

EARLY-ONSET ALZHEIMER'S DISEASE, CRITICAL ILLNESS INSURANCE AND LIFE INSURANCE

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ABSTRACT

Early-onset Alzheimer's disease (EOAD) is a disorder with a dominantly inherited form, listed as being of significance for insurance by the Association of British Insurers. Mutations in the Presenilin-1 (PSEN-1) gene are responsible for a large proportion of cases. Gui & Macdonald (2002) estimated rates of onset of EOAD associated with PSEN-1 mutations, which we use here in a Markov model of critical illness insurance. We investigate: (a) premium ratings given either a known mutation or a family history; and (b) the effects of moratoria on the use of genetic test results and family history. In the process, we obtain new estimates of survival rates after onset of EOAD, and extend the analysis to life insurance, using a semi-Markov model.

KEYWORDS

Critical Illness Insurance; Early-Onset Alzheimer's Disease; Life Insurance; Presenilin-1 Gene; Rate of Onset; Survival After Onset

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1. INTRODUCTION

1.1 *Early-Onset Alzheimer's Disease*

Alzheimer's disease (AD) is the most common form of dementia, and is a major health problem in many countries. Clinically, it is characterised by a gradual and progressive decline in cognitive functions. Early-onset Alzheimer's disease (EOAD) is an autosomal dominant form of AD occurring before about age 65. Whereas AD after that age is relatively common, EOAD is rare. The amyloid precursor protein (APP), presenilin-1 (PSEN-1) and presenilin-2 (PSEN-2) genes have been confirmed as causing EOAD. They are highly penetrant; the absence of AD by age 60 among confirmed carriers is rare.

PSEN-2 gene mutations are very rare while the percentages of EOAD cases due to mutations in the PSEN-1 and APP genes have not been consistently reported in the literature (Campion *et al.*, 1999); estimates range from 20% to 70%. The ages at onset of EOAD also vary considerably (PSEN-1 24–60, APP 40–65 and PSEN-2 45–84 (Campion *et al.*, 1999)).

1.2 *Insurance Questions*

We can pose quantitative questions from the points of view of an applicant for insurance and of the insurer:

- (a) If an insurer is allowed to use genetic information, what would be the increased premium offered to a person with a known mutation, or just with a family history?
- (b) If an insurer is not allowed to use genetic information, what might be the costs of adverse selection, if persons possessing knowledge of their own increased risk were more likely to buy insurance?

Both of these can be approached using simple multiple-state models. The first is slightly easier, since it does not involve mutation frequencies but only the rates of onset and survival of persons *known* to be at risk. The second does need estimates of mutation frequencies, which determine the size of the ‘pool’ of potential adverse selectors. It is also necessary to include in the model the various underwriting classes that are in use, that may in part be determined by any moratorium on using genetic information.

1.3 *Presenilin-1 Gene Mutations*

The PSEN-1 gene (also known as S182) was localised on chromosome 14 in 1992 and isolated in 1995 (Sherrington *et al.*, 1995). It encodes a transmembrane protein that is produced at low level in many different cell types, and is almost homogeneously expressed in the brain and in peripheral tissues.

To date, nearly 100 different mutations causing EOAD have been found (Gui & Macdonald, 2002). PSEN-1 mutations are usually associated with very aggressive EOAD, with duration of dementia ranging from about 5 to 25 years and mean duration of 11.5 ± 5.6 years (Ishii *et al.*, 2001). These mutations appear to be highly penetrant by the age of about 60; Rogoava *et al.* (2001) reported that 90% of those with PSEN-1 mutations were affected by age 60. The lower ages at onset are around 30 though Wisniewski *et al.* (1998) has reported an individual in a Polish EOAD family with onset at 24.

1.4 *Genetic Testing for EOAD*

Genetic testing for EOAD is, so far, confined to research laboratories: commercial tests are not yet available in the United Kingdom for any of the genes involved. Nevertheless, the introduction of genetic tests for the disease raises concerns on many issues, from the psychological impact of knowing one's own genetic susceptibility to an incurable disease, to the potential for discrimination in access to insurance and long-term care.

Genetic testing is only ever likely to be recommended for individuals from families with a history of EOAD (Finckh *et al.*, 2000). Rogoava *et al.* (2001) found a high frequency of PSEN-1 mutations in a referral-based study of 372 AD patients and 42 asymptomatic persons with a strong family history of AD, suggesting that screening in these families should be highly cost effective. Because EOAD is rare and dominantly inherited, genetic testing is unlikely to be recommended to aid diagnosis of the sporadic form of AD. The test may improve the accuracy of diagnosis slightly, but a positive test result does not contribute significantly to the treatment for the patient. Given the widespread use of moratoria on insurers making use of genetic test results, family histories of EOAD will remain important in the future; the advent of DNA-based tests will not lessen their relevance.

1.5 Plan of This Paper

In Section 2 we review briefly the epidemiology of EOAD associated with PSEN-1 mutations. For rates of onset we summarise Gui & Macdonald (2002), and for rates of survival after onset we obtain estimates in Section 2.3. In Section 3.3 we use a model of a CI insurance policy to investigate premium ratings given either a genetic test that shows a PSEN-1 mutation to be present, or a family history of PSEN-1 mutations; we extend this in Section 4 to a model of an insurance market, in which we can assess the possible costs of adverse selection under various moratoria on the use of genetic information. In Section 5 we propose a semi-Markov model for life insurance in the presence of PSEN-1 mutations, and in Sections 6 and 7 we use this to investigate premium ratings and adverse selection, respectively. Conclusions are in Section 8.

2. THE EPIDEMIOLOGY OF EOAD

2.1 The Epidemiological Literature

The epidemiology of EOAD is sparse (Dartigues & Letenneur, 2000), and there is a lack of informative community-based studies. For actuarial applications we need rates of onset of symptoms, survival rates after onset, mutation frequencies and possibly also rates of progression of dementia through several stages. No rates of onset have been published in the literature of genetic epidemiology. There are very few estimates of EOAD prevalence and little is known about the mutation frequencies of these three genes. (Despite this, EOAD is included in the list of disorders regarded as significant for insurance by the Association of British Insurers (ABI).)

However, estimates of incidence rates of EOAD in respect of PSEN-1 mutations have been derived by Gui & Macdonald (2002), based on pedigrees published in the molecular genetics literature; we are not aware of any others. From the same sources, it is possible to estimate rates of mortality after onset, which we do in Section 2.3 of this paper; these estimates are new.

Published data on APP and PSEN-2 mutations are too scarce to allow incidence rates or survival rates to be estimated along similar lines.

2.2 Rates of Onset of EOAD Associated With PSEN-1 Mutations

Gui & Macdonald (2002) obtained estimates of rates of onset of EOAD associated with PSEN-1 mutations. They had the following features:

- (a) A non-parametric approach was used, based on a Nelson-Aalen estimate. The complicating factor was that the risk set at any given age (healthy persons at risk of contracting EOAD) is a mixture of mutation carriers and non-carriers; the classical Nelson-Aalen estimate gives the integrated intensity of onset in respect of this mixed group, from which the rate of onset among mutation carriers could be found numerically.
- (b) Rates of onset for males and females separately were obtained, but were of much poorer quality than those for males and females combined. We use only the latter here.

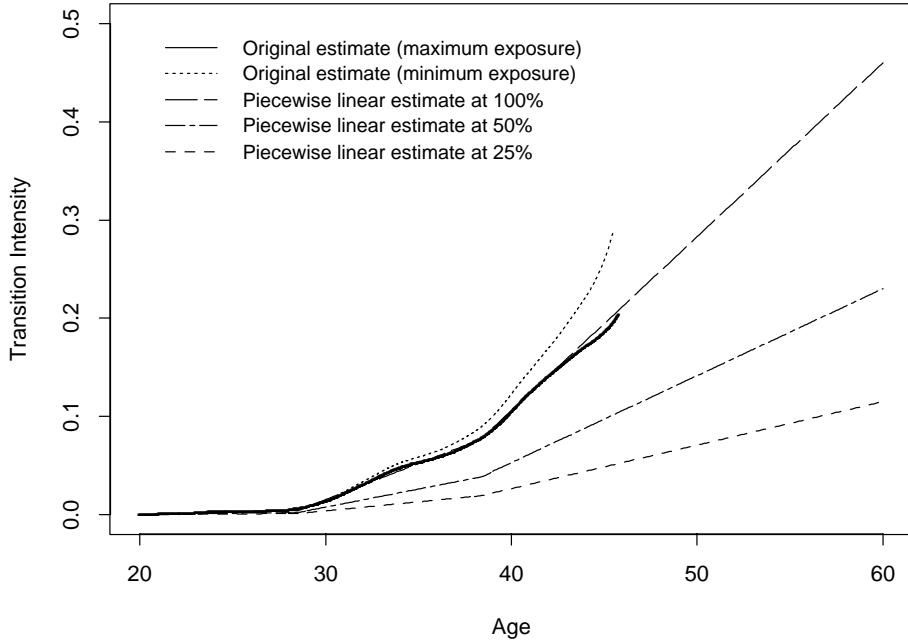


Figure 1: Estimated and smoothed/extrapolated incidence rates (100%, 50% and 25% of those estimated from the data with maximum possible exposures) of EOAD associated with PSEN-1 mutations. Source: Gui & Macdonald (2002).

