THE IMPACT OF GENETIC INFORMATION ON THE INSURANCE INDUSTRY: CONCLUSIONS FROM THE 'BOTTOM-UP' MODELLING PROGRAMME

BY

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ABSTRACT

We quantify the overall impact of genetic information on the insurance industry using the 'bottom-up' approach, in which detailed models are constructed of representative major genetic disorders. We consider six such disorders, namely adult polycystic kidney disease, early-onset Alzheimer's disease, Huntington's disease, myotonic dystrophy (MD), hereditary non-polyposis colorectal cancer; and breast/ovarian cancer. Actuarial models based on the epidemiological literature exist for all these except MD. We parameterise a suitable model of MD, then synthesize the results from all six models to estimate the adverse selection costs arising from restrictions on insurers' use of genetic information. These are all very small, only in the most extreme cases rising above 1% of premiums. In the worst case — females displaying 'extreme' adverse selection in a 'small' critical illness insurance market, with the use of family history banned — the cost is about 3% of premiums. Our model includes the most common single-gene disorders relevant to insurance, and includes representatives of most important classes of these disorders. While the 'bottom-up' approach could be continued by modelling more and more diseases, we suggest that our model is adequate to draw robust conclusions.

KEYWORDS

Adverse Selection; Critical Illness Insurance; Family History; Genetic Tests; Life Insurance; Single-Gene Disorder.

1. INTRODUCTION

Since the development of genetic tests in the 1990s, the possible use of genetic information by insurers has been contentious. The actuarial input to this discussion has been to suggest modelling approaches that in some way quantify the financial risks involved. The financial risk faced by individuals is of being charged unaffordable premiums, or denied cover. The financial risk faced by

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insurers is that adverse selection may appear if they may not use genetic information known to the applicant. Some definitions of 'genetic information' include family histories. In this paper, we focus on the possible costs of adverse selection arising in this way.

Two main approaches have been suggested. The 'top-down' approach (Macdonald, 1997, 1999, 2003b) is to make exaggerated assumptions about the prevalence and severity of genetic disorders likely to affect insurers. If the resulting costs are small, the problem does not seem uncontrollable. Otherwise, however, we need the more refined 'bottom-up' approach of modelling individual disorders, until a representative estimate of costs can be obtained. This is a substantial programme of work, which has been pursued in many papers, referred to in later sections. Our aim is to summarize and synthesize this work, with the addition of a new model of myotonic dystrophy (MD) in order to draw the first substantial overall conclusions from the 'bottom-up' approach.

We focus on the cost of adverse selection caused by moratoria on the use of genetic information in the critical illness (CI) and life insurance markets. In Section 2, we briefly introduce the issues related to genetics and insurance. Section 3 discusses the selection of disorders to include in the model. In Section 4, we reprise a CI market model and the methodology of calculating the cost of adverse selection. In Section 5, we calculate the costs of adverse selection, measured as increases in premium rates, under various moratoria. A life insurance market model, and costs of adverse selection in a life insurance market are presented in Sections 6 and 7, respectively. Our conclusions are given in Section 8. The new study of MD is in the Appendix

CI insurance, which is also known as dread disease insurance, is widely sold in the United Kingdom and elsewhere. At its simplest, it pays a lump sum on the occurrence or diagnosis of a specified serious illness, such as heart attack, stroke or cancer, known as a CI event. This is known as 'stand-alone' CI insurance. It may also be sold as a rider to a life insurance contract, known as 'accelerated benefits', paying out on the earlier of a CI event or death. In fact, the great majority of contracts sold in the UK are accelerated benefits, but we focus on stand-alone CI insurance, chiefly because it is simpler. A model of standalone CI insurance requires onset rates of CI events, while a model of accelerated benefits also requires survival rates after the occurrence of a CI event.

2. Background

2.1. The Right to Underwrite and Adverse Selection

Concerns about genetics, from both insurers and individuals, began to emerge in the mid-1990s, and are conveniently summarized in HGAC (1997). The different viewpoints amount to a clash between two basic principles, namely solidarity and mutuality. Solidarity is exemplified, in the UK, by the National Health Service, in which everybody is included and is treated equally, and payment is compulsory (through taxation, though other mechanisms exist). Mutuality is

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exemplified by life insurance, which everyone has the option, but no obligation, to buy. The life insurance company can charge premiums related to individual risk, and also has the option to deny cover on reasonable grounds.

The insurer's 'right to underwrite' can affect the affordability of insurance. Individuals may then be wary of acquiring information that, if it had to be disclosed to an insurer, would greatly increase the cost of insurance. An extreme example, possibly second only to knowledge of an existing disorder, is a genetic test that reveals an exceptionally high risk of suffering a serious disease in the future. The use of such test results by insurers is often called 'genetic discrimination', and is described as leading to the creation of an uninsurable 'genetic underclass'. These concerns could deter people from taking genetic tests and this could delay their receiving treatment.

The insurance industry is concerned about the possibility of adverse selection, which arises when customers have better information about their health risks than has the insurer. Thus if an adverse genetic test result, a very significant risk factor, can be withheld from the insurer, the applicant may obtain cover for a fraction of the true cost. The insurer will have to make up this loss by raising premiums generally. Simple economic principles tell us that some lower-risk individuals will reduce their cover, raising premiums yet again, and so on into an 'adverse selection spiral'. At the extreme, the viability of the market could be threatened.

However, we can refine our consideration of the points above, which will narrow down greatly the practical problem of quantifying them.

(a) With rare exceptions, the only genetic disorders likely to affect long-term insurance are those in which symptoms develop in the middle years of life, called 'late-onset disorders'. Thus, a person remains healthy for long enough to buy insurance, and suffers onset or dies during the term of the insurance. This rules out most recessive disorders, which tend to manifest themselves early in life. The class of late-onset dominantly inherited disorders, although extensive in its variety, affects a very small proportion of the population.
(b) So far — although this could change — genetic testing is usually undertaken because there is already reason to suspect that an inherited factor is present. In the case of late-onset dominantly inherited disorders, the reason is often the presence of a family history of the disorder. Most such disorders involve defects in a single gene.
(c) Disorders that can be treated effectively pose no great threat to life insurance, although they might to critical illness (CI) insurance.
(d) The great majority of the genetic contribution to disease is expected to be complex, involving networks of many genes interacting with environment and lifestyle. Research, especially epidemiological research, is at an early stage. However, we have no strong reason to suppose that genetic tests for such contributions ('disorders' may be too strong a word) will have predictive value exceeding that of uncontroversial risk factors in use today, such as blood pressure and cholesterol levels.

Therefore, the disputed ground is quite small, being confined to rare, severe, late-onset, single-gene, dominantly inherited disorders, lacking completely effective treatments. In 1996, the genetics advisor of the Association of British Insurers (ABI), Professor A J Raeburn, drew up a list of eight disorders that, at the time, seemed to cover most relevant disorders. They were:

(a) two untreatable brain disorders, Huntington's disease (HD) and early-onset Alzheimer's disease (EOAD);
(b) a degenerative disorder of the motor system, hereditary motor and sensory neuropathy (HMSN);
(c) three rare inherited variants of cancers; breast/ovarian cancer (BC/OC), a colonic cancer, familial adenomatous polyposis (FAP), and a cancer of the endocrine system, multiple endocrine neoplasia type 2 (MEN2);
(d) a degenerative muscular disorder, myotonic dystrophy (MD);
(e) a degenerative kidney disorder, adult polycystic kidney disease (APKD).

APKD was quickly dropped from the list, because it is usually diagnosed by ultrasound rather than by genetic testing. However, in his evidence in response to a discussion paper from the Human Genetics Commission (HGC, 2000) Professor Raeburn stated that hereditary non-polyposis colorectal cancer (HNPCC) was likely to be the next disorder in respect of which the ABI would research the insurance implications (Raeburn, 2000).

We discuss the selection of disorders to include in a model in Section 3.

2.2. Moratoria and Adverse Selection

Different countries have taken different approaches to regulating insurers' use of genetic information, sometimes in respect of particular products. In the U.K., since 1996 this has taken the form of a voluntary moratorium on the part of the ABI, later strengthened into a concordat between the ABI and relevant government departments. In its current form, the main features are as follows:

(a) Genetic tests are narrowly defined to mean direct examination of DNA or chromosomes.
(b) Insurers will not use genetic test results obtained as a result of participation in research.
(c) Insurers will not use genetic test results for life insurance policies with sums assured below £500,000, or CI or income protection insurance (IPI) with sums assured below £300,000 (the 'sum assured' under an IPI policy is a matter for interpretation).
(d) For policies with sums assured exceeding the limits above, insurers will use genetic test results only if they have been approved for such use in respect of that type of policy. Until 2009, the approval process required the ABI to submit evidence of the technical, clinical and actuarial relevance of the test to a quasi-governmental body called the Genetics and Insurance Committee (GAIC). GAIC was disbanded in 2009 and a new approval process is not yet in place.

We will refer to all similar arrangements as 'moratoria', whether they are voluntary arrangements or mandatory bans. We consider three types of moratorium. All of them rule out the use of adverse genetic test results, the differences lie in what else is ruled out.

