1. INTRODUCTION

Since 1995 discussions between the United Kingdom (UK) Government and the insurance industry have led to an agreement on the issue of non-discrimination for persons at risk of genetic conditions. In this regard, the mandate of the Association of British Insurers (ABI) entails researching ways in which the genetically disadvantaged can have access to insurance. The ABI is a trade association representing approximately 400 companies which transact 96% of the insurance business in the UK. The particular focus of the Working Party, which was set up to fulfil this mandate, is in assessing the cost of four proposed schemes for pooling genetic risk and offering subsidised premium rates to such individuals.

The four schemes under consideration by the ABI are the establishment of a new company, a reinsurance pool, an assessmentism system and reimbursement of extra premiums. While each scheme represents a different pooling arrangement whereby the cost will be met, McGleenan (2001) suggests that the (final) cost in the private insurance market will be borne by the shareholder, policyholder or taxpayer. However, the aim of the present study is not to address who will eventually bear the cost of the chosen pooling scheme – that is purely a political issue – but rather to focus on the cost to the original insurer of offering insurance to 'extra risk' individuals at these subsidised rates. This approach is possible, because from an actuarial point of view, all four schemes are the same.

This work is done in the context of critical illness insurance (where benefits are payable on diagnosis of a serious illness) for eight genetic disorders listed by the ABI as being important. These are Huntington's disease, familial adenomatous polyposis, myotonic dystrophy, Alzheimer's disease, multiple endocrine neoplasia, hereditary motor and sensory neuropathy, adult polycystic kidney disease - which was subsequently dropped from the list because a non-DNA based test is used for its detection - and hereditary breast cancer.

1.1. Genetic Disorders, the Inheritance Process and Mutation Penetrance

Genetic disorders result from mutations in two types of cells that are present in the human body – somatic (e.g. hairs, skin and blood cells) and germ cells (sperm and eggs).[1] Their

[1] While the nucleus of each germ cell contains a single copy of each of the 23 chromosomes (one for sex determination and 22 different autosomes), the chromosomes in the somatic cells exist in pairs making 46 in total [Fischer & Berberich, 1999].

presence may be detected by genetic testing, which according to Fischer & Berberich (1999), entails the examination of an individual's genetic material, deoxyribonucleic acid (DNA), with the detection of alterations in one's genetic make-up indicating the likelihood of a disorder (better known as a genetic disease). DNA is a threadlike molecular structure built from four building blocks called nucleotides – adenine (A), guanine (G), cytosine (C) and thymine (T) [Fischer & Berberich, 1999 and Regenauer & Schmidtke, 2001]. The DNA sequence contains the entire genetic information used by a cell in order to perform its functions, while a gene is the sequence of nucleotides used by a cell to manufacture an individual protein.[2] A specialised form of cell division takes place during which the DNA is duplicated. However, this replication process is susceptible to error and hence there exists the possibility of hereditary information being altered. Furthermore, external factors such as chemicals, radiation and viruses may influence the mutation of genes. Unfortunately, these blunders can lead to serious illnesses or even death. In particular, mutations in germ cells may be passed onto the next generation.

The literature acknowledges four types of genetic disorders - monogenic, chromosomal, somatic and polygenic.

- *Monogenic (single-gene) disorders*

  These occur where a single gene is altered with the consequence that the pattern for a specified protein is flawed thereby leading to the manifestation of the disease. Huntington's and Sickle cell diseases are examples of monogenic disorders. Over 6,000 genes are known in which mutation leads to various monogenic disorders.

- *Chromosomal aberrations*

  Changes (additions or deletions) in the chromosomes result in chromosomal abnormalities, with Down Syndrome being the most prevalent manifestation.

- *Somatic disorders*

  These are mutations in somatic (non-germ) cells and because they are localised, genetic testing of the nuclear DNA of an asymptomatic individual does not guarantee presymptomatic detection of the disease. Furthermore, they remain in the corresponding body tissue and are not passed on to future generations. Therefore, one can observe that a genetic disease is not necessarily an inherited disease [Regenauer & Schmidtke, 2001].