- (c) There is an intrinsic bound to the integrated intensity of onset of a genetic disorder such as EOAD in respect of a mixed group of mutation carriers and non-carriers. This is because non-carriers will never get EOAD, so the lifetime probability of EOAD is less than 1. If μ_x^* is that intensity, $\exp(-\int_0^x \mu_t^* dt) > 0$ at the highest age x , so $\int_0^x \mu_t^* dt$ must be bounded. For a rare dominantly inherited condition like EOAD, the bound is $\log 2$. However, the Nelson-Aalen estimate can exceed that bound, in which case the rate of onset in respect of mutation carriers explodes to infinity. This is made much more likely if there is *ascertainment bias*, meaning that families are selected for study because they have large numbers of cases of EOAD. This is almost certain to be the case for these estimates, and the $\log 2$ bound was exceeded at about age 50; the rates of onset for mutation carriers were unreliable beyond about age 46.
- (d) Some assumptions about the numbers exposed to risk had to be made because of missing data; therefore, two estimates were given, one using the minimum possible exposures and another using the maximum possible exposures. Because ascertainment bias is very likely, we will use the lower estimate, based on maximum possible exposures.

Figure 1 shows the estimated rates of onset in respect of known PSEN-1 mutation carriers, with minimum and maximum possible exposures. For application, the lower estimate has to be smoothed and extrapolated to age 60. Then, it is necessary to consider the strong possibility that these are too high, because they are based on families selected for high incidence of EOAD, and are not based on prospective population studies. Other

studies into AD (Macdonald & Pritchard, 2000, 2001) and breast and ovarian cancer (Macdonald, Waters & Wekwete, 2003a, 2003b) reduced the observed rates of onset by 50% and 75% to allow for this, and we will do likewise here.

Given the limited information available, we carried out the smoothing and extrapolation by fitting the following piecewise linear function (with quadratic smoothing at the corners) to the estimates:

$$\mu_x^{fitted} = \begin{cases} 0.0 & \text{if } x < 20.0, \\ f1(x) & \text{if } 20.0 \leq x < 28.0, \\ (29.0 - x)f1(x) + (x - 28.0)f2(x) & \text{if } 28.0 \leq x < 29.0, \\ f2(x) & \text{if } 29.0 \leq x < 38.0, \\ (39.0 - x)f2(x) + (x - 38.0)f3(x) & \text{if } 38.0 \leq x < 39.0, \\ f3(x) & \text{if } x \geq 39.0, \end{cases} \quad (1)$$

where $f1 = -0.0112324 + 0.000553792x$, $f2 = -0.205248 + 0.00735054x$, and $f3 = -0.602651 + 0.0177141x$. Note that the results are not too sensitive to the extrapolation to age 60; rates of onset are so high up to age 46 that about 80% of mutation carriers will have EOAD by then (Gui & Macdonald, 2002). It is these fitted rates of onset that we will reduce by 50% and 75% as a sensitivity analysis for possible ascertainment bias.

2.3 Estimating Mortality Rates After Onset of EOAD

Survival data are available from the same sources as were used to estimate rates of onset, namely published pedigrees (described fully in Gui & Macdonald (2002)). Age at death after onset is one of the most carefully reported items of information in any pedigree, in the sense that it is rarely missing, though it might often be hard to establish accurately the duration since onset. The problems described in Gui & Macdonald (2002), of dealing with incomplete reporting of lifetimes censored before onset are here mostly absent, and the pedigree data lead to a straightforward survival analysis. The main question is whether mortality rates after onset of EOAD depend on age, or duration since onset, or both.

We divided the survival data into three groups depending on age at onset (n = number of cases of EOAD): 20–39 ($n = 64$), 40–49 ($n = 68$) and 50–59 ($n = 43$): we have an enlarged first group as the number of cases of onset at ages 20–29 was very small. Nelson-Aalen estimates of the integrated hazard are shown in Figure 2. We compared duration-dependent survival curves for each group (Peto-Wilcoxon test, see Venables & Ripley (1999)). Table 1 shows there is no significant difference in survival between the 20–39 and the 40–49 age-at-onset groups, while there does appear to be some difference between the 50–60 age-at onset group and the other two. We decided to use ages at onset 20–49 only, with mortality rates depending on duration, for two reasons:

- (a) Survival following onset at ages over 50 is not very important for this study; for CI insurance it is irrelevant, and for life insurance not extending beyond age 60 it is relatively insignificant because of the high penetrance of PSEN-1 mutations.
- (b) Smith (1998) presented a model of Huntington's disease (HD) with duration-dependent rates of mortality after onset HD, and the ABI used this as the basis of a submission

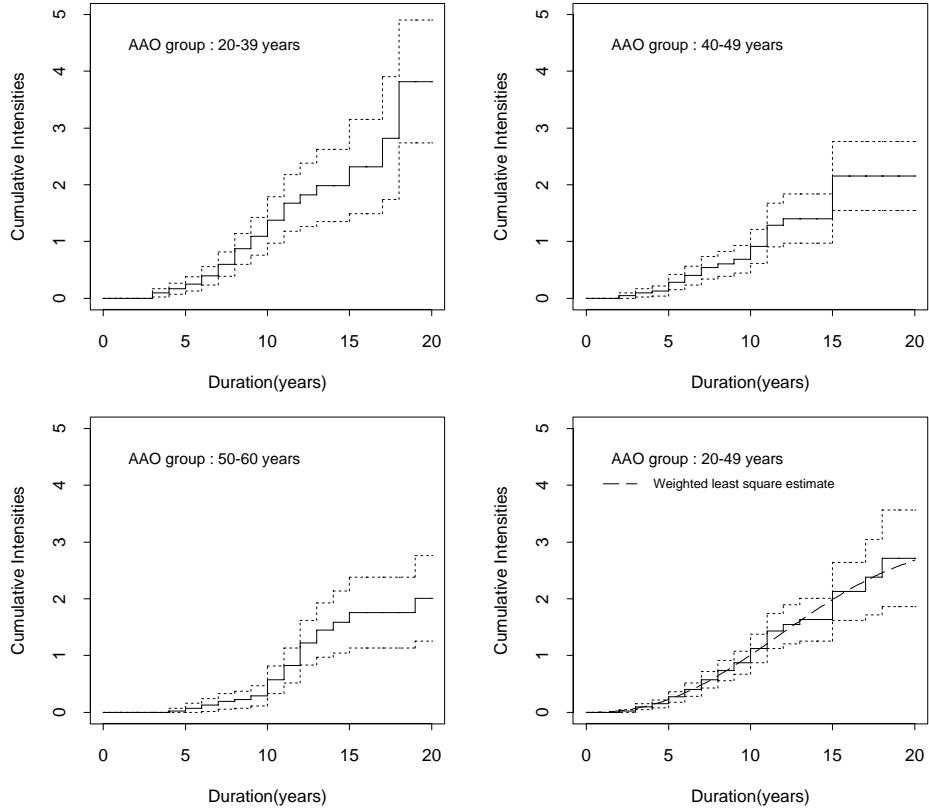


Figure 2: Nelson-Aalen estimates of the duration-dependent integrated hazard of death after onset of EOAD, and approximate 95% confidence intervals, for persons with PSEN-1 mutations. Ages at onset 20–39, 40–49, 50–60 and 20–49. The graduated estimate for AAO 20–49 is also shown.

to the Genetics and Insurance Committee in the U.K. to be allowed to use DNA-based test results for HD in life insurance underwriting. Although this application succeeded in the first instance, Wilkie (2000) pointed out the anomaly that mortality could be assumed to fall substantially following onset of HD, because the duration-related mortality rates were substantially lower than the normal age-related rates of mortality at certain ages. Here, we avoid this anomaly by assuming that mortality after onset of EOAD is no better than normal age-related population mortality. Since we superimpose a known age effect upon the mortality rates modelled from the pedigree data, we prefer to discard data for ages at onset 50 and over.