(a) The simplest moratorium bans the use of adverse genetic test results only. A favourable 'clear' test result, showing the risky mutation to be absent, may be used to the applicant's benefit. Family history may be used. The moratorium in the UK is of this form.
(b) A moratorium may ban the use of all genetic test results, while still allowing family history to be used. Thus a clear test result cannot override the presence of a family history.
(c) A moratorium may extend to the use of family history, as well as all genetic test results. The moratorium in Sweden is of this form.

Each type of moratorium introduces a different risk of adverse selection. Our aim is to quantify that risk.

3. Selection of Genetic Disorders for Inclusion in a Model

The number of human disorders linked to dominantly inherited single genes is about 200 (Pasternak, 1999). Ideally we would include in the model all those that met the criteria to be relevant for long-term insurance (Section 2.1), for which Professor Raeburn's list for the ABI, with the addition of HNPCC, would seem to be a good starting point.

An important factor, however, is our reliance on published epidemiology. We usually have no access to data with which to estimate disease onset rates associated with particular mutations, nor rates of mortality after onset. Only if these have been estimated and described in sufficient detail can we parameterise an actuarial model. The problems this causes have been discussed in Macdonald (2003a).

Including the study of MD undertaken in this paper, the actuarial models available to us are described in the papers cited in Table 1. These are the disorders we include in the overall model. Note the following.

(a) Two of the disorders in Professor Raeburn's list were considered and eliminated as being of little relevance; MEN2 in Gui (2003) and FAP in MacCalman (2009). In both cases, the reason was that detection and treatment at very early ages — often before the purchase of life insurance would be considered — leads to an excellent prognosis.
(b) We include APKD, although it was dropped from Professor Raeburn's original list. APKD causes cysts to appear in the kidneys, usually by age 30. These lead to kidney failure years later, and it is the latter that triggers a CI insurance claim or, depending on the treatment available, a life insurance claim. The cysts are reliably detectable using ultrasound, and DNA-based

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TABLE 1

THE SIX GENETIC DISORDERS MODELLED, THE GENES IMPLICATED AND REFERENCES

Genetic Disorders	Mutations	Reference
APKD	APKD1 and APKD2	Gutiérrez & Macdonald (2003, 2007)
EOAD	PSEN-1	Gui & Macdonald (2002) Espinosa & Macdonald (2007) Gui (2003)
HD	Huntingtin gene (HTT)	Gutiérrez & Macdonald (2004) MacCalman (2009)
MD	DMPK gene	presented in the Appendix
HNPCC	MLH1 & MSH2	Lu *et al.* (2007)
BC & OC	BRCA1 & BRCA2	Macdonald, Waters & Wekwete (2003a, 2003b) Gui *et al.* (2006)

genetic tests are not generally used. However, an ultrasound test that reliably diagnoses APKD is certainly a genetic test, just not DNA-based, so to exclude it would be more a reflection of the ABI's narrow definition of 'genetic test' than of biology. Also, if a moratorium excluded the use of family histories, a family history of APKD would certainly be covered.

(c) APKD is caused by mutations in either of two genes, APKD1 or APKD2. Their epidemiology (prevalence and penetrance) is substantially different. We use the models fitted by Gutiérrez & Macdonald (2007). Post-onset mortality (meaning after end-stage renal disease or kidney failure) depends on the availability of kidneys for transplantation. Gutiérrez & Macdonald considered four scenarios, but for simplicity we choose just one, namely that the transition intensity between pre-transplant and post-transplant states is 0.05 *per annum*.

(d) EOAD is caused by mutations in any of three genes, Presenilin-1 (PSEN1), Presenilin-2 (PSEN2) or the Amyloid Precursor Protein gene (APP). PSEN2 and APP mutations are very rare; their associated onset rates were considered in Gui (2003) on the basis of negligible amounts of data and are not considered here. Onset rates in respect of PSEN1 mutations were estimated by Gui & Macdonald (2002) and, with improved methods, by Espinosa & Macdonald (2007). We use the latter. Lifetime penetrance was a free parameter in their model, and we have assumed it to be 0.8. Post-onset mortality rates are taken from Gui (2003).

(e) HD is caused by mutations in the Huntingtin gene. The mutation takes the form of an expanded number of repeats of the trinucleotide CAG, larger numbers being associated with significantly earlier onset. Gutiérrez & Macdonald (2004) modelled the effect of CAG repeat length, but for our purposes a simpler model that averages this effect out is sufficient. MacCalman (2009) fitted Normal distributions to age-at-onset (a very

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common assumption for HD) and we use her estimates with mean about 45 years and variance about 14.5 years (the exact estimates in MacCalman (2009) were 45.038543 and 14.516176 years respectively). Post-onset mortality rates were taken from Gutiérrez & Macdonald (2004). These authors used an accelerated lifetime model applied to the post-onset mortality rates to represent the timing of a CI claim, which may be assumed to occur some time between onset and death. Harper (1996) suggested a qualitative model for the progress of HD, proceeding through three stages. The accelerated lifetime model represents CI claims being paid when the disease reaches Harper's stage 2 or stage 3, with a median time to claim of 1/3 or 2/3, respectively, of the median survival time. Since the former is more conservative, we have used that assumption.

(f) MD is described in detail in the Appendix. Like HD, it is caused by a trinucleotide expansion, in this case of a CTG sequence. We will consider two cases separately, as if they were different mutations: not more than 250 CTG repeats (denoted 250-) and more than 250 CTG repeats (denoted 250+). Also like HD, MD is progressive and a CI claim would be likely to be admitted some time between onset and death. In this case there is no suggestion that progression falls into clear stages, but we have used the same accelerated lifetime model applied to post-onset survival rates, parameterising it so that the mean time from onset to a claim is 1/3 of the mean survival time.

(g) HNPCC is caused by mutations in any of several genes, of which two, MLH1 and MSH2, account for 90% of cases. Mutations in the same genes are also associated with other cancers, in particular of the endometrium in women. We therefore take onset rates for HNPCC, endometrial cancer and other extra-colonic cancers from Lu *et al.* (2007). Post-onset mortality rates are taken from Yu (2010, Chapter 3). Note that HNPCC is a promising target for screening programs and early intervention, possibly leading to a substantial reduction in mortality, see Macdonald & Yu (2010). Since we ignore this, costs associated with HNPCC may be too high.

(h) Inherited variants of BC and OC may be caused by mutations in either of the BRCA1 or BRCA2 genes. However, these do not account for all familial clustering, and recent research suggests that a number of other genes, each individually of smaller effect, play a significant part. We ignore the latter, which again may have the effect of overstating costs. Onset rates and post-onset mortality rates are taken from Gui *et al.* (2006).

HNPCC and BC/OC differ from the other disorders above in one important respect: they are inherited variants of otherwise common diseases, while the others have no known cause except mutations in the relevant genes. Thus, a family history of APKD, EOAD, HD or MD shows conclusively that a mutation 'runs in the family'. A similar family history of colorectal cancer or of BC/OC admits the possibility that it is a chance event with no involvement of gene mutations.

Each of the studies cited above addressed two questions: what is the cost of insuring mutation carriers? and what is the potential cost of adverse selection?

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The answers to the second question bore the caveat that no broader conclusions could be drawn about the cost of adverse selection, because disorders were considered one at a time. Our aim is to remove that caveat.

4. Critical Illness Insurance Market Models

A moratorium (see Section 2.2) forces applicants with different levels of risk into the same underwriting class. In this case, applicants knowing their increased level of risk might buy more insurance, and a premium set according to the average risk in the underwriting class will not be sufficient to cover the actual claims. Insurers would have to increase the premium rate in order to recover the loss caused by the behaviour of 'adverse selectors'. The increase in the premium rate is the cost of adverse selection, which will depend on the type of insurance, the size of the market for that insurance and the form of moratorium imposed, as well as on the epidemiology of each genetic disorder of interest.

Figure 1 shows a CI insurance market model, capturing the following features: insurance purchasing behaviour, development of a family history, and genetic testing. It is a continuous-time, discrete-state Markov model, parameterised by the transition intensities. We assume that genetic testing is only undertaken if a family history indicates that it may be relevant. Once insurance has been purchased, the acquisition of more genetic information is deemed irrelevant.

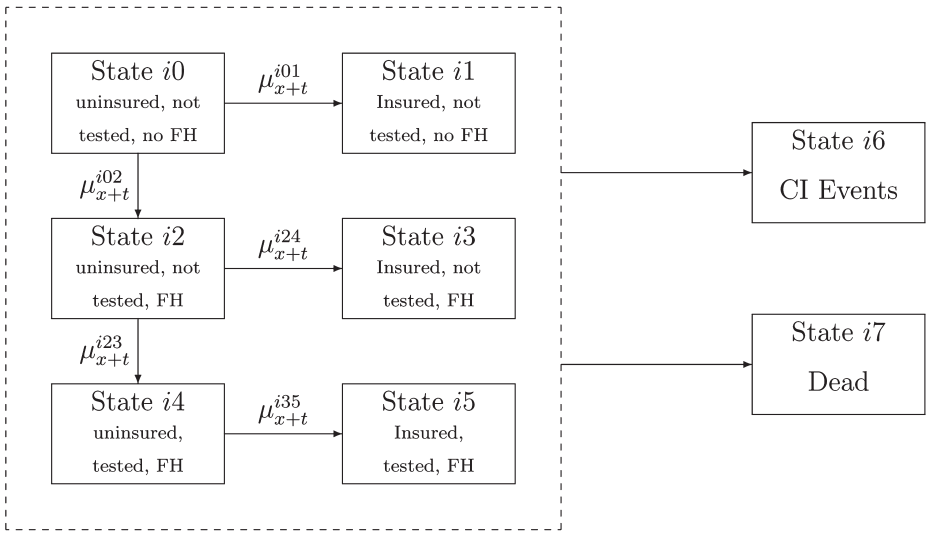

Figure 1: A Markov model of family history, genetic testing, insurance purchase and CI insurance events for a person in the i^{th} risk subpopulation (FH = family history present).

