms of HD, more than 50% of those tested should turn out to be negative, unless all those tested are very young. Yet again the benefits of testing for those who prove to be negative are underestimated.

9.5 At the top of page 9 the ABI states "there is less correlation of CAG repeat size with age at death". I do not see where this comes from. I have looked for evidence of this, and have not spotted it, but I have not had time to read all of the references thoroughly.

9.6 On page 10: "… because the number of CAG repeats is often inherited exactly, the ages of onset of different affected members of a given family are correlated". No reference is given and I have not spotted this observation in nay of the references.

9.7 On page 11: "If a person has tested HD positive and the CAG repeat size is known, it may well be possible to predict the earliest likely age at death and the range." What exactly does this mean; it is an actuarial sort of statement, but made in non-actuarial language. The earliest possible age at death for someone aged x is always x; the highest possible age at death is uncertain, but is well over 110, perhaps over 120. A better statement would be that "… the probability distribution of ages at death can be estimated more accurately".

9.8 On page 14: "we believe that a repeat size of 36 or more should be reported but that for those with a value of 36 exactly, penetrance by age 84 is low". This is not validated by Brinkman's figures. He has 13 cases with exactly 36 CAG repeats, of whom one had developed HD at the age of 65, and the others were ranged from 9 to 85. If one looks at Figure 3, even those with 39 CAG repeats look as if the curve will go up to 1 eventually, and if one imagines plausible curves for those with 38, 37 and 36 CAG repeats it is not easy to see them being still at *low* levels by age 84. This is where a fuller multi-dimensional analysis of Brinkman's data would have been helpful.

10 *Conclusion*

10.1 In conclusion I only need to repeat the remarks I made in Section2:

- there is no doubt that the extra mortality risk for an applicant for life insurance who has had a genetic test and has been found to be HD positive is in many cases more than +50%;
- it is also the case that, when an applicant has had a genetic test and has been found to be negative, that applicant can be assessed on normal underwriting criteria;
- the evidence presented by the ABI in support of their case is, in detail, very unsatisfactory, and, in my opinion, it would give a quite wrong message if the GAIC were to approve the detailed underwriting criteria that have been presented.

Professor A. D. Wilkie, CBE, MA, FFA, FIA
7 September 2000

Appendix

I have put certain technical material into this Appendix. I believe this to be of interest and relevance, but it does not have a substantial bearing on the results in the main part of my report.

A1 *The hazard rate*

A1.1 Actuaries normally look at mortality and other transition rates (or "forces") in terms of the *hazard rate* at each age and/or duration, and not in terms of the total distribution of the relevant event. The hazard rate is also known is the "force of mortality", conventionally denoted m_x or $m(x)$, or the "transition force" or "transition intensity" or "transition rate", all these terms having the same significance. For a statistical distribution of a continuous random variable (like age at death), with distribution function $F(x)$, survivor function $S(x) = 1 - F(x)$, and density function $f(x) = dF(x)/dx$, the hazard rate is given by $\lambda(x) = f(x)/S(x)$. It represents the instantaneous probability density of a transition from one state (e.g. alive) to another state (e.g. dead) for someone who is in the first state at age (or duration) x, or perhaps at age x and duration z if the hazard rate is represented as a function of both age and duration.

A1.2 If the transitions are in one direction only, such as from alive to dead, and there are no other causes of transition, the survival function, conditional on starting at some initial age, say $x0$, can be calculated from the hazard rate, by:

$$S(x) = \exp(-\int_{x0}^{x} \lambda(y)dy)$$

A1.3 For a normal (Gaussian) distribution the density function can be calculated explicitly, the distribution function can be calculated numerically, and both are given readily by computer routines. The hazard rate can therefore be readily calculated by computer for any value of x, although calculation without a computer is laborious.

A1.4 A major reason for using the hazard rate in actuarial work is that one is almost always interested in the distribution of future events for someone who has already attained a certain age. An applicant aged 50 is necessarily alive, and the distribution of deaths at earlier ages is of no relevance to his (or her) present prospects, which are entirely determined by that part of the distribution of ages at death that is above age 50. The hazard rate at any age remains the same, wherever the conditional distribution starts, whereas other features of a distribution change.

A1.5 Further, the hazard rate at any age can be directly estimated from a count of the number of events at that age, and the value of the "number of years exposure" at that age among all those observed, whether they survived or died. The hazard rate is the basis of what is described in the literature as the "life table method", or "Kaplan-Meier estimation" (though the Kaplan-Meier method estimates discrete probabilities of death or survival over each small segment of the age range, rather than continuous hazard rates).