The following Weibull function of duration d was a good fit (weighted least squares) to the integrated intensity for AAO 20–49:

$$\mu_d^* = 0.012250264 d^{1.37601} \exp(-0.00168128 d^{2.37601}). \quad (2)$$

and is also shown in Figure 2. For reasons given above, in the model we use the intensity $\max[\mu_{x+t}^{ELT15}, \mu_d^*]$.

Table 1: Peto-Wilcoxon test comparing the survival curves of the three different age-at-onset groups.

Groups Compared (Age at Onset in Years)	<i>P</i> -value
20–39 and 40–49	0.188
40–49 and 50–60	0.0329
20–39 and 50–60	0.000139
20–39, 40–49 and 50–60	0.00175

2.4 Mutation Frequencies

In a population-based prevalence study of EOAD in the French city of Rouen, with an at-risk population of 94,593, Campion *et al.* (1999) estimated the prevalence of familial EOAD at 25.4 per 100,000 at risk. Older prevalence studies by Kokmen *et al.* (1989), Schoenberg *et al.* (1985) and Sulkava *et al.* (1985) reported prevalences per 100,000 at-risk individuals of 26.9, 45.2 and 18.2 respectively. These figures are reasonably consistent with Campion *et al.* (1999).

Of the 184 affected subjects tested for mutations by Campion *et al.* (1999), 14.7% carried APP gene mutations while 58.8% had PSEN-1 gene mutations.

Given these figures from Campion *et al.* (1999), we estimate the mutation frequency for the PSEN-1 gene at 15 per 100,000, which is close to the frequency of 1 in 10,000 used by Cruts *et al.* (1995) in their linkage analysis.

3. PREMIUM RATINGS FOR CRITICAL ILLNESS INSURANCE

3.1 Critical Illness Insurance

Critical illness (CI) insurance contracts pay a sum assured on contracting any of a specified list of serious conditions. It is often sold as a rider to a life insurance contract, known as ‘accelerated benefits’. It is usual to stipulate that the insured person must survive for at least 28 days after the ‘onset’ of the condition (if that can be meaningfully identified) so that there is a clear distinction between critical illness and death. Figure 3 shows a model of EOAD and CI insurance.

3.2 Transition Intensities in the Critical Illness Insurance Model

For onset of EOAD associated with PSEN-1 mutations, we use the estimates described in Section 2.2.

There is no industry standard model for CI insurance. We use the model from Gutiérrez & Macdonald (2001), described briefly in the Appendix. This is quite similar to the models used by Dinani *et al.* (2000) and Macdonald, Waters & Wekwete (2003b) which so far as we know are the only other published models. Note that all of our results are based on relative rather than absolute CI insurance costs, so they are quite insensitive to the details of the basic CI insurance model.

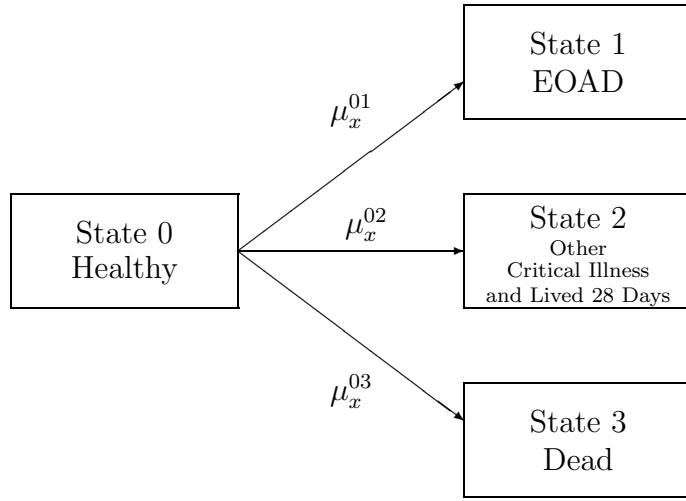


Figure 3: A model for EOAD and critical illness insurance.

3.3 Premiums Based on Known PSEN-1 Mutations

Table 2 shows level premiums, payable continuously, for level CI cover for female and male PSEN-1 mutation carriers. The premiums are expressed as percentages of the ‘standard’ premium rate, taken to be that paid by non-mutation carriers. The premiums are shown with estimated EOAD onset intensities of 100%, 50% and 25% of those fitted to the data. We used a Runge-Kutta algorithm with step-size 0.0005 years to solve Theile’s equations for the expected present values (EPVs) of benefits and premiums, with a force of interest of $\delta = 0.05$ per annum.

- (a) Premiums for cover expiring at age 30 appear to be high, especially for males, but these may be unreliable as they are based on a tiny number of cases, and measured against very low standard CI premiums at these ages.
- (b) At practically all ages and terms, and even with the rates of onset reduced to 25% of those observed, the premiums would exceed the limits that currently might be offered in practice (about 300% of standard rates). The highest is over 4,000% of the standard premium. The only possible exception might be females age 20, for a term of 10 years, given the lowest rates of onset.

3.4 Premiums Based on Family History of EOAD

Table 3 shows level premiums for level CI cover based on a family history of EOAD known to be associated with PSEN-1 mutations, where the applicant for insurance has not had a genetic test, or has but the result is not known by the insurer. Here ‘family history’ means that one of the applicant’s parents or siblings is known to have had EOAD, or (less likely in practice) is known to have had a genetic test that shows a PSEN-1 mutation to be present. Because EOAD is very rare, we can assume that any cases that arise in families that carry PSEN-1 mutations have that as their cause. Because PSEN-1 mutations are rare and dominantly inherited, we can assume each child of affected parents carries the

mutation with probability 1/2. The EPV of the CI benefit, given family history only, is a weighted average of the EPVs of the benefit in respect of healthy carriers and non-carriers, the weights being the probabilities of surviving in state 0 of the model in Figure 3 until the inception of the policy. These probabilities are found by solving the Kolmogorov equations from age 0, also using a Runge-Kutta algorithm with step-size 0.0005 years. The EPV of a £1 per annum level premium is found similarly, and hence the rate of premium. The figures in Table 3 are percentages of the 'standard' premium rates.

- (a) For CI cover expiring at age 30, if rates of onset were 25% of those observed, an extra premium of +50% to +100% might be offered, and if rates of onset were 50% of those observed, about double these ratings might be offered.
- (b) For CI cover commencing at age 50, extra premiums of less than +100% could be offered, or less than +50% assuming the lower rate of onset. This is because an at-risk person, healthy at age 50, has only a small probability of being a mutation carrier.
- (c) At all other ages and terms, extra premiums would exceed +200% and in some cases +1,000%.

The main conclusion is that older people in at-risk families can be offered very much better terms than if they were known PSEN-1 mutation carriers. For exactly the same reason, that their very survival implies much reduced risk, it is perhaps unlikely that they would be advised to be tested on clinical grounds, so no conflict between medical and insurance interests should arise. However, this is likely to be a rather small segment of the CI insurance market.

In fact, the premiums based on a family history of EOAD, but not known to be associated with mutations in any particular gene, should probably be lower than those in Table 3, because:

- (a) PSEN-1 mutations are thought to cause an aggressive form of EOAD, though rates of onset associated with mutations in other genes are not available to confirm this; and
- (b) all forms of EOAD are rare, and not all show clear dominant inheritance, so the assumption that 50% of offspring of affected parents will carry causative mutations is an upper bound.

4. THE POTENTIAL COST OF ADVERSE SELECTION IN CI INSURANCE

4.1 *Genetic Information, Moratoria and Adverse Selection*

Adverse selection may arise if persons who know they are at increased risk because they have some genetic information are more likely to buy insurance and need not share that information with the insurer. In the late 1990s, most attention was directed towards DNA-based genetic tests, because it was their novelty that had brought the question of genetics and insurance out into the open, but now 'genetic information' may be interpreted more widely to include:

- (a) DNA-based test results;
- (b) tests for gene products altered by mutated genes; or
- (c) family histories of Mendelian or complex disorders.

Table 2: Level net premiums for level CI cover with known PSEN-1 mutations, as a percentage of the standard level premiums. Rates of onset of EOAD are 100%, 50% and 25% of those observed.