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In the ith risk subpopulation, μ_{x+t}^{ijk} is the transition intensity between states ij and ik ($j \neq k$) at age $x + t$, and we define:

$$ {}_tp_x^{ijk} = \mathrm{P}[\text{In state } ik \text{ at age } x + t \mid \text{In state } ij \text{ at age } x]. $$

The risk subpopulations are defined by the six genetic disorders, plus the great majority who are not affected. For APKD, EOAD, HD and MD, family history (which we assume here to mean that a parent has been affected) confers a 50% risk of carrying a mutation (at birth). For HNPCC and BC/OC, family history (carefully defined) confers a probability of carrying a mutation determined through Bayes' Theorem. Table 2 shows the risk subpopulations in our model, as well as the estimated prevalences (taken from the studies cited previously).

The details of this model, including the onset rates of CI events, have been extensively discussed in Gutiérrez & Macdonald (2003). Therefore we only mention its main features briefly as follows:

(a) We assume that the CI insurance market operates between ages 20 and 60. An insured person pays premiums continuously while in State $i1$, $i3$ or $i5$, and receives a lump-sum benefit upon transition into State $i6$. Individuals could buy insurance before or after taking a genetic test. They could also become uninsurable because of contracting a critical illness, or they could die.

(b) The proportion of the population falling in each risk sub-population is shown in Table 2. The proportions of carriers and non-carriers of each mutation are the same, since a mutation will be inherited from the affected parent with probability 1/2.

(c) Sub-populations 2–13 cover the diseases with no cause except gene mutations. Because of high penetrance, persons in these groups are assumed to have a family history, consisting of an affected parent. So the starting state for these populations is State $i2$, 'No Insurance, with family history (FH)'. Sub-populations 14–21 refer to inherited variants of common disorders. Persons in these groups start in State $i0$, 'No Insurance, without family history (FH)'.

(d) Family history is an important underwriting factor in practice. In this model, for sub-populations 2–13, a family history is assumed to be present from outset, so μ_{x+t}^{i02} is irrelevant, but for sub-populations 14–21, a family history may emerge later, so $\mu_{x+t}^{i02} > 0$. For details of the calculation of these intensities please refer to the studies of HNPCC and BC/OC cited in Table 1.

(e) The incidence of genetic testing is governed by the intensity μ_{x+t}^{i02}. We assume a baseline test rate of 0.014 *per annum* for ages 20–40, which implies that about 10% would be tested after 8 years. Two other scenarios that we consider are a rate of 0.014 *per annum* for ages 20–60 (genetic testing continues for longer), and 0.035 per annum for ages 20–40 (implying about 24% would be tested after 8 years) These rates and proportions may seem to be quite high; however testing for dominantly inherited single-gene

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TABLE 2

TWENTY-ONE RISK SUB-POPULATIONS AND THEIR PROPORTIONS.

		Proportions
Sub-population 1	not mutation carriers, not having family history	0.984162
Sub-population 2	carrying mutation APKD1, with family history	0.00085
Sub-population 3	not carrying mutation APKD1, but with family history	0.00085
Sub-population 4	carrying mutation APKD2, with family history	0.00015
Sub-population 5	not carrying mutation APKD2, but with family history	0.00015
Sub-population 6	carrying mutation PSEN-1, with family history	0.00015
Sub-population 7	not carrying mutation PSEN-1, but with family history	0.00015
Sub-population 8	carrying mutation CAG, with family history	0.000188
Sub-population 9	not carrying mutation CAG, but with family history	0.000188
Sub-population 10	carrying mutation CTG repeat 250+, with family history	0.0000355
Sub-population 11	not carrying mutation CTG repeat 250+, but with family history	0.0000355
Sub-population 12	carrying mutation CTG repeat 250–, with family history	0.0000355
Sub-population 13	not carrying mutation CTG repeat 250–, but with family history	0.0000355
Sub-population 14	carrying mutation MLH1, with family members being mutation carriers	0.000769
Sub-population 15	not carrying mutation MLH1, with family members being mutation carriers	0.000769
Sub-population 16	carrying mutation MSH2, with family members being mutation carriers	0.000714
Sub-population 17	not carrying mutation MSH2, with family members being mutation carriers	0.000714
Sub-population 18	carrying mutation BRCA1, with family members being mutation carriers	0.002328
Sub-population 19	not carrying mutation BRCA1, with family member being mutation carriers	0.002328
Sub-population 20	carrying mutation BRCA2, with family members being mutation carriers	0.002699
Sub-population 21	not carrying mutation BRCA2, with family members being mutation carriers.	0.002699

disorders is not carried out among the general population, but is largely confined to persons who know they are at risk because of their family history.

(f) The intensities μ^{i01}_{x+t}, μ^{i23}_{x+t} and μ^{i45}_{x+t} are the annualized rates of insurance purchase. The purchase rates in 'unaffected' sub-population 1 define the size of the market. A purchase rate of 0.05 per annum represents what we call a large market. A purchase rate of 0.01 per annum represents what we call a small market. We call these the 'normal' purchase rates. In sub-populations 2–21, persons with no family history buy insurance at the normal rate. In a large market, persons who have a family history are assumed to have three choices of their purchasing behaviours: normal rate, half of normal rate, or nil, meaning they do not purchase insurance at all. In a small market, these persons are assumed not to purchase insurance at all. Persons who have a family history but have had a clear test result are assumed to buy insurance at the normal rate.

(g) The model is not quite as simple as Figure 1 makes it appear, for the following reasons:
   (1) All states in the dashed box in Figure 1 have access to states *i*6 and *i*7. Persons transferring from uninsured states into states *i*6 and *i*7 before they buy insurance become uninsurable.
   (2) As discussed in Section 3, in the case of HD or MD, 'onset' means the earliest symptoms, which will not trigger a CI payment. In both cases an accelerated lifetime model is used to model claims. For more details, see Gutiérrez & Macdonald (2004).

(h) One of the forms of moratorium described in Section 2.2 may be imposed, forcing a rearrangement of underwriting classes, such that some of them, at least, contain people subject to different levels of risk, but who must all be charged the same rate of premium, which clearly must now involve some averaging over the different risk levels. A moratorium on adverse test results will partition the population into two underwriting classes, namely people with and without a family history. If 'clear' test results may be used, people with a family history but a clear genetic test result move into the non-family-history class. A moratorium that includes family history will put everyone into a single underwriting class.

(i) The form of adverse selection may include:
   (1) An increased rate of insurance purchase. We define as 'moderate' adverse selection a purchase rate double the normal rate, that is 0.1 per annum in the large market and 0.02 per annum in the small market. These assumption imply that about 63% and 18% of at-risk people would buy insurance in 10 years in the large and small markets, respectively. We define as 'severe' adverse selection a purchase rate of 0.25 per annum. This assumption is deliberately high; it implies that about 91% of at-risk people would buy insurance in 10 years in both large and small markets.
   (2) An increased sum assured. In (1) we assume that 'adverse selectors' buy the same amount of insurance as normal, but they could opt for

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higher sums assured. Gutiérrez & Macdonald (2004) found that the cost of adverse selection arising from this cause is very nearly proportionate to the multiple of the average sum assured taken out by 'adverse selectors', therefore we omit any examples in what follows.

(j) In this market model, a person can purchase insurance at any age between 20 and 60 (at which age all policies expire). If they were charged level premiums, that rate of premium would depend on age at purchase, whereas the insured states in Figure 1 include persons who purchased insurance at any earlier age. That is, level premiums are not adapted to the Markov model with age as the time parameter. Numerically, the problem is not insoluble but it is messy. An alternative is to charge a rate of premium equal at any time to the actual risk, namely the transition intensities into claim states. Because an underwriting class may now contain persons subject to different levels of risk, we weight the intensities over all states within a given underwriting class, denoted C, as follows:

$$\rho^{C}_{x+t} = \frac{\sum_{ij \in C} p_{i\,t} p^{i0j}_{x} \mu^{ij6}_{x+t}}{\sum_{ij \in C} p_{i\,t} p^{i0j}_{x}}, \tag{1}$$

where p_i is the proportion who start in State $i0$ at age x (State $i2$ for sub-populations 2 to 13), and label ij stands for the state j in the CI market model for sub-population i. This rate of premium depends only on age and satisfies the equivalence principle.