[2] Regenauer & Schmidtke (2001) reported that in the entire human genome, there are between 70,000 and 100,000 different genes, with specific instructions for constructing cells, organs and other body matter. However, since the official mapping of the human genome (2001), this number was revised down to around 30,000 [Sudbery, 2002].

- *Polygenic disorders*

  These result from the interaction of several mutations which leads to an illness. However, apart from the mutation of several genes, one or more environmental factor(s) usually contribute to the manifestation. For this reason, they are regarded as multifactoral disorders and they are in fact very common in the population. In this way, the contribution of the gene is regarded as a predisposition, rather than a strongly predictive indication as sometimes observed in monogenic disorders. Common diseases with a multifactoral genetic contribution include coronary heart disease and strokes [Regenauer & Schmidtke, 2001].

The seven disorders on the ABI's list are single-gene disorders. Single-gene disorders may be inherited as dominant traits, recessive traits or X-linked traits. For autosomal dominant disorders, only one parent need be a mutation carrier for the offspring to be affected by the disease. According to the Mendelian laws of inheritance of rare dominant traits, 50% of the offspring would be mutation carriers and the other 50% would be non-carriers. On the other hand, autosomal recessive disorders require both parents to be mutation carriers for the offspring to be affected, and a child carries two copies of the mutation with a 25% probability. In the case of the X-linked disorders, if a mother is carrying a mutation in the X-chromosome then her sons have a 50% chance of developing the illness, while her daughters have a 50% of becoming carriers [Regenauer & Schmidtke, 2001]. While all seven of the disorders on the ABI's list may be inherited as dominant traits, recessive forms of some disorders such as hereditary motor and sensory neuropathy may also exist.

Of course, the likelihood that mutation carriers will be affected by the disease depends on the mutation penetrance of the gene. Mutation penetrance refers the probability that defective genes will lead to the development of the illness or disorder. Mutation in genes which are associated with a high probability of manifestation (normally by retirement age) are known as highly penetrant disorders and are usually associated with early age of onset e.g. Huntington's disease and early-onset Alzheimer's disease. On the other hand, the age of onset of some diseases such as breast cancer varies widely, and there is a great deal of uncertainty associated with the mutation penetrance by very high ages. However, from the insurer's point of view, it is the penetrance of the disorder below retirement age when most contracts are in force that is important. The penetrance at these earlier years (even for HD) is less clear and hence one can say that there is great uncertainty in the penetrance of all the disorders.

1.2. Insurance, Genetic Testing and Adverse Selection

While the existence of genetic disorders need not affect the underwriting process, certain types of legislation governing the use of genetic information may cause the process to break down. This assertion is based on the following. During the underwriting process, information such as sex, lifestyle, medical test results and family history are drawn upon to inform the setting of premiums. This process normally reveals three types of risk - standard, extra or 'too high'. In the case of standard or extra risk, persons of similar risk are then pooled together and charged accordingly. This is based on the principle of mutuality [Australian Law Reform Commission, section 11.26 to 11.28, 2001]. On the other hand, persons falling into the latter category are normally denied insurance, as the possible experience may be too uncertain, even averaging across individuals.[3]

Hence, individuals with a known family history of a genetic disorder present themselves as 'extra risk' to insurers who then normally charge additional premiums to compensate for the added risk. In contrast, if legislation were in place that prohibited the use of family history or other types of genetic information, it would be impossible in the underwriting process to ascertain the risk profile of individuals. Thus, it quite possible that persons at risk of these genetic disorders could benefit from premiums below those appropriate for their risk profile. The insurer may then be exposed to negative actions of policyholders who because of this asymmetric information may now be able to afford insurance or buy it at a rate in excess of the normal rate of purchase. This occurrence is known adverse selection.