EOAD Onset Rate at	Entry Age	Females					Males				
		Term (Years)				Term (Years)					
		10 %	20 %	30 %	40 %	10 %	20 %	30 %	40 %		
100%	20	635.23	2,040.43	1,958.24	1,375.30	1,020.61	2,910.53	2,294.84	1,372.66		
	30	3,251.01	2,896.21	2,040.24		4,263.13	3,175.89	1,935.66			
	40	4,177.72	3,022.60			4,158.54	2,660.51				
	50	3,714.51				2,985.17					
50%	20	368.66	1,153.03	1,319.29	1,020.22	562.10	1,625.21	1,539.38	1,014.91		
	30	1,728.84	1,766.02	1,354.03		2,252.02	1,931.88	1,282.30			
	40	2,273.90	1,776.91			2,263.39	1,565.30				
	50	1,994.18				1,610.60					
25%	20	234.59	649.11	817.03	708.71	331.50	895.33	946.23	703.28		
	30	928.29	1,024.22	865.97		1,194.34	1,116.02	820.13			
	40	1,226.00	1,032.14			1,220.50	913.02				
	50	1,076.98				878.81					

Table 3: Level net premiums for level CI cover for persons with family histories of EOAD known to be associated with PSEN-1 mutations, as a percentage of the standard level premiums. Rates of onset of EOAD are 100%, 50% and 25% of those observed.

EOAD Onset Rate at	Entry Age	Females					Males			
		Term (Years)				Term (Years)				
		10 %	20 %	30 %	40 %	10 %	20 %	30 %	40 %	
100%	20	366.60	1,033.72	935.00	643.69	558.56	1,452.48	1,086.63	643.43	
	30	1,518.81	1,181.50	769.20		1,974.59	1,290.28	734.97		
	40	1,066.80	604.68			1,062.96	544.88			
	50	197.65				178.56				
50%	20	234.07	616.09	672.47	513.82	330.61	847.52	775.97	511.94	
	30	866.04	817.11	594.35		1,112.11	888.74	567.09		
	40	728.62	488.06			725.82	440.54			
	50	178.05				162.54				
25%	20	167.23	371.76	446.37	385.42	215.64	493.63	508.83	383.12	
	30	498.28	523.65	431.65		626.21	565.81	412.23		
	40	463.23	363.14			461.53	330.09			
	50	152.94				142.31				

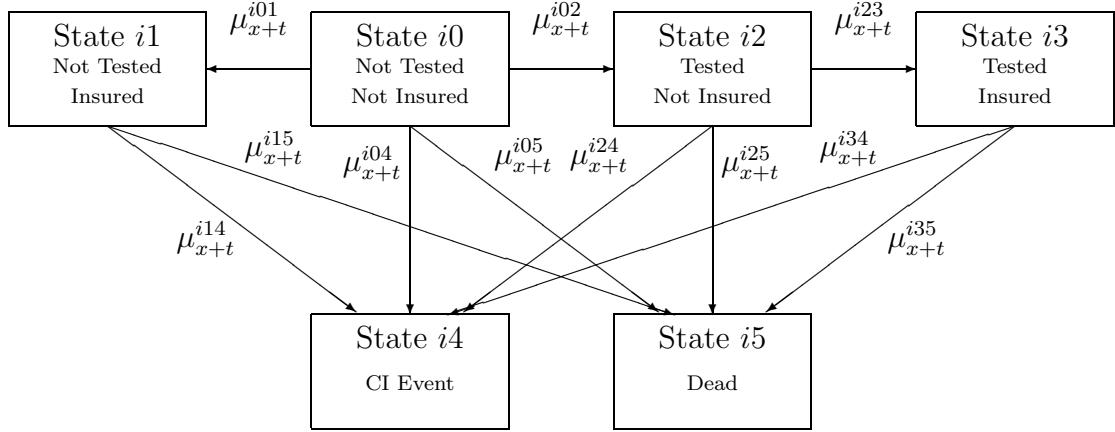


Figure 4: A Markov model of genetic testing, insurance purchase and CI insurance events for a person in the i^{th} risk subpopulation.

Governments may impose moratoria or outright bans on insurers using some or all of these. For example, in the U.K. there is currently an agreed moratorium on the use of DNA-based test results, while in Sweden there is a moratorium covering family history as well. The potential costs of adverse selection will depend on the type of insurance, the nature of the market for that insurance and the form of moratorium imposed, as well as on the details of each particular genetic disorder.

Figure 4 shows a Markov model for the life history of a person in the i^{th} of M subpopulations (to be defined shortly). It represents all the relevant events in a CI insurance market; in fact it is a model of the insurance market and not just of a single insurance contract, unlike the model in Figure 3.

We use the approach of Macdonald (2001) and Gutiérrez & Macdonald (2001). The M subpopulations are defined by the presence or absence of PSEN-1 mutations, and the presence or absence of a family history of EOAD (we ignore family histories that are due to APP or PSEN-2 mutations, which are relatively less common). This leads to $M = 3$ subpopulations, shown in Figure 5:

- (a) not at risk, not having a family history of EOAD ($i = 1$);
- (b) at risk because of family history but not a mutation carrier ($i = 2$);
- (c) at risk and a mutation carrier ($i = 3$).

We suppose that a proportion p_i are in the i^{th} subpopulation at birth. This model captures all the important features of the problem:

- (a) The proportion p_3 starting in the ‘uninsured, untested’ state 30 represents the population frequency of mutations. The same proportion starts in state 20, not carrying a mutation but not knowing that.
- (b) The rate of genetic testing may represent any possibility from a low level of testing restricted to at-risk families, to screening of the population.
- (c) The rate of insurance purchase by persons not at risk represents the size of the market.

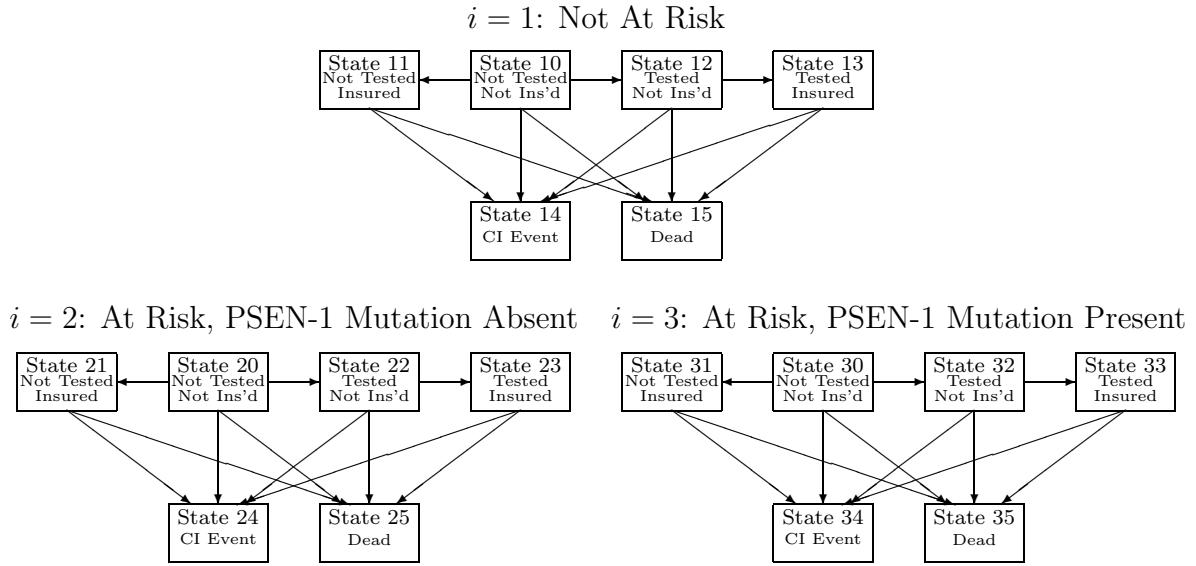


Figure 5: A Markov model of a CI insurance market allowing for a family history of EOAD and genetic testing.

- (d) Adverse selection is represented by:
 - (1) the rate of insurance purchase given a family history but before testing;
 - (2) the rate of insurance purchase after receiving an adverse test result; and
 - (3) the amounts of insurance purchased.
- (e) Underwriting classes will consist of collections of states, depending on any moratorium, within each of which a premium based on the equivalence principle, assuming no adverse selection, can be charged.

4.2 Parameterisation

We suppose that 15 per 100,000 of the population are in each of states 20 and 30 at birth (Section 2.4).

The intensities of occurrence of CI claims and deaths (net of CI claims) are given in the Appendix, and rates of onset of EOAD (in subpopulation $i = 3$ only) were given in Section 2.2. The two remaining intensities in each subpopulation are the rate of genetic testing and the rate(s) of insurance purchase, some of which may represent adverse selection, and some a response to high premium ratings where these may be charged.