(k) Using these premium rates, we apply Thiele's equations to calculate the expected insurance loss conditional on being in any state. Expected losses are first calculated assuming that there is no moratorium and no adverse selection, in which case the total insurance loss is zero, because the equivalence principle is correctly applied. However, if there is adverse selection, the expected insurance loss will be non-zero. This is the cost of adverse selection. To cover the cost, we suppose that insurance companies increase all rates of insurance premium uniformly by the proportion:

$$\frac{\text{EPV of loss with adverse selection} - \text{EPV of loss without adverse selection}}{\text{EPV of premiums payable with adverse selection}}.$$

We take this increase in the premium as our measure of the cost of adverse selection.

5. Overall Cost of Adverse Selection in the Critical Illness Insurance Market

5.1. Moratoria on Genetic Test Results

Table 3 shows the cost of moderate adverse selection in our model CI market, following Equation (2) after imposing a moratorium on the use of genetic test

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TABLE 3

PERCENTAGE INCREASES IN CI INSURANCE PREMIUM RATES ARISING FROM MODERATE ADVERSE SELECTION. MORATORIA ON THE USE OF GENETIC TEST RESULTS, FAMILY HISTORY UNDERWRITING STILL ALLOWED. CI MARKET OPERATING BETWEEN AGES 20 AND 60.

Size of Market	Insurance Purchase of At-Risk Individuals	Age		Moratorium on Using			
				All test results		Adverse test results	
		Rate of Testing	Range of Testing	Females %	Males %	Females %	Males %
Large	Normal	0.014	20–40	0.01301	0.01242	0.01210	0.01155
	Half	0.014	20–40	0.03182	0.03037	0.01396	0.01332
	Nil	0.014	20–40	0.15143	0.14531	0.04368	0.04176
Small	Nil	0.014	20–40	0.17318	0.16273	0.07778	0.07304
Large	Normal	0.014	20–60	0.01443	0.01376	0.01339	0.01277
	Half	0.014	20–60	0.03629	0.03455	0.01618	0.01542
	Nil	0.014	20–60	0.17390	0.16715	0.05255	0.05038
Small	Nil	0.014	20–60	0.19230	0.18089	0.08689	0.08170
Large	Normal	0.035	20–40	0.02785	0.02659	0.02311	0.02206
	Half	0.035	20–40	0.06756	0.06441	0.02397	0.02287
	Nil	0.035	20–40	0.32112	0.30797	0.09134	0.08725
Small	Nil	0.035	20–40	0.37104	0.34851	0.16621	0.15603

results, with family history underwriting allowed. We set the genetic testing rate at 0.014 per annum between ages 20 and 40 as our baseline, and compare it with two other scenarios: a rate of 0.014 per annum between ages 20 and 60; and a rate of 0.035 per annum between ages 20 and 40.

Table 4 shows the cost of severe adverse selection, after imposing a moratorium on using genetic test results but not on using family history. Since we are probing the most extreme case here, we assume the rate of genetic testing to be 0.035 per annum between age 20 and 40.

TABLE 4

PERCENTAGE INCREASES IN CI INSURANCE PREMIUM RATES ARISING FROM SEVERE ADVERSE SELECTION. MORATORIA ON THE USE OF GENETIC TEST RESULTS, FAMILY HISTORY UNDERWRITING STILL ALLOWED. CI MARKET OPERATING BETWEEN AGES 20 AND 60.

Size of Market	Insurance Purchase of At-Risk Individuals	Age		Moratorium on Using			
				All test results		Adverse test results	
		Rate of Testing	Range of Testing	Females %	Males %	Females %	Males %
Large	Normal	0.035	20–40	0.04835	0.04623	0.03979	0.03805
	Half	0.035	20–40	0.09299	0.08877	0.04139	0.03955
	Nil	0.035	20–40	0.39975	0.38243	0.16993	0.16168
Small	Nil	0.035	20–40	1.23750	1.15633	1.03234	0.96352

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Generally, the increases are all very small, even with severe adverse selection, although these increases are certainly larger than those caused by any single genetic disorder on its own. We observe the following features:

(a) In Table 3, the costs of adverse selection are all less than 0.4% of premiums. Only in a small market and under the most adverse assumptions does the cost approach 0.4%.
(b) The costs are more substantial in the smaller market and when there is extreme adverse selection. In Table 4, we can see that in a small market insurers might have to increase premium rates generally by up to 1.3%, but in the larger market the increase is not higher than 0.4% and in some circumstances much less than this.
(c) Premium increases are lower if the moratorium applies only to adverse test results (as in the UK), because tested persons who are not mutation carriers will be charged standard premiums. These persons are removed from the underwriting class rated for family history, which then contains a higher proportion of mutation carriers, so the premium charged in respect of this class is higher.
(d) A longer period of genetic testing has little effect on the cost of adverse selection. This is because of the high penetrance of all these mutations, removing a large proportion of potential applicants before age 40, and also ensuring that an older unaffected person with a family history has a low probability of being a mutation carrier.
(e) The cost of adverse selection is greater for females than for males. This is partly because the standard rates of premium are lower for females at many ages, and partly because males have a very low risk of BC, and no risk at all of OC and endometrial cancer.

5.2. Moratoria on Genetic Test Results and Family History

A moratorium on genetic test results and family history causes premiums to increase in two different ways.

(a) Persons in the higher-risk sub-populations can now purchase normal amounts of insurance cover at ordinary rates. This will increase premium rates, but this is arguably not adverse selection if their behaviour is just reverting to the norm.
(b) Beyond that, insurance buyers may increase their purchase rate and/or quantum of cover in reaction to the information they have and the relatively lower premiums they have been charged.

Table 5 shows the increases in standard premium rates (OR) arising from the creation of the new underwriting class ((a) above), and also those arising from moderate or severe adverse selection ((b) above) Genetic testing takes place between ages 20 and 40, at rate 0.014 *per annum* with moderate adverse selection and 0.035 *per annum* with severe adverse selection. We observe that the highest

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TABLE 5

PERCENTAGE INCREASES IN STANDARD PREMIUM RATES FOR CI INSURANCE ARISING FROM NEW UNDERWRITING CLASSES, AND IN ALL PREMIUMS ARISING FROM MODERATE OR SEVERE ADVERSE SELECTION, FOLLOWING A MORATORIUM ON THE USE OF ALL GENETIC TEST RESULTS AND FAMILY HISTORY. CI MARKET OPERATING BETWEEN AGES 20 AND 60.

Size of Market	OR Premium Increase Arising from New Underwriting Classes		Premium Increase Arising From Moderate Adverse Selection		Premium Increase Arising From Severe Adverse Selection	
	Females %	Males %	Females %	Males %	Females %	Males %
Large	0.76114	0.73181	0.18087	0.17420	0.30023	0.28954
Small	0.71512	0.67144	0.42624	0.39955	2.13984	2.01271

cost of adverse selection (premium increases of over 2%) appears in a small market and when there is severe adverse selection, and that the cost of adverse selection in the large market is much smaller than in the small market.

6. A LIFE INSURANCE MARKET MODEL

Figure 2 shows a model of a person's life history in a life insurance market, which we assume to operate between ages 20 and 60. As in Table 2, we partition the population into 21 risk sub-populations depending on whether they are mutation carriers, have family histories, or have family members carrying mutations. This model is very similar to the CI insurance model, except for the following:

(a) The model is semi-Markov, because the post-onset mortality rates depend on duration. An insured person pays premiums while in states $i1$, $i3$, $i5$, $i6$, $i7$ and $i8$, and receives a lump-sum benefit upon transition into State $i9$. Individuals could buy insurance before or after taking a genetic test. They could also become uninsurable because of contracting a relevant genetic disorder or premature death.
(b) The states $i6$, $i7$ and $i8$, 'Onset of Relevant Diseases', stands for the onset of any of the genetic disorders APKD, EOAD, HD, MD, HNPCC, BC or OC, while insured.
(c) All uninsured states in the dashed box have access into State $i9$, 'Onset of Relevant Diseases, uninsured', and all states in the dashed box have access into State $i10$, 'Dead', which together represent all the ways in which an uninsured person may become uninsurable.
(d) The intensity of entry into State $i9$ from an uninsured state is the sum of the relevant onset rates of genetic disorders, and the rate of mortality from other causes. The intensities of entry into 'Onset of Relevant Diseases" states from the insured states is the relevant onset rates. The intensities of

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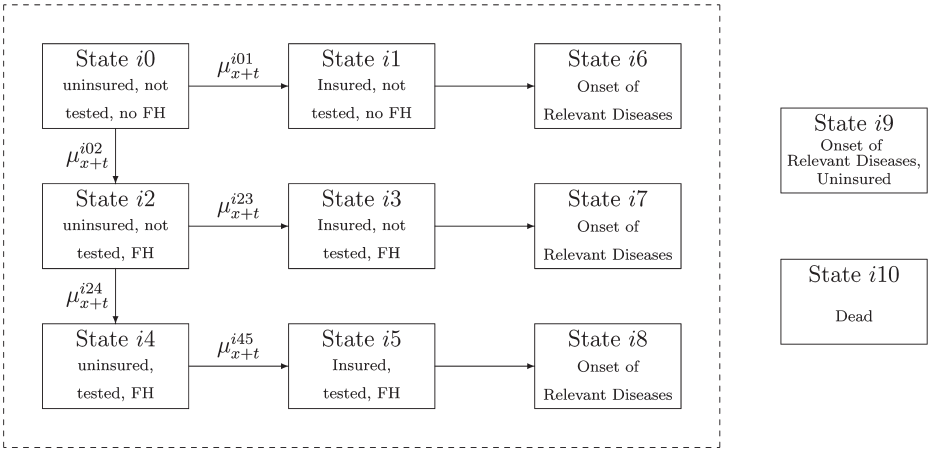

FIGURE 2: A semi-Markov model of family history, genetic testing, insurance purchase and life insurance events for a person in the i^{th} risk sub-population (FH = family history present).

entry into state $i10$ are the relevant post-onset mortality rates. Please refer to the individual studies in Table 1 for details.