A1.6 Direct estimation of the hazard rate avoids the problem that Roos (1991) observes, that HD positives who are still young at the time of investigation can have only a low age at onset, but might well develop HD at a higher age in due course. He solves this problem by

separating out those who were born before 1925, but this throws away the experience of those born since then, whose experience can still be used in the estimation of the hazard rates for their past lifetimes.

A2 *The hazard rate for the normal distribution*

A2.1 The hazard rate for a unit normal distribution can be calculated and is plotted in Figure A1. It can be seen that it starts out very low for low values of x, hardly greater than zero, and rises steadily. Between about –2.5 and +2.5 it rises approximately as a quadratic curve, $\lambda(x) = ax^2 + bx + c$, but above +2.5 the curve straightens out and is almost linear, $\lambda(x) = ax + b$.

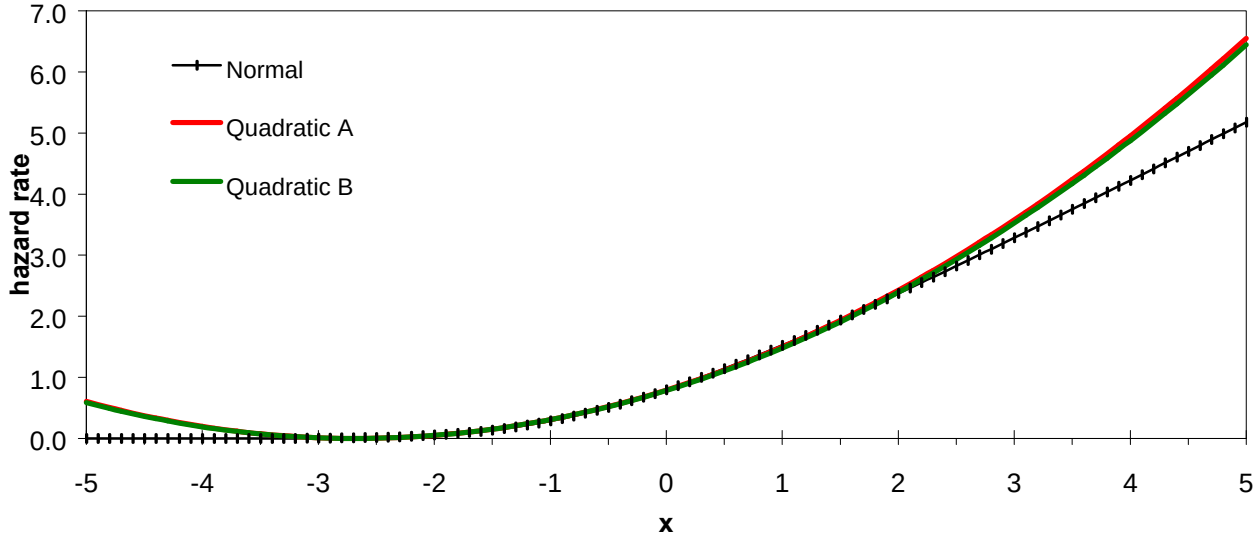
A2.2 In the range –2.5 to +2.5 one can approximate the normal hazard rate very closely by a quadratic function. The quadratic function I have used is of the form:

$$\lambda(x) = a(x - d)^2 \qquad x \geq d$$

which has only two parameters, a and d, and is valid only for values of x greater than or equal to d. I have estimated the parameters in two ways (A) by approximating closely the hazard rates and (B) approximating closely the distribution function. They give only slightly different answers:

(A) $a = 0.111417$ $d = -2.667310$
(B) $a = 0.109201$ $d = -2.680969$

Figure A1: Hazard rates of Normal distribution and approximating quadratics



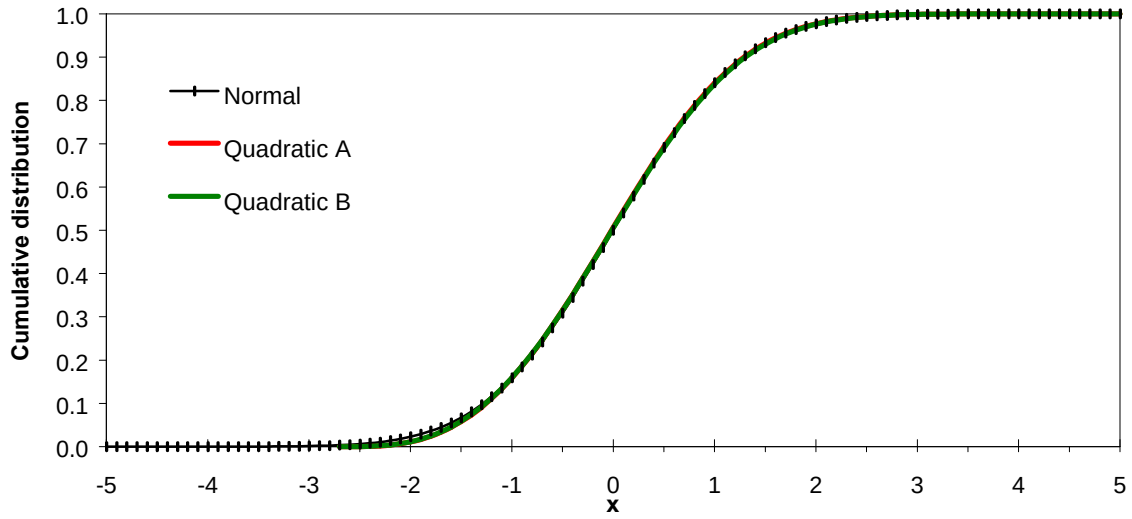
A2.3 The two curves of these quadratic hazard rates are also shown in Figure A1. They obviously diverge from the curve for the normal below –2.7, but they are not used below that point. Between –2.7 and about +2.0 the three curves are very close, but above that point the quadratics rise above the curve for the normal.

A2.4 Figure A2 shows the distribution functions for all three formulae. They are very close. The distribution function for the quadratics can be directly calculated from:

$$F(x) = 1 - S(x) = 1 - \exp(-\int_{x0}^{x}\lambda(y)dy) = 1 - \exp(-a(x-d)^3/3)$$

[This, incidentally, shows that the fairly simple expression on the right of the above equation is a reasonable approximation to the normal distribution function; however, better ones are known.]

Figure A2: Distribution functions of Normal distribution and approximating quadratics



A2.5 The differences between the cumulative distributions in Figure A2 seem very small, indeed difficult to see, but the different hazard rates are of great importance to an applicant for life insurance who is aged two standard deviations above the mean age of onset of HD, without yet showing signs of symptoms. It makes a big difference to one's assessment for such an applicant whether one chooses to use a normal hazard rate or a quadratic one.

A2.6 A more general three parameter quadratic, of the form:

$$\lambda(x) = a(x-d)^2 + c$$

does not fit any better, unless c is made negative, which produces a negative hazard rate for x in the neighbourhood of d, and this is inadmissible

A3 *The normal distribution and Newcombe's data.*

A3.1 Smith justifies his use of the normal distribution by fitting a normal distribution to one of the sets of data in the paper by Newcombe (1981). In fact Newcombe presents three distributions described by him as Options 0, 1 and 2. Newcombe gives the percentage survival functions at quinquennial ages. Smith has fitted a normal distribution only to Newcombe's Option 2 (or only quotes the results of this).

A3.2 I have fitted normal distributions to all three of Newcombe's survival tables. I get:

	Mean	s.d.
Option 0	46.78	13.54
Option 1	48.97	14.38
Option 2	48.15	14.16

Note that both the means and the standard deviations are rather higher than in Roos's data.

A3.3 I have also fitted a 2-parameter quadratic hazard rate, $\lambda(x) = a(x - d)^2$, to each of these Options, by minimising the sums of squares of the deviations of the survival functions. I get:

	a	*d*
Option 0	0.00004330	10.2865
Option 1	0.00003627	10.2470
Option 2	0.00003783	9.9623

The sum of squares of the errors for these fits is distinctly better than for the normal.

A3.4 However, these functions have the awkward feature of having a zero hazard rate at age *b*, with a higher hazard rate below that age. Assuming that the earliest actual age of onset in Newcombe's data is 8 years (it is not clear that this is so; he quotes the survival function for age 8, but does not say at what age it is unity; perhaps at age 0). I have therefore refitted the data, with the value of *d* fixed at 8. I get:

	a	*d*
Option 0	0.00003653	8
Option 1	0.00003092	8
Option 2	0.00003284	8

A3.5 The fits are necessarily less good when the value of *d* is fixed than when it is optimised, but the results are still about the same as for the normal distribution. The sums of squares for the different fits are:

	Normal	Fitting *a* and *d*	Fitting *a* with *d* =8
Option 0	0.003528	0.000468	0.002077
Option 1	0.001436	0.000466	0.001915
Option 2	0.001306	0.000440	0.001692

A3.6 Adherence to a survival function at a discrete set of ages is not the most satisfactory test of what is has been described as a "graduation by mathematical formula". If the source data were available, in the form either of complete data with dates of commencement and termination of observation for each case, and dates of events, or alternatively with a count of events and a measure of the "exposed to risk" at each age (or other time unit), a proper fit to the data, and tests of that fit, could be obtained. This is an established actuarial technique, well known also to some statisticians, but it is seldom referred to in basic statistical textbooks.

END