- (a) *The Rate of Genetic Testing:* Little information is available about the level of DNA-based testing for EOAD. In an observational study of 251 individuals at 50% risk for EOAD or frontotemporal dementia by Steinbart *et al.* (2001), 8.4% of at risk persons requested genetic testing. These individuals were mainly concerned about the early symptoms of the disease, family and financial planning, and anxiety associated with carrying the risk.

Huntington's disease (HD) is comparable to EOAD in that it is rare, dominantly inherited, highly penetrant and untreatable. Genetic testing for HD families has now

been available in a clinical (rather than research) setting for some time, and some experience has been gained. The proportion of at-risk persons who choose to be tested is quite low, ranging from 6% (Panegyres *et al.*, 2000) to 10–20% (Meiser & Dunn, 2000). Again, the reasons for the low rate of requests are likely to be issues like employment, insurability and the psychological implications of knowing a test result. We use an annual intensity of 0.01 to represent a very moderate rate for genetic testing, which implies that almost 10% of at-risk individuals will have the test within ten years. For reasons outlined in Section 1.4, this intensity is likely to over-estimate the increases in premiums payable for CI insurance under investigation in this paper.

- (b) '*Normal*' Rates of Insurance Purchase: We consider two different market sizes: a large market with an annual rate of insurance purchase $\mu_{x+t}^{101} = 0.05$, and a small market with rate $\mu_{x+t}^{101} = 0.01$.

In the at-risk subpopulations, insurance may be purchased at a lower rate if higher premiums may be charged, whether because of family history or a disclosed genetic test result. We suppose that in the larger market, persons charged an extra premium either buy no insurance, or buy insurance at half the normal rate (0.025 per annum), or buy insurance at the normal rate. The former is probably more realistic; in some jurisdictions persons with a family history may be declined, while in other jurisdictions they must be offered a premium but Table 3 makes it clear that it would be extremely high. In the smaller market, we suppose that persons charged an extra premium buy no insurance.

- (c) Rates of Insurance Purchase With Adverse Selection: It is impossible to say what rates of insurance purchase might be given some adverse genetic information. No research has yet been done that shows how elasticity of demand might vary. What we can do is suggest rates of purchase that are higher than normal, up to some extreme level that would give an upper bound to the costs of adverse selection. We therefore suppose:

- (1) that an extreme level of adverse selection in both markets is a rate of purchase of 0.25 per annum; this would result in most people buying insurance within a very few years of receiving adverse information; and
- (2) for sensitivity testing, that a more moderate level of adverse selection is that 'adverse selectors' buy insurance at twice the 'normal' rate (0.10 per annum in the 'large' market and 0.02 per annum in the 'small' market).

4.3 Computation

We followed the methods presented in Macdonald (2001) to calculate the EPVs of benefits, premiums and insurance losses for the different combinations of market size and insurance buying behaviour. These quantities will define the costs of changing underwriting classes and of adverse selection under the various moratoria considered. A force of interest $\delta = 0.05$ was used.

We compute the occupancy probability, tp_x^{ijk} , the probability that a life in state ij (of the i^{th} sub-population) at age x is in state ik at age $x + t$, by solving Kolmogorov's forward equations:

$$\frac{d}{dt} {}_t p_x^{ijk} = \sum_{l \neq k} {}_t p_x^{ijl} \mu_{x+t}^{lk} - \sum_{l \neq k} {}_t p_x^{ijk} \mu_{x+t}^{kl} \quad (3)$$

with boundary conditions ${}_0 p_0^{ijk} = p_i$ if $j = k = 0$, zero otherwise.

A rate of premium must be calculated within each underwriting class. Suppose there are W underwriting classes denoted Φ_1, \dots, Φ_W , each being a collection of insured states (excluding 'CI Event' and 'Dead', see Section 4.4). The rate of premium ρ_x^w payable per unit sum assured at age x in the underwriting class Φ_w is then defined as the weighted average of the intensities from the states in Φ_w to the CI claim state(s) *in the absence of adverse selection*:

$$\rho_x^w = \frac{\sum_{ij \in \Phi_w} {}_x p_0^{i0j} \mu_x^{ij4}}{\sum_{ij \in \Phi_w} {}_x p_0^{i0j}}. \quad (4)$$

This is the 'current cost' method of charging, in which the premium rate paid between ages $x + t$ and $x + t + dt$ is just the expected cost of claims during dt . It is a function of the current age alone (in a Markov model) so while it satisfies the equivalence principle it avoids the problem that level premiums would depend on the age at which insurance was purchased.

With these premium rates, policy values are then computed using Thiele's equations, solving backwards using the fact that the reserve at expiry is zero in all states. If state ij belongs to underwriting class Φ_w then:

$$\frac{d}{dt} {}_t V_x^{ij} = \delta {}_t V_x^{ij} + \rho_{x+t}^w - \sum_{k \neq j} \mu_{x+t}^{ijk} (b_{x+t}^{ijk} + {}_t V_x^{ik} - {}_t V_x^{ij}) \quad (5)$$

where b_{x+t}^{ijk} is the benefit paid on transition from state ij to state ik . We used a Runge-Kutta algorithm with step-size 0.0005 years to solve Kolmogorov's and Thiele's equations.

We calculate the EPV of the loss in this market (discounted benefits minus premiums) with and without adverse selection; normally the latter EPV should be nil. We also calculate the EPV of all the premiums payable in the market with adverse selection present. Then:

$$\frac{\text{EPV}[\text{Loss with adverse selection}] - \text{EPV}[\text{Loss without adverse selection}]}{\text{EPV}[\text{Premiums with adverse selection}]}$$

is the proportion by which all premiums would have to increase to absorb the cost of the adverse selection.

4.4 Moratoria and Underwriting Classes

We study the effect three forms of moratoria on the use of genetic information:

- (a) a moratorium on all genetic test results;
- (b) a moratorium on adverse genetic test results only;
- (c) a moratorium on all genetic test results and family history.

Table 4: Possible underwriting classes with three sub-populations: $i = 1$ not at risk of EOAD; $i = 2$ at risk of EOAD but not PSEN-1 mutation carriers; $i = 3$ at risk of EOAD and PSEN-1 mutation carriers. (T) denotes persons who have had a genetic test and (U) denotes persons who have not.

No.	Genetic Testing Exists?	Factors Allowed in Underwriting?			Composition of Underwriting Classes		
		Negative		Positive	Rated for OR Class	Rated for Family History	Rated for Genetic Test
		Family History	Test Results	Test Results			
1	No	Yes	n/a	n/a	$i = 1$	$i = 2, 3$	
2	Yes	Yes	No	No	$i = 1$	$i = 2, 3$	
3	Yes	Yes	Yes	No	$i = 1$ and $i = 2$ (T)	$i = 3$ and $i = 2$ (U)	
4	Yes	Yes	Yes	Yes	$i = 1$ and $i = 2$ (T)	$i = 2$ (U) and $i = 3$ (U)	$i = 3$ (T)
5	Yes	No	No	No	$i = 1, 2, 3$		

Some moratoria in theory apply to all genetic test results (for example that in the U.K.) but in practice insurers are likely to grant standard rates to persons who have been shown, by a test, to be non-carriers; this is why (a) and (b) above are both considered. Table 4 shows the composition of the underwriting classes under different moratoria.

4.5 Moratoria on Genetic Test Results

Table 5 shows the percentage increases in all premium rates arising from both moderate and severe adverse selection following a moratorium on the use of genetic test results, with family history underwriting allowed, in a CI insurance market operating between ages 20 and 60. The increases are all very small, even with severe adverse selection.

Because these percentage increases are extremely small, appearing as 0% in many cases if rounded to integers, it is sensible to show at least some significant figures. It will eventually be useful to aggregate the costs in respect of different genetic disorders to obtain a global estimate of the effect of adverse selection, and then knowing whether 0% means 0.49% or 0.049% will be useful. For this reason we show three decimal places, but we do not mean thereby to imply unwarranted accuracy.

Premium increases are *lower* if the moratorium applies only to adverse test results. This is because the underwriting class based on family history will then contain a higher proportion of mutation carriers, and the premium charged within that class will increase.

Table 6 shows the premium increases if the rates of onset of EOAD are 50% or 25% of those observed (see Section 2.2). For brevity, we show severe adverse selection only. The effect of moderate adverse selection with the observed rates of onset is about the same as severe adverse selection with the lowest rates of onset.

Although small in absolute terms, these increases result from considering just one gene, with mutation frequency 15 per 100,000, that does not even account for all of

Table 5: Percentage increases in premium rates for CI cover, arising from moderate and severe adverse selections following a moratorium on the use of genetic test results, with family history underwriting allowed, for a market operating between ages 20 and 60.