(e) As in the CI insurance market, we need to charge a rate of premium which depends only on age $x + t$ and satisfies the equivalence principle. The premium rate for underwriting class C is:

$$\rho^{C}_{x+t} = \frac{\sum_{ij \in C} p_i \left({}_t p^{i0j}_x \mu^{ij9}_{x+t} + \int_0^t {}_{t,z} p^{i0j}_x \mu^{ij9}_{x+t,z} \, dz \right)}{\sum_{ij \in C} p_i \left({}_t p^{i0j}_x + \int_0^t {}_{t,z} p^{i0j}_x dz \right)}. \tag{3}$$

(f) Following Gutiérrez & Macdonald (2004) we suppose that upon entering state $i6$, $i7$ or $i8$, the insurer terminates the contract by reinsuring it, paying a single premium equal to the policy value. For example, consider state $i6$. Define the policy value for a person age $x+t$ who has been in state $i6$ for z years to be ${}_{t,z}V^{i6}_x$. Then on entry to state $i6$ the insurer has an outgo of:

$${}_{t,0}V^{i6}_x = \int_0^{n-t} e^{-\delta s} {}_s p^{i66}_{x+t,0} \left(\mu^{i69}_{x+t+s,s} - \rho^{C}_{x+t+s} \right) ds. \tag{4}$$

Define ${}_{t,0}V^{i7}_x$ and ${}_{t,0}V^{i8}_x$ similarly. The left side of Equation (4) does not depend on duration since onset (although the right side does) so the cashflows are once more adapted to a Markov model, and we can use Thiele's equations as before.

All other features of this model, (other intensities, large and small markets, moratoria and so on) are the same as in the CI insurance market model, see Section 4.

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7. Overall Cost of Adverse Selection in the Life Insurance Market

7.1. Moratoria on Genetic Test Results

Table 6 shows the costs of adverse selection in a life insurance market under moderate adverse selection, corresponding exactly to Table 3. Table 7 likewise corresponds exactly to Table 4 in the case of severe adverse selection. All the observations we made in respect of the CI market model apply equally here, except for the magnitude of the premium increases, upon which we make the following comments:

(a) In Table 6, the costs of adverse selection are generally not substantial, if we take 0.1% as the threshold. Only in the small market could the cost be high, e.g. between 0.1% and 0.16%.
(b) The costs of adverse selection are more substantial in the smaller market and when there is extreme adverse selection. In Table 7, we can see that in a small market insurers have to increase their premium rates generally by nearly 1% in order to recover the loss, which cannot be treated as negligible.
(c) Noticing that CI insurance and life insurance are both protection type, the magnitude of the cost of adverse selection largely depends on the difference between the premium rates for family history class and non-family history class. In most cases, we can see that the extra premium expressed as percentages of standard risk is higher in respect of CI insurance than that in respect of life insurance. Therefore the cost of adverse selection is lighter in a life insurance market than in a CI insurance market.

TABLE 6

Percentage increases in life insurance premium rates arising from moderate adverse selection. Moratoria on the use of genetic test results, family history underwriting still allowed. Life insurance market operating between ages 20 and 60.

Size of Market	Insurance Purchase of At-Risk Individuals	Age		Moratorium on Using			
				All test results		Adverse test results	
		Rate of Testing	Range of Testing	Females %	Males %	Females %	Males %
Large	Normal	0.014	20–40	0.01281	0.00832	0.01274	0.00830
	Half	0.014	20–40	0.02895	0.01900	0.01534	0.01001
	Nil	0.014	20–40	0.07217	0.05170	0.02217	0.01568
Small	Nil	0.014	20–40	0.07712	0.05633	0.03499	0.02549
Large	Normal	0.014	20–60	0.01348	0.00883	0.01341	0.00809
	Half	0.014	20–60	0.03103	0.02056	0.01658	0.01095
	Nil	0.014	20–60	0.07968	0.05754	0.02518	0.01801
Small	Nil	0.014	20–60	0.08327	0.06121	0.03793	0.02782
Large	Normal	0.035	20–40	0.02800	0.01816	0.02764	0.01803
	Half	0.035	20–40	0.06272	0.04106	0.03274	0.02141
	Nil	0.035	20–40	0.15418	0.11039	0.04680	0.03310
Small	Nil	0.035	20–40	0.16631	0.12138	0.07529	0.05481

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TABLE 7

PERCENTAGE INCREASES IN LIFE INSURANCE PREMIUM RATES ARISING FROM SEVERE ADVERSE SELECTION. MORATORIA ON THE USE OF GENETIC TEST RESULTS, FAMILY HISTORY UNDERWRITING STILL ALLOWED. LIFE INSURANCCE MARKET OPERATING BETWEEN AGES 20 AND 60.

Size of Market	Insurance Purchase of At-Risk Individuals	Age		Moratorium on Using			
				All test results		Adverse test results	
		Rate of Testing	Range of Testing	Females %	Males %	Females %	Males %
Large	Normal	0.035	20–40	0.05564	0.03553	0.05490	0.03523
	Half	0.035	20–40	0.09622	0.06213	0.06558	0.04218
	Nil	0.035	20–40	0.19926	0.01420	0.09186	0.06472
Small	Nil	0.035	20–40	0.60482	0.43511	0.51366	0.36842

7.2. Moratoria on Using Genetic Test Results and Family History

As introduced in Section 5.2, premium rates increase for two reasons when a moratorium is imposed on using genetic test results and family history. Table 8 shows the increases in standard premium rates arising from new underwriting classes and also in all premium arising from moderate or severe adverse selection, when a moratorium on the use of all genetic test results and family history is imposed, assuming the life insurance market operates between ages 20 and 60. The rate of genetic testing is 0.014 per annum with moderate adverse selection, and 0.035 per annum with severe adverse selection between ages 20 and 40. We can observe that:

(a) The highest cost of adverse selection, over 1% of premiums, appears in a small market and when there is severe adverse selection. In a large market, the cost of adverse selection, although not negligible, is still much smaller than the case in a small market.

TABLE 8

PERCENTAGE INCREASES IN STANDARD PREMIUM RATES FOR CI INSURANCE ARISING FROM NEW UNDERWRITING CLASSES, AND IN ALL PREMIUMS ARISING FROM MODERATE OR SEVERE ADVERSE SELECTION, FOLLOWING A MORATORIUM ON THE USE OF ALL GENETIC TEST RESULTS AND FAMILY HISTORY. LIFE INSURANCE MARKET OPERATING BETWEEN AGES 20 AND 60.

Size of Market	OR Premium Increase Arising from New Underwriting Classes		Premium Increase Arising From Moderate Adverse Selection		Premium Increase Arising From Severe Adverse Selection	
	Females %	Males %	Females %	Males %	Females %	Males %
Large	0.82454	0.51648	0.11460	0.06955	0.20705	0.12547
Small	0.72673	0.44995	0.21477	0.13170	1.26950	0.77738

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(b) The cost of adverse selection in a life insurance market is generally lighter that the corresponding case in a CI market, although there are a few exceptions.

8. Conclusions and Discussion

8.1. Overall Conclusions

If moderate adverse selection were to occur because of a moratorium on using genetic test results, with family history underwriting still allowed, its cost would probably be very small, of the order of 0.1% of premium income. Any more substantial costs, while still small in absolute terms, would require a combination of smaller markets and consistently adverse behaviour on the part of at-risk applicants.

A moratorium extended to the use of family history will increase the premium in two ways. First, there is consolidation of underwriting classes. This gives rise to premium increases ranging roughly from 0.4% to 0.8%, that are not very different in the large and small markets. Second, there could be adverse selection by at-risk individuals. This gives rise to premium increases much smaller than the range above in the large market, and much larger in the small market. However, even in the small market and under the most adverse assumptions the cost barely exceeds 2% of premium income. In the worst scenario considered — females displaying severe adverse selection in a small critical illness insurance market — the total cost was about 3% of premiums. However, to remind the reader of all the assumptions lying behind the terms we have defined, we should perhaps describe this as 'severe' adverse selection in a 'small' critical illness insurance 'market'.

Insurers rightly must be concerned about adverse selection. Whether premium increases of the size indicated above could lead to a classic adverse selection spiral is an economic question not addressed here. However, Macdonald & Tapadar (2010) looked at this question in the setting of multifactorial disorders and found "… no convincing evidence that adverse selection is a serious insurance risk, even if information about multifactorial genetic disorders remains private". Pragmatically, one must doubt that such small changes in price, when compared with differences between competing insurers and price changes over recent decades, will have any measurable effect.

8.2. Selection and Coverage of Genetic Disorders in the Model

We have selected six autosomal dominant single-gene disorders out of approximately 200 known to medical science (Pasternak, 1999). Compiling a study based on the epidemiology of individual disorders is the essence of the 'bottom-up' approach, but adding more and more disorders must at some point yield diminishing returns. We should ask whether we can learn enough from

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what has been done, or if the 'bottom-up' programme is still incomplete in any essential way.

(a) We have been strongly influenced by the ABI's list of disorders regarded as significant for insurance, compiled by Professor A.J. Raeburn, a clinical geneticist (See Section 2.1). Our model includes HD, MD, EOAD, and BC/OC from that list, plus APKD which was originally on the list and HNPCC which a later statement by Professor Raeburn in effect elevated to the list. Those we have omitted, we believe, would not add materially to the model, for the following reasons.
   (1) HMSN is a very rare disease and most patients affected are very young, usually below age 20, before they would be likely to purchase insurance.
   (2) MEN2 is an example of a cancer for which genetic testing and early treatment should lead to substantially better outcomes (Gui, 2003), hence we may doubt that it would have a substantial impact on the insurance industry.
   (3) FAP is a type of hereditary colorectal cancer, in which polyps develop at an early stage. Because these polyps can be easily detected and removed by means of a screening programme, the risk associated with FAP is limited, and like MEN, ought to be very substantially lowered by genetic testing within at-risk families (MacCalman, 2009).

   Indeed, disorders such as MEN2 and FAP, for which genetic testing may become part of routine screening and treatment, present different problems for the insurance industry, which must take care that its practices, or just the public's perception of its practices, do not impede advances in clinical medicine.

(b) APKD, originally on the ABI's list, was later removed because it is typically detected by ultrasonography and not genetic testing. By including it, we depart from underwriting practice by regarding ultrasonography as a type of genetic test. However, APKD is one of the most common dominant single-gene disorders, so its inclusion makes the study more robust.

(c) We were restricted to disorders for which there was sufficient published epidemiology. Only in one case (EOAD) did we attempt our own epidemiological study. (The existence of some very useful studies of APKD was another reason for its inclusion.) Fortunately, epidemiologists have tended to focus on disorders that they regard as significant for much the same reasons as we do.

(d) Our selected studies also, inevitably, ignore quite substantial geographical variations in genetic disorders. For example, MD appears to be particularly prevalent in Northern Ireland, while HD has higher than average incidence in parts of northern Scotland. We have used UK studies where we could, not least because the modelling of CI events was based on UK data, but the epidemiology of single-gene disorders also varies worldwide. To the extent that our model does not represent these variations, it is incomplete. However, given the order of magnitude of our conclusions it

seems unlikely that the overall result would be different in any other part of the world. We suggest that the size and nature of the insurance market is likely to be a much more important factor.

(e) Our six genetic disorders include representatives of brain disorders, musculoskeletal disorders, cancers and disorders of internal organs, as well as disorders that are purely genetic in origin, and inherited variants of common disorders. Each may be expected to bring different patterns of diagnosis and development to the insurance claims process.

(f) We have attempted to err on the conservative side in making assumptions. Moreover, onset rates estimated from pedigree data may often be biased upwards to an unknown degree because of the ascertainment problems inherent in analysing pedigrees (see Hodge (2002) and references therein). These act counter to the omission of less relevant or extremely rare disorders.

(g) Our choice to model stand-alone CI insurance, instead of accelerated benefits, is also conservative. Adding death benefits would increase the premiums before and after adverse selection by similar amounts, hence would reduce the percentage premium increases required to meet the cost of adverse selection.

Overall, we suggest that we have achieved sufficient representative coverage of relevant disorders, including the most common ones, and moreover have used most of the useable epidemiology. In some cases the epidemiology has developed further since our individual studies were carried out, and we have not usually gone back and reparameterised our models, but we do not think this is material. The 'bottom-up' approach could be an endless task, but we choose to end it here and we suggest that the results in this paper, while they could be refined, are sufficient for the purpose.

8.3. Further Modelling Questions

Single gene disorders can present extremely elevated risk, but are rare. Multifactorial disorders will, in all likelihood, present modestly altered risks, but will be common. Yet because both are 'genetic' what we learn from studying them may be treated alike as far as insurance is concerned. The programme of research summarised here was an effort to bring actuarial evidence into the debate over single gene disorders. Something like it will be needed as testing for multifactorial disorders begins to be developed.

Some of the biggest gaps in the modelling relate to economic or behavioural questions that are hard to study empirically. We have suggested here that these can be discounted, because conservative assumptions still gave such small costs. This was because the 'actors' in the model, whose behaviour might be changed by genetic information, made up a very small proportion of the population. As genetic information begins to affect a larger part of the population, these inadequacies of the model may start to matter.

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APPENDIX

This appendix presents an individual study of myotonic dystrophy (MD), the only disorder in Table 1 which has not yet been modelled.

A. INTRODUCTION

MD is the most common form of adult-onset muscular dystrophy. The standard reference work, on which much of the following is based, is Harper (2001). A hallmark of MD is 'myotonia', meaning that affected patients find it very hard to relax their hand after grasping an object. MD was first described by Steinert in 1904 (Harper, 2001) and was first studied systematically by Bell (1947) and Thomasen (1948), who established autosomal dominant inheritance. The gene locus was mapped in 1971, and in 1992, the cause of MD was discovered to be an expanded trinucleotide (CTG) repeat sequence.

There are three forms of MD; type 1 (MD1), type 2 (MD2) and type 3 (MD3). Very few papers refer to the rare MD3, and we will not consider it here. MD1 is the most common form, accounting for about 98 percent of all cases. MD2 has milder clinical presentation than MD1. Therefore here we will only consider MD1 and hereafter MD actually refers to MD1.

There are three types of MD; congenital (CMD), classical and mild. These are differentiated by the number of CTG repeats in the relevant gene. Normal people have fewer than 50 CTG repeats. Mild MD is usually associated with 50–100 CTG repeats, classical adult onset with 100–1,000 CTG repeats and the more severe CMD with over 1,000 CTG repeats. A larger number of CTG repeats is associated with earlier age at onset. CMD is more severe than the other two cases, and the onset at birth makes the carriers uninsurable. We consider only adult-onset MD.

Our purpose here is to assess the impact of genetic information relating to MD — genetic tests or family history — on CI and life insurance. The two questions we wish to address are premium increases if genetic information may be used in underwriting, and adverse selection if it may not. Since the body of this paper reports results on adverse selection in the whole model, including MD, we omit results on adverse selection arising from MD alone. These can be found in Yu (2010).

In Section B, we introduce the three features of MD epidemiology most relevant insurance underwriting, namely onset rates, post-onset mortality rates

and prevalence. In Section C, we propose a CI insurance model, allowing for delay between onset and claim payment. In Section D, we calculate CI premium rates based on genetic test results or family history. In Sections E and F we do the same for life insurance.

B. Epidemiology of Myotonic Dystrophy

B.1. The Penetrance of Myotonic Dystrophy

The age-related cumulative risk (penetrance) of MD, denoted $F(x)$, is defined as the probability of developing MD by age x, if there were no other causes of decrement (Macdonald, 2003a). When x approaches a suitably high age, we obtain the lifetime penetrance. Nesterov *et al.* (1983) found the penetrance of the MD gene to be 83% in Ukrainian families and 91% in Russian families. Höweler (1986) studied 14 MD families, and found that 46% of subjects were affected. Harper (2001) mentions an earlier study (Harper, 1973) with more robest ascertainment in which almost 50% of offspring were affected. Therefore, we assume that the penetrance of MD is close to 100%.

B.2. The Onset Rate of Myotonic Dystrophy

Given estimates of the penetrance $F(x)$, the rate of onset (hazard rate), $\mu(x)$, is:

$$\mu(x) = \frac{F'(x)}{1 - F(x)}, \tag{5}$$

which can be computed by analytical or numerical differentiation.

Frohock (2003) studied MD patients and obtained Kaplan-Meier estimates of the cumulative onset probability. Unlike HD, in which there is a relatively limited range of viable trinucleotide expansion numbers, the number of CTG repeats in MD could range from 50 to several thousand. In Frohock (2003), MD mutations are categorized into two groups: genotype I, with more than 250 CTG repeats (we denote this group CTG250+), and genotype II, with not more than 250 CTG repeats (here denoted CTG250–). We smoothed Frohock's Kaplan-Meier estimates by parametric functions with the results shown in Equations (6) and (7).

$$F(x)^{MD,CTG250+} = \frac{\exp(-3.952\times10^{-6}x^3 - 1.624\times10^{-4}x^2 + 0.1206x - 4.951)}{1 + \exp(-3.952\times10^{-6}x^3 - 1.624\times10^{-4}x^2 + 0.1206x - 4.951)}, \tag{6}$$

$$F(x)^{MD,CTG250-} = \frac{\exp(4.343\times10^{-5}x^3 - 0.006044x^2 + 0.4437x - 8.731)}{1 + \exp(4.343\times10^{-5}x^3 - 0.006044x^2 + 0.4437x - 8.731)}. \tag{7}$$

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For mutation CTG250+ carriers, data after 50 years old is scarce and the penetrance is nearly complete by then, so we assume that the onset rate levels off after age 50.