Adverse Selection	Market Size	Rate of Purchase by Persons Rated-up	Moratorium on using:			
			All test results		Adverse results	
			Female	Male	Female	Male
Moderate	Large	Same as 'normal'	0.003	0.003	0.003	0.003
		Half of 'normal'	0.008	0.007	0.007	0.007
		Uninsured	0.016	0.015	0.015	0.014
	Small	Uninsured	0.016	0.014	0.015	0.014
Severe	Large	Same as 'normal'	0.007	0.006	0.007	0.006
		Half of 'normal'	0.012	0.011	0.012	0.011
		Uninsured	0.021	0.020	0.021	0.019
	Small	Uninsured	0.066	0.060	0.064	0.059

Table 6: Percentage increases in premium rates for CI cover, arising from severe adverse selection following a moratorium on the use of genetic test results, with family history underwriting allowed, for a market operating between ages 20 and 60. EOAD rates of onset 50% and 25% of those observed.

EOAD Onset Rate at	Market Size	Rate of Purchase by Persons Rated-up	Moratorium on using:			
			All test results		Adverse results	
			Female	Male	Female	Male
50%	Large	Same as 'normal'	0.005	0.005	0.005	0.005
		Half of 'normal'	0.010	0.009	0.010	0.009
		Uninsured	0.019	0.018	0.019	0.017
	Small	Uninsured	0.059	0.055	0.057	0.053
25%	Large	Same as 'normal'	0.004	0.003	0.003	0.003
		Half of 'normal'	0.007	0.007	0.007	0.006
		Uninsured	0.014	0.013	0.014	0.013
	Small	Uninsured	0.044	0.041	0.042	0.039

Table 7: Percentage increases in standard premium rates for CI cover, arising from new underwriting classes, moderate and severe adverse selections following a moratorium on the use of genetic test results and family history, for a market operating between ages 20 and 60. Rates of onset of EOAD 100%, 50% and 25% of those observed.

EOAD Onset	Market Rate at	Size	New Underwriting Classes		Moderate Adverse Selection		Severe Adverse Selection	
			Female	Male	Female	Male	Female	Male
			%	%	%	%	%	%
100%	Large	0.118	0.110	0.050	0.047	0.084	0.080	
		0.103	0.094	0.095	0.088	0.549	0.508	
50%	Large	0.102	0.095	0.038	0.035	0.060	0.056	
		0.095	0.085	0.084	0.077	0.429	0.395	
25%	Large	0.077	0.071	0.025	0.024	0.039	0.037	
		0.075	0.067	0.064	0.059	0.301	0.277	

EOAD. It would be unwise to conclude that adverse selection in total would be negligible, until comparable figures are available for more of the major single gene disorders.

4.6 A Moratorium on Genetic Test Results and Family History

Table 7 shows the percentage increases in standard premium rates following a moratorium on the use of genetic test results and family history, for a CI insurance market operating between ages 20 and 60. The increases split into two parts:

- (a) Everyone will have access to insurance on the same terms, including those who would previously have been rated up. If these people just buy insurance at the ‘normal’ rate, and do not buy above-average amounts of cover, the standard premium rate will increase but this cannot be called adverse selection. It is simply because new, more inclusive, underwriting classes have been imposed. The behaviour of those who were previously rated up is not relevant since they were not charged the standard premium rate before. The market size has only a small effect.
- (b) In addition to these increases, adverse selection might occur; in Table 7 we show the effect of moderate and severe levels of adverse selection. Now, the ‘adverse selectors’ includes those with a family history who have not had a genetic test, as well as those who have had an adverse test result. The previous behaviour of those who were rated up before is not relevant here either. The market size now has a very large effect if adverse selection is severe.

We see that just redefining the underwriting class has a larger effect than adverse selection with a moratorium on test results only, and that adverse selection then has a much smaller effect in the larger market, and a similar effect in the smaller market. Bearing in mind

Table 8: Percentage increases in CI premium rates arising from severe adverse selection following a moratorium on the use of genetic test results, with family history underwriting allowed, for a market operating between ages 20 and 60. Rate of genetic testing 0.02 per annum.

Market Size	Rate of Purchase by Persons Rated-up	Moratorium on using:			
		All test results		Adverse results	
		Female %	Male %	Female %	Male %
Large	Same as 'normal'	0.013	0.012	0.012	0.011
	Half of 'normal'	0.022	0.021	0.021	0.020
	Uninsured	0.039	0.037	0.037	0.035
Small	Uninsured	0.120	0.110	0.113	0.104

the rarity of PSEN-1 mutations, this shows that a small CI insurance market may be vulnerable to adverse selection.

4.7 Adverse Selection Extending to Higher Sums Assured

Tables 5 to 7 do not show the effect of 'adverse selectors' opting for larger sums assured. Some jurisdictions have recognised that any tendency, on the part of those with adverse genetic information, to select abnormally high sums assured, is a form of adverse selection that goes beyond any notion of fairness in access to insurance, and have imposed ceilings on any moratorium, above which genetic test results may be taken into consideration. In the U.K., for example, from 2001 these ceilings are £500,000 for life insurance and £300,000 for CI insurance.

To investigate the impact of an increase in sum assured of the at risks, we doubled and quadrupled the sum assured purchased by 'adverse selectors'. As expected, the results were to double and quadruple the premium increases shown in Tables 5 to 7, so we omit the details.

4.8 The Rate of Genetic Testing

We chose a rate of genetic testing of 0.01 per annum, consistent with a low demand for testing, confined to a clinical setting. We doubled this to 0.02 per annum. The effect, given a moratorium on the use of genetic test results and family history were negligible, as expected because the genetic risk has no effect on access to insurance. The premium increases under the moratoria on use of genetic test results alone are shown in Table 8. The premium increases are roughly twice those shown before, and still very small.

5. A MODEL OF EOAD AND LIFE INSURANCE

5.1 The Model

In Section 2.3, we found that probabilities of survival after onset of EOAD depend on duration since onset as well as age. Therefore a Markov model is inappropriate: Figure 6 shows a semi-Markov model for a person in the i^{th} of several subpopulations.

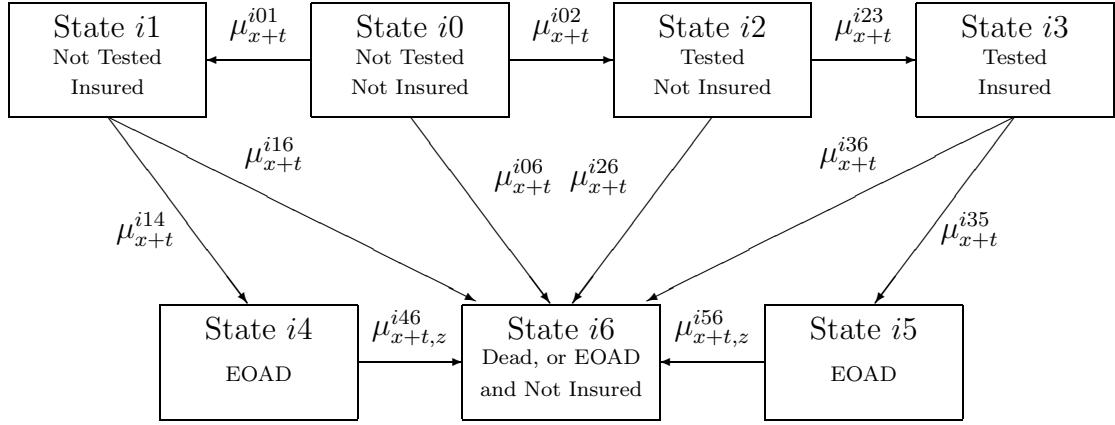


Figure 6: A semi-Markov model of genetic testing, insurance purchase and life insurance events for a person in the i^{th} subpopulation. z is duration since onset of EOAD.

- (a) There are two states representing onset of EOAD while insured, $i4$ and $i5$. This is because the sum assured could depend on knowledge of a genetic test result, either because of adverse selection among mutation carriers, or the offer of ordinary rates to non-carriers who have been tested.
- (b) Transitions from the states $i4$ and $i5$ may depend on both age and duration. We need to define appropriate probabilities, first for transitions into these states; for $j \neq 4, 5$, $k = 4, 5$:

$${}_{z,t}p_x^{ijk} = P[\text{In state } ik \text{, duration } z \text{ at age } x + t \mid \text{In state } ij \text{ at age } x] \quad (6)$$

and then for surviving after entering them; for $k = 4, 5$:

$$tp_{x,z}^{ikk} = P[\text{In state } ik \text{ at age } x + t \mid \text{In state } ik \text{, duration } z \text{ at age } x]. \quad (7)$$

- (c) Onset of EOAD while uninsured removes the person from the insurance market, which we represent by transition into the absorbing state, which is now labelled ‘Dead, or EOAD and Not Insured’. We could define a separate absorbing state for this event but that is unnecessary.