B.3. Post-Onset Mortality

Mladenovic *et al.* (2006) provides Kaplan-Meier estimates of the post-onset 15-year duration-dependent survival probability for three cohorts, CMD (onset before age 20), classical onset (onset between age 20 and age 50), and mild onset (onset after age 50). CMD is not relevant for insurance, and we decided not to use the mild onset case, because of lack of data. Instead, for both mild onset and classical onset, we use the estimate for classical onset, which is a conservative assumption. We fitted the following parametric function of duration since onset, denoted z, to the Kaplan-Meier estimate for the classical onset case.

$$F(z)^{MD,\,Mortality} = \frac{\exp(0.001903z^3 - 0.06907z^2 + 1.007z - 6.082)}{1 + \exp(0.001903z^3 - 0.06907z^2 + 1.007z - 6.082)}. \quad (8)$$

Wilkie (2000) pointed out the anomaly that $\mu_z^{MD,\,Mortality}$ might be less than the normal age-related mortality rates, denoted $\mu_x^{Standard}$, at certain ages. To avoid this we assume that mortality after onset of MD is the higher of $\mu_z^{MD,\,Mortality}$ and $\mu_x^{Standard}$.

B.4. Prevalence Rate and Distribution of Mutations

Overall, the prevalence rate of MD is about 1 in 8,000, but prevalence rates in different areas vary greatly, as shown in Table 9. Since in this paper, we are

TABLE 9

PREVALENCE OF MYOTONIC DYSTROPHY, PER 100,000 OF POPULATION

Source	Place	Frequency
Osame & Furusho (1983)	Kagoshima and Koinawa districts, Japan	5.5
Hsiao *et al.* (2003)	Taiwan	0.46
Ford, Kidd & Hammond-Tooke (2006)	Otago, New Zealand	11.6
Bouchard *et al.* (1988)	Saguenay, Quebec (Canada)	210.5
Grimm (1975)	Germany	5.5
Mladenovic *et al.* (2005)	central Serbia	3.8
López De Munain *et al.* (1993)	Basque Country, Spain	26.5
Medica, Markovi & Peterlin (1997)	Istria, Croatia	18.1
Klein (1958)	Switzerland	4.9
Mostacciulol *et al.* (1987)	Veneto, Italy	36.3
Siciliano *et al.* (2001)	Padova and North-West Tuscany, Italy	9.31
Magee & Nevin (1999)	Northern Ireland	119.5
MacMillan & Harper (1991)	Wales (South)	7.1

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mainly interested in the UK, we use the estimate of 7.1 per 100,000 (MacMillan & Harper, 1991). This result is also cited in Harper (2001).

The distribution of mutation genotypes is estimated by reference to Frohock (2003), which provides the CTG repeat numbers of a sample of symptomatic and asymptomatic patients. She found 39 patients with genotype CTG250–, and 44 with genotype CTG250+. Therefore we assume that the mutation-carrying children have a 50% chance, at birth, of having either genotype.

C. A Critical Illness Insurance Model

C.1. Models for Critical Illness Insurance

Since we adopt the CI insurance model used by Gutiérrez & Macdonald (2003), as presented in Figure 3, and use the model for delayed claims from Gutiérrez & Macdonald (2004), we describe the model very briefly here. The only innovation is the substitution of the epidemiological parameters given above. Intensity μ_x^{i01} is found from the onset rates of MD in Section B.2. Intensities μ_x^{i02} and μ_x^{i03} have been estimated in Gutiérrez & Macdonald (2003).

C.2. The Timing of a Critical Illness Insurance Claim

The onset of the MD is associated with less severe symptoms, such as myotonia and cataract. These will not trigger the CI insurance payment. In practice, a claim is delayed until more severe symptoms develop some time after onset. This feature could be reflected by adding a new state to the model, as shown in Figure 4. Since the intensity μ_z^{i14} is assumed to be duration dependent, this model is semi-Markov. We assume that $\mu_x^{i02} = \mu_x^{i12}$ and $\mu_x^{i03} = \mu_x^{i13}$.

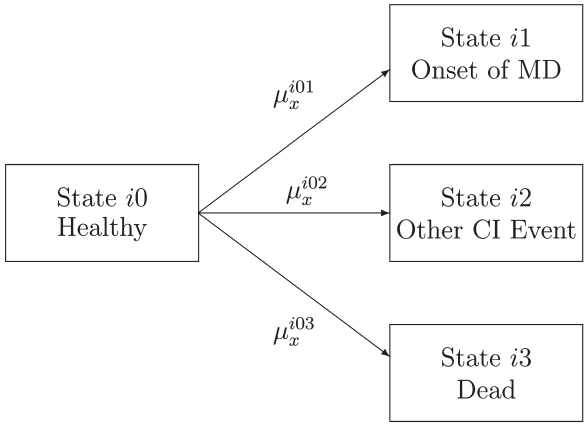

Figure 3: A multiple-state Markov model for myotonic dystrophy and critical illness insurance for an insurance applicant with genotype g_i.

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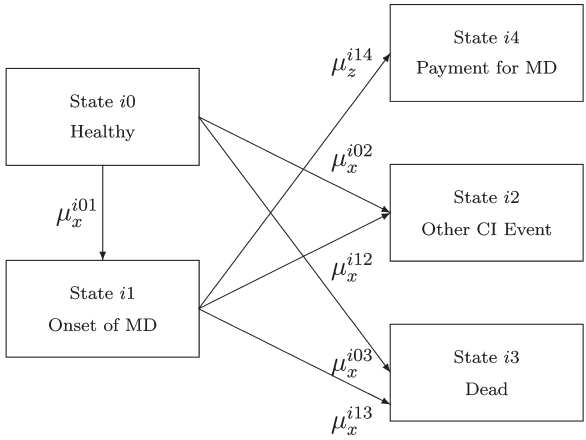

FIGURE 4: A semi-Markov model for myotonic dystrophy and critical illness insurance for insurance applicants with genotype g_i. The variable z is the duration since onset of myotonic dystrophy.

A similar feature affects HD. Harper (1996) characterised the progression of HD through three stages, each of roughly equal duration. The second or third of these might reasonably represent a CI claim. In the absence of any quantitative estimates of progression rates between stages, Gutiérrez & Macdonald (2004) applied an accelerated lifetime model to the post-onset survival rates. We will do the same here, and we continue to use the terms Stage II and Stage III to represent the times at which an insurer might pay a CI claim in respect of MD. However, unlike HD, these two stages do not carry any medical explanation, but simply their mathematical meaning.

Given the distribution $F_X(x)$ of a random variable X representing post-onset lifetime, we multiply the timescale by a constant $\phi \geqslant 1$ to obtain a new random variable Y such that:

$$F_Y(x) = \mathrm{P}[X \leq \phi x] = F_X(\phi x). \tag{9}$$

If X has intensity $\mu_X(x)$, then Y has intensity $\mu_Y(x) = \phi\mu_X(\phi x)$, and the median of Y is $1/\phi$ times the median of X. Thus $\phi = 3$ and $\phi = 1.5$ correspond to a median time to claim of 1/3 (Stage II) or 2/3 (Stage III), respectively, of the median lifetime after onset.

D. Critical Illness Insurance Underwriting

D.1. Underwriting of an Applicant who is a MD Mutation Carrier

Knowing a genetic test result, based on the model shown in Figure 4, we can calculate the level rate of premium for a unit sum assured for healthy insurance

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TABLE 10

LEVEL NET PREMIUM RATES FOR CARRIERS OF MD MUTATIONS, AS A PERCENTAGE OF THE PREMIUM FOR STANDARD RISKS. CLAIMS ARISING AT STAGE II ($\phi = 3.0$). CRITICAL ILLNESS INSURANCE CONTRACTS WITH UNIT SUM ASSURED.

Female				Male			
Age (Years)	Term (Years)	CTG250– %	CTG250+ %	Age (Years)	Term (Years)	CTG250– %	CTG250+ %
20	10	921	4,333	20	10	1,512	7378
	20	1,079	4,791		20	1,517	6891
	30	895	3,224		30	1,037	3785
	40	691	2,198		40	689	2203
30	10	735	3,467	30	10	939	4547
	20	757	2,810		20	821	3075
	30	612	1,962		30	582	1863
40	10	477	1,528	40	10	474	1517
	20	480	1,317		20	431	1162
50	10	301	752	50	10	260	618

TABLE 11

LEVEL NET PREMIUM RATES FOR CARRIERS OF MD MUTATIONS, AS A PERCENTAGE OF THE PREMIUM FOR STANDARD RISKS. CLAIMS ARISING AT STAGE III ($\phi = 1.5$). CRITICAL ILLNESS INSURANCE CONTRACTS WITH UNIT SUM ASSURED.

Female				Male			
Age (Years)	Term (Years)	CTG250– %	CTG250+ %	Age (Years)	Term (Years)	CTG250– %	CTG250+ %
20	10	376	1,475	20	10	551	2,464
	20	644	2,670		20	805	3,819
	30	620	2,124		30	610	2,485
	40	517	1,488		40	420	1,486
30	10	314	1,176	30	10	350	1,521
	20	477	1,634		20	432	1,782
	30	441	1,236		30	329	1,170
40	10	227	554	40	10	197	550
	20	322	780		20	230	690
50	10	167	307	50	10	130	264

applicants who are mutation CTG250+ or CTG250– carriers, and for non-mutation carriers (whom we take to define standard risks). Tables 10 and 11 show the net level premium rates for different entry ages and policy terms, payable continuously, for a unit sum assured for both males and females, as a percentage of the premium for standard risk, assuming claims arise at Stage II or Stage III, respectively. We assume a constant force of interest $\delta = 0.05$. We observe the following.

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(a) As suggested by Brackenridge & Elder (1998), applicants might be accepted at a rate of +200% to +300% for certain CI insurance products, but most insurers would decline cases where the premium rating was over +200% to +250%. Therefore, almost all mutation carriers, either CTG250+ or CTG250–, become uninsurable. The premium charged for a healthy mutation carrier could be as high as 74 times standard.
(b) In Table 10, the exceptions are male and female mutation CTG250– carriers at age 50 purchasing 10-year policies. In Table 11, male and female mutation CTG250– carriers at ages 40 and 50 purchasing 10-year contracts might be insurable.
(c) Since the epidemiology of MD is not gender-differentiated (in this study), differences between males and females arise from differences between the intensities μ_x^{i02} and μ_x^{i03} for males and females.
(d) The extra premium rates are very sensitive to the entry age. The relative level of extra premium rate decreases with increased policy term and increased entry age.

D.2. Underwriting Based on Family History Only

We assume that we cannot infer from the parent's age at onset whether a CTG250– or CTG250+ mutation is implicated. Therefore at birth, by Mendel's laws and our assumed prevalences, a child of an affected parent has a 25% chance to be a mutation CTG250+ carrier, a 25% chance to be a mutation CTG250– carrier, and a 50% chance to be a non-mutation carrier (NC). Denote this probability as p_i for genotype g_i. Let OP_x^{i0} be the probability that a new-born with genotype i remains in State 0 at age x. The underwriter who knows that an applicant has an affected parent wishes to know the probability:

$$\mathrm{P}[\text{genotype } g_i \mid \text{healthy at age } x \text{ and with family history}]$$

denoted P_i, which can be calculated as:

$$P_i = \frac{p_i \, OP_x^{i0}}{\sum_{j=1}^{3} p_j \, OP_x^{j0}}. \tag{10}$$

In this case, the net level premium will be the ratio of the EPV of 1 unit of benefit to the EPV of 1 unit of premium each weighted by the P_i. Table 12 shows the net level premiums, payable continuously, as a percentage of the standard rate, for different entry age and policy term. We make the following comments.

(a) In most cases, applicants with a family history are uninsurable. The premiums charged can be as high as 20 times the standard premium. However, more people at higher ages could be accepted at increased premium rates, because survival free of onset reduces the probability of being a mutation carrier.

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TABLE 12

LEVEL NET PREMIUM RATES FOR CRITICAL ILLNESS INSURANCE APPLICANT WITH FAMILY HISTORY OF MD, AS A PERCENTAGE OF THE PREMIUM FOR STANDARD RISKS. CRITICAL ILLNESS INSURANCE CONTRACTS WITH UNIT SUM ASSURED.

Female				Male			
Age	Term	Claim Arising At Stage II (%)	Claim Arising At Stage III (%)	Age	Term	Claim Arising At Stage II (%)	Claim Arising At Stage III (%)
20	10	1,231	478	20	10	2,046	743
	20	1,237	776		20	1,746	1,052
	30	823	616		30	954	680
	40	574	451		40	575	427
30	10	651	289	30	10	827	342
	20	511	364		20	551	371
	30	370	294		30	356	265
40	10	235	147	40	10	234	141
	20	213	172		20	199	153
50	10	141	114	50	10	132	108

(b) the level of premiums is lower than in Tables 10 and 11. This is the effect of averaging over the three sub-populations, and the ageing effect mentioned in (a).
(c) As in Tables 10 and 11, the extra premiums are more sensitive to age than to policy term.

E. A LIFE INSURANCE MODEL

In Section B.3, we found that mortality after onset of MD depends on duration since onset as well as age. Therefore, for a life insurance policy, we use a semi-Markov model adopted from Gutiérrez & Macdonald (2004) shown in Figure 5,

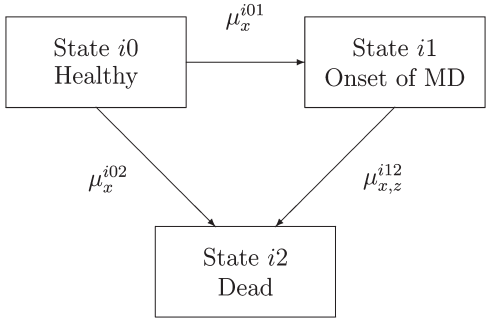

FIGURE 5: A multiple-state semi-Markov model for myotonic dystrophy in life insurance for insurance applicants with genotype g_i. Mortality after onset depends on age x and duration since onset z.

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to calculate net level life insurance premium rates. Intensity μ_x^{i01} follows the definition of the onset rate of MD, which is specified in Section B.2. For intensity μ_x^{i02}, because the impact of MD on mortality is negligible, so we use the life table ELT15 without any adjustment. Post-onset mortality $\mu_{x,z}^{i12}$ was defined in Section B.3.

In this model, insured applicants pay premiums continuously while remaining in States $i0$ and $i1$, and the claim is paid when they enter State $i2$ either directly from State $i0$, or through State $i1$. We calculate the net level premium for a unit sum assured. We assume a constant force of interest $\delta = 0.05$.

We can easily write out expressions for the EPVs of a unit of premium and a unit of benefit as follows, assuming the entry age is x and the policy term is n:

$$\text{EPV}[\text{Premium}] = \int_x^{x+n} e^{-\delta t}\, {}_tp_x^{i00}\, dt + \int_x^{x+n} e^{-\delta t}\, {}_tp_x^{i00}\, \mu_{x+t}^{i01} \int_0^{n-t} e^{-\delta s}\, {}_sp_{x+t,0}^{i11}\, ds\, dt, \tag{11}$$

$$\text{EPV}[\text{Benefit}] = \int_x^{x+n} e^{-\delta t}\, {}_tp_x^{i00}\, \mu_{x+t}^{i02}\, dt + \int_x^{x+n} e^{-\delta t}\, {}_tp_x^{i00}\, \mu_{x+t}^{i01} \int_0^{n-t} e^{-\delta s}\, {}_sp_{x+t,0}^{i11}\, \mu_{x+t+s,s}^{i12}\, ds\, dt. \tag{12}$$

Then the net level premium for a unit of benefit payable continuously should be EPV[Benefit] / EPV[Premium].

F. Life Insurance Underwriting

F.1. Underwriting of MD Mutation Carriers

Table 13 shows the net level life insurance premium rates for mutation CTG250+ and CTG250– carriers, as a percentage of standard premium rates.

(a) Generally, females mortality is lower than that of males. Therefore premium increases are higher for females, especially for cover expiring at later ages.
(b) The premium increases are lower than those for CI insurance.
(c) As suggested by Brackenridge & Elder (1998), applicants might be accepted at a rate of +200% to +300% for certain life insurance products, but most insurers would decline cases where the premium rating was over +200% to +%250. We see that male mutation CTG250– carriers at high ages are more likely to be insured at an increased rate than females, and that mutation CTG250+ carriers are generally uninsurable with few exceptions at higher ages.

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TABLE 13

LEVEL NET PREMIUM RATES, AS A PERCENTAGE OF THE PREMIUM FOR STANDARD RISKS.

Female				Male			
Age (Years)	Term (Years)	CTG250– %	CTG250+ %	Age (Years)	Term (Years)	CTG250– %	CTG250+ %
20	10	317	1,171	20	10	182	506
	20	678	2,739		20	365	1,311
	30	844	3,058		30	491	1,659
	40	730	2,203		40	445	1,264
30	10	345	1,346	30	10	234	781
	20	582	2,025		20	387	1,254
	30	600	1,782		30	394	1,102
40	10	246	629	40	10	189	426
	20	348	854		20	244	544
50	10	154	271	50	10	127	186

TABLE 14

LEVEL NET PREMIUM RATES FOR A HEALTHY APPLICANT WITH A FAMILY HISTORY OF MD, EXPRESSED AS A PERCENTAGE OF THE PREMIUM FOR STANDARD RISK.

Age (Years)	Term (Years)	Females %	Males %
20	10	397	213
	20	823	432
	30	894	518
	40	663	412
30	10	328	221
	20	453	311
	30	408	283
40	10	155	133
	20	184	149
50	10	111	106

F.2. Underwriting Based on Family History Only

Table 14 shows the net level premium rates for insurance applicants with a family history, as a percentage of the standard premium rates. The methodology is the same as for CI insurance. We see that males are more likely to be insured at an increased premium rate, except for applicants aged 20 seeking cover for over ten years. Females are only likely to be insured, at an increased premium rate, at high ages.

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G. Adverse Selection

Costs of adverse selection arising from MD alone are reported in Yu (2010). Since MD is included in the 'bottom-up' model described in the body of this paper, for brevity we omit these MD-only results.

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