Using the equivalence principle, the rate of premium payable at age $x + t$ for a unit sum assured, in a given underwriting class, should be the weighted average intensity into ‘dead’ states from the insured states in that underwriting class, in the absence of adverse selection. Let Φ_w^N and Φ_w^E be the insured states in the w^{th} underwriting class, containing non-EOAD and EOAD states respectively. Then the rate of premium is:

$$\rho_{x+t}^w = \frac{\sum_{j \in \Phi_w^N} tp_x^{i0j} \mu_{x+t}^{ij6} + \sum_{j \in \Phi_w^E} \int_0^t z, t p_x^{i0j} \mu_{x+t+z, z}^{ij6} dz}{\sum_{j \in \Phi_w^N} tp_x^{i0j} + \sum_{j \in \Phi_w^E} \int_0^t z, t p_x^{i0j} dz}. \quad (8)$$

We can compute the integrals in Equation (8) using (for example):

$$z, t p_x^{i04} dz = {}_{t-z} p_x^{i01} \mu_{x+t-z}^{i14} {}_z p_{x+t-z, 0}^{i44} dz = {}_{t-z} p_x^{i01} \mu_{x+t-z}^{i14} \exp \left(- \int_0^z \mu_{x+t-z+r, r}^{i46} dr \right) dz \quad (9)$$

for state $i4$, and similarly for state $i5$.

For the purpose of computing the reserves in Thiele's equations (Equation (5)), we can exploit the particular form of the model in Figure 6, and bring it back within a Markov framework. Instead of setting up the reserve ${}_{t,0} V_x^{i4}$ or ${}_{t,0} V_x^{i5}$ on onset of EOAD at age $x+t$ (in the obvious notation), and then later paying the sum assured on death, we pay sums assured ${}_{t,0} V_x^{i4}$ or ${}_{t,0} V_x^{i5}$ on entering states $i4$ or $i5$, respectively, and the normal sum assured on death while in states $i1$ or $i3$. In other words, in Equation (5) put $b_{x+t}^{i14} = {}_{t,0} V_x^{i4}$ and $b_{x+t}^{i35} = {}_{t,0} V_x^{i5}$, and $b_{x+t}^{i46} = b_{x+t}^{i56} = 0$. These sums assured depend on age alone, and the duration dependent intensities are redundant. Of course, this trick would not work for more complex models, or for second and higher moments.

For a policy with unit sum assured, entry age x and term n years, and if state ij belongs to underwriting class Φ_w , we have:

$${}_{t,0} V_x^{ij} = \int_0^{n-t} e^{-\delta z} {}_z p_{x+t, 0}^{ijj} (\mu_{x+t+z, z}^{ij6} - \rho_{x+t+z}^w) dz \quad j = 4, 5 \quad (10)$$

and we can easily write down similar expressions for computing the EPVs of level benefits and premiums.

5.2 Parameterisation

The parameterisation is the same as in Section 4.2, with one addition: mortality rates in non-EOAD states are those of the English Life Tables No. 15, and mortality rates after onset of EOAD are as described in Section 2.3.

6. PREMIUM RATINGS FOR LIFE INSURANCE

6.1 Life Insurance Premiums Based on Known PSEN-1 Mutations

Table 9 shows level premiums for level life insurance cover for female and male PSEN-1 mutation carriers, based on estimated EOAD onset intensities of 100%, 50% and 25% of those fitted to the observed data. The premiums are payable continuously and expressed as percentages of the 'standard' premium rate.

- (a) Because of their lower mortality in general, premium increases are markedly higher for females, especially for cover expiring at later ages, and the higher rates of onset of EOAD.
- (b) The increases are lower than those for CI insurance, except for cover expiring at age 30.
- (c) In many cases, notably with the lower rates of onset of EOAD, the increased premiums are mostly less than 500% of standard rates which is about the limit for an offer of cover in practice. Therefore unless the highest penetrance estimates turn out to be well-founded, terms could be offered to most people with a known PSEN-1 mutation. Again, the fact that PSEN-1 mutations are believed to be associated with aggressive EOAD suggests that this conclusion should hold for familial EOAD in general.

6.2 Life Insurance Premiums Based on Family History of EOAD

Table 10 shows level premiums for level life insurance cover based on a family history of EOAD known to be associated with PSEN-1 mutations, expressed as percentages of the 'standard' premium rate.

- (a) For life cover expiring at age 30, extra premiums may not be needed, especially with the lower rates of onset of EOAD.
- (b) For life cover commencing at age 50, extra premiums of 50% or less could be offered.
- (c) For almost all ages and policy terms, the increased premiums are less than 500% of the standard, so terms could be offered within current practice.

7. THE POTENTIAL COSTS OF ADVERSE SELECTION IN LIFE INSURANCE

7.1 Moratoria and Underwriting Classes

The model of Figure 6 is extended to a model of three subpopulations just as in Figure 5, and we consider exactly the same moratoria and underwriting classes as in Section 4.4. We use the same rates of insurance purchase and genetic testing as for CI insurance, though here it is the larger market that is most relevant.

7.2 Moratoria on Genetic Test Results

Table 11 shows the percentage increases in standard life insurance premium rates arising from moderate and severe adverse selections following a moratorium on the use of genetic test results with family history underwriting allowed, for a market operating between ages 20 and 60. All are less than 0.1%, and may be regarded as negligible if PSEN-1 is taken alone. Table 12 shows the premium increases as a result of severe adverse selection with rates of onset of EOAD of 50% and 25% of those observed.

7.3 Moratorium on All Genetic Test Results and Family History

Table 13 shows the percentage increases in standard life insurance premium rates arising from new underwriting classes, and moderate and severe adverse selection in addition, following a moratorium on the use of genetic test results and family history. The results and conclusions are similar to those in respect of CI insurance: the only noticeable increases result from severe adverse selection in a small market with the highest rate of onset.

Table 9: Level net premiums for level life cover with known PSEN-1 mutations, as a percentage of the standard level premiums.

EOAD Onset	Rate at	Entry Age	Females				Males			
			Term (Years)				Term (Years)			
			10	20	30	40	10	20	30	40
100%		20	177.56	835.96	1,617.25	1,400.08	130.17	443.26	905.35	817.54
		30	1,109.99	2,099.51	1,735.59		668.22	1,314.64	1,078.53	
		40	1,469.02	1,679.81			971.14	1,057.05		
		50	898.53				556.86			
50%		20	138.87	484.54	1,004.96	1,014.61	115.12	279.30	579.71	602.17
		30	626.79	1,270.33	1,213.76		396.30	810.13	763.14	
		40	891.78	1,171.67			603.19	746.59		
		50	614.17				392.65			
25%		20	119.46	296.68	599.65	673.58	107.57	191.69	364.64	413.59
		30	369.15	738.72	781.26		251.37	487.28	504.06	
		40	528.31	745.76			371.98	488.39		
		50	397.28				268.61			

Table 10: Level net premiums for level life cover for persons with family histories of known PSEN-1 mutations, as a percentage of the standard level premiums.

EOAD Onset	Rate at	Entry Age	Females				Males			
			Term (Years)				Term (Years)			
			10	20	30	40	10	20	30	40
100%		20	138.77	466.03	836.79	709.51	115.08	270.73	491.25	436.91
		30	592.90	1,031.90	812.54		377.33	666.48	527.38	
		40	577.56	581.61			404.12	393.07		
		50	154.77				131.51			
50%		20	119.43	291.75	545.17	539.04	107.56	189.41	336.04	341.32
		30	358.03	658.68	607.96		245.14	439.13	402.98	
		40	380.73	447.86			278.49	310.53		
		50	136.50				120.85			
25%		20	109.73	198.20	347.67	380.10	103.78	145.78	231.20	253.24
		30	232.09	409.21	420.92		174.29	287.52	290.55	
		40	253.34	319.56			197.40	232.31		
		50	121.62				112.29			

Table 11: Percentage increases in life insurance premium rates arising from moderate and severe adverse selections, following a moratorium on the use of genetic test results, with family history underwriting allowed, for a market operating between ages 20 and 60.

Adverse Selection	Market Size	Rate of Purchase by Persons Rated-up	Moratorium on using:			
			All test results		Adverse results	
			Female %	Male %	Female %	Male %
Moderate	Large	Same as 'normal'	0.004	0.002	0.004	0.002
		Half of 'normal'	0.008	0.005	0.008	0.005
		Uninsured	0.017	0.010	0.016	0.010
Severe	Small	Same as 'normal'	0.008	0.005	0.008	0.005
		Half of 'normal'	0.014	0.008	0.013	0.008
		Uninsured	0.024	0.014	0.023	0.014
		Uninsured	0.073	0.044	0.070	0.042

7.4 Adverse Selection Extending to Higher Sums Assured

As for CI insurance, the premium increases if 'adverse selectors' opt for higher than average sums assured are proportionate to the level of sum assured they choose, relative to the average.

7.5 Increasing the Rate of Genetic Testing

Increasing the rate of genetic testing to 0.02 per annum had exactly the same effects as in Section 4.7.

8. CONCLUSIONS

8.1 Epidemiology and Models

In this paper we have carried out the further research suggested in Gui & Macdonald (2002), applying the results of that investigation of the epidemiology of EOAD to life insurance and CI insurance. In so doing, we have obtained new estimates of rates of survival after onset of EOAD, associated with PSEN-1 gene mutations. These are duration-dependent, so the previous modelling framework from (for example) Gutiérrez & Macdonald (2001) has been extended to semi-Markov models.

A significant problem of genetic epidemiology is ascertainment bias; rates of onset may be based on families selected because of the severity of the condition, and may be significantly overstated. We allowed for this by using rates of onset that were 100%, 50% and 25% of those fitted to the data. In some cases these differences affected the conclusions.

Together with Gui & Macdonald (2002), this paper shows that it is possible, with the help of good published pedigree data, to model the likely impact on insurance of

Table 12: Percentage increases in life insurance premium rates arising from severe adverse selection following a moratorium on the use of genetic test results, with family history underwriting allowed, for a market operating between ages 20 and 60. EOAD rates of onset 50% and 25% of those observed.

				Moratorium on using:			
EOAD		Market	Rate of Purchase by	All test results	Adverse results		
Onset	Rate at	Size	Persons Rated-up	Female	Male	Female	Male
50%	Large		Same as 'normal'	0.006	0.004	0.006	0.003
			Half of 'normal'	0.010	0.006	0.010	0.006
			Uninsured	0.019	0.011	0.018	0.010
	Small		Uninsured	0.057	0.034	0.054	0.032
			Same as 'normal'	0.004	0.002	0.004	0.002
			Half of 'normal'	0.007	0.004	0.006	0.004
			Uninsured	0.012	0.007	0.011	0.007
	25%		Uninsured	0.037	0.022	0.034	0.020

Table 13: Percentage increases in standard life insurance premium rates arising from new underwriting classes and severe adverse selection following a moratorium on the use of genetic test results and family history, for a market operating between ages 20 and 60.

EOAD	Onset	Market	New		Moderate		Severe	
			Underwriting		Adverse		Adverse	
			Classes	Selection	Selection	Selection	Female	Male
100%		Large	Female	Male	Female	Male	Female	Male
			%	%	%	%	%	%
50%		Large	0.147	0.084	0.061	0.036	0.103	0.062
			0.126	0.072	0.112	0.067	0.657	0.396
25%		Large	0.115	0.065	0.043	0.026	0.070	0.042
			0.103	0.058	0.089	0.053	0.477	0.286
		Small	0.077	0.043	0.027	0.016	0.043	0.025
			0.070	0.039	0.060	0.036	0.307	0.183

information relating to a specific genetic disorder, from the perspectives of both the individual and the insurer. They also, together, show that this can be quite an extensive undertaking.

8.2 Premium Ratings

Our conclusions regarding premium ratings are different for CI and life insurance.

- (a) CI insurance premium increases implied by known PSEN-1 mutations or a family history of PSEN-1 mutations were extremely high, even with the reduced rates of onset. Only in a few cases would the premium fall within the limits currently offered.
- (b) Life insurance premium increases, on the other hand, were only outside the limits currently offered if a PSEN-1 mutation was confirmed by a genetic test, and given the highest rates of onset. With a few exceptions, terms could be offered otherwise, in particular if only a family history were known.

8.3 Adverse Selection

It is difficult to draw firm conclusions about the costs of adverse selection, should one of various kinds of moratorium be imposed. The reason is that the cost, in terms of premium increases, appears to be negligible except in the case of small markets, extreme behaviour on the part of 'adverse selectors' and high rates of onset of EOAD. In this respect our conclusions were the same for CI and life insurance, except that our models of the smaller and larger markets may be more appropriate for CI and life insurance, respectively. However we have only considered here one very rare disorder, whereas a moratorium would apply to all genetic disorders. Except in those extreme cases where this work by itself suggests that adverse selection could be a problem, we should regard the premium increases arising from adverse selection as one part of a program that should be extended to cover all the major late-onset single-gene disorders.

8.4 Implications for Policy

Interest in the United Kingdom centres on the reformed Genetics and Insurance Committee (GAIC). Until 2001, GAIC had a rather narrow remit to consider applications from insurers to be allowed to use genetic test results in certain circumstances. Considerations such as the possible effect of adverse selection if test results were ignored, and the appropriate levels of premium rates if they were used, fell outside its remit. Following a report of the Human Genetics Commission in 2001, GAIC is to be reconstituted with a much broader remit, possibly covering exactly the kind of questions addressed here. Since PSEN-1 is one of the genes identified as being significant for insurers by the ABI, it is possible that research such as this will be needed to inform the policy-making process, in the U.K., through GAIC.

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APPENDIX
THE CRITICAL ILLNESS INSURANCE MODEL

Gutiérrez & Macdonald (2001) obtained the following model for CI insurance based on medical studies and population data. Full references can be found in that paper.

(a) Rates of onset were found for:

(1) *Cancer (excluding non-malignant skin cancers)*: For males:

$$\begin{aligned}\mu_x^c &= \exp(-11.25 + 0.105x) \quad (x < 51) \\ \mu_x^c &= \exp(0.2591585 - 0.01247354x + 0.0001916916x^2 - 8.952933 \times 10^{-7}x^3) \quad (x \geq 60)\end{aligned}$$

with linear interpolation between ages 51 and 60, and for females:

$$\begin{aligned}\mu_x^c &= \exp(-10.78 + 0.123x - 0.00033x^2) \quad (x < 53) \\ \mu_x^c &= -0.01545632 + 0.0003805097x \quad (x \geq 53).\end{aligned}$$

(2) *Heart Attack*: For males:

$$\begin{aligned}\mu_x^h &= \exp(-13.2238 + 0.152568x) \quad (x < 44) \\ \mu_x^h &= (-0.01245109 + 0.000315605x) \quad (x > 49)\end{aligned}$$

with linear interpolation between ages 44 and 49, and for females:

$$\mu_x^h = \left(0.598694 \left(\frac{0.15317^{15.6412} \exp(-0.15317x)x^{14.6412}}{\Gamma(15.6412)} \right) \right).$$

(3) *Stroke*: For males:

$$\mu_x^s = \exp(-16.9524 + 0.294973x - 0.001904x^2 + 0.00000159449x^3)$$

and for females:

$$\mu_x^s = \exp(-11.1477 + 0.081076x).$$

- (b) 28-day survival factors for heart attack and stroke victims were taken from Dinani *et al.* (2000) (this relates to the common contractual condition, that payment depends on surviving for 28 days). Let p_x^h and p_x^s be the 28-day survival probabilities after the first-ever heart attack or stroke, respectively, and $q_x^h = 1 - p_x^h$, $q_x^s = 1 - p_x^s$ the corresponding mortality rates. From Dinani *et al.* (2000), $q_x^h = 0.21$ at ages 20–80 for females, and q_x^h for males is given in Table 14. From the same source, $p_x^s = (0.9 - 0.2x)/0.9$ for both males and females.
- (c) Other minor causes of CI insurance claims amount to about 15% of those arising from cancer, heart attack and stroke. Therefore the aggregate rate of CI claims is:

$$\mu_x^{CI} = 1.15(\mu_x^c + p_x^h \times \mu_x^h + p_x^s \times \mu_x^s).$$

Table 14: 28-Day mortality rates ($q_x^h = 1 - p_x^h$) following heart attack. Based on Dinani *et al.* (2000).

age	q_x^h	age	q_x^h	age	q_x^h	age	q_x^h
20–39	0.15	47–52	0.18	58–59	0.21	65–74	0.24
40–42	0.16	53–56	0.19	60–61	0.22	75–79	0.25
43–46	0.17	57	0.20	62–64	0.23	80+	0.26

(d) Population mortality rates (English Life Tables No. 15) were adjusted to exclude deaths which would have followed a CI insurance claim.