Therefore, the advent of genetic testing for genetic disorders has heightened fears of adverse selection within the insurance industry. But the realisation of these uncertainties depends on the mutation frequencies in the population and rate of testing for the genetic disorders associated with them. These factors come together to determine how much asymmetric information exists in the system and hence the possibility of newly insured clients 'selecting against the office'. In addition, the rate of onset of a serious illness or rate of mortality (related to a genetic cause) would be a contributing factor in the determination of the financial impact of adverse selection on the insurance industry.

[3] According to Leigh (1990), in the United Kingdom, 95% of applicants for life insurance are accepted at standard rates, 4% at increased rates and the other 1% declined.

To date, only the monogenic disorders have been identified as having a potentially serious impact on the life insurance industry because of their high risks. In particular, according to Harper and Clarke (1997) only the autosomal dominant disorders are regarded as relevant to life insurance industry, while the effect of genetic testing for polygenic disorders is uncertain. However Macdonald (2001) suggested that the life insurance market was large enough to deal even with monogenic disorders, but the same could not be alleged for the critical illness insurance market which is significantly smaller. Furthermore, it is felt that testing for chromosomal and somatic disorders will not have a significant impact on the industry [Macdonald, 1999].

1.3. Social Impact of Genetic Testing

The general consensus in the early 1990s was that insurers would request genetic tests results from prospective policyholders. The belief that these results would then be used during the underwriting process to predict future lifetimes accurately caused fears of discrimination towards genetically disadvantaged individuals. However, genetic testing would not eliminate the randomness in the prediction of future lifetimes of the insured because it does not say definitively when the onset of such diseases will occur. In addition, the predictive power of DNA testing may be limited not only by incomplete mutation penetrance, but variable expressivity and imprinting.[4]

However, the initial fears of legislators did result in a speedy reaction to the plight of genetically disadvantaged individuals in context of insurance purchasing as well as the insurers' fears of adverse selection. Various moratoria were implemented from 1996 to ensure that the necessary research is conducted before a 'solution' which is acceptable to both parties (insurers and genetically disadvantaged individuals) is put forward. The ABI Working Party is very prominent in this process and the proposed pooling mechanisms represent a step towards the 'best' solution.

1.4. Plan of the Dissertation

The aim of the present paper is to quantify the costs of offering insurance to 'extra' risk individuals at subsidised rates. Here subsidised rates are those adjusted for family history of a

[4] Expressivity refers to the quantitative differences in the manifestation of the disease or symptoms, while imprinting occurs when genetic information manifests itself differently depending on the parent from whom the disorder is inherited [Regenauer and Schmidtke, 2001].

genetic disorder assuming that this is the only information available to the insurer. In this case, the exercise is tantamount to quantifying the cost of adverse selection in the system. However, when this assumption is relaxed and family history information also cannot be used, it will be shown that other costs arise that are not only related to adverse selection. Each of these cases will be dealt with in turn. We will do this in the context of the critical illness insurance market, largely due to the 'relatively' easy application of the Markov multi-state modelling approach and data availability. The work here is an approximation, based on the assumption that the major monogenic disorders highlighted by the ABI as relevant to the insurance industry can be allocated to a few representative categories. This is all that is possible now in the absence of more detailed information from epidemiological research into some individual disorders.

The remainder of the paper is presented as follows. Section 2 gives a brief synopsis of the events leading up to the current situation of genetics and the insurance industry. This is followed by Section 3 on modelling where a Markov multi-state model (following Macdonald, Waters & Wekwete, 2003a) is developed for the critical illness insurance market. The model is parameterised in Section 4 and 5 mainly by drawing on approaches employed in modelling four different disorders. The results and discussion are presented in Section 6. Section 7 concludes the paper.

2. ACCESS FOR ALL

Ideally, one would like to move towards a situation where persons with genetic conditions have access to insurance. To do otherwise would signal a move towards a class society divided along the lines of 'good' and 'bad' genes. This would jeopardise the work done on eliminating discrimination on the grounds of ethnicity, sexual orientation, disability, etc.

2.1. The ABI's Mandate

To this end, the ABI was charged by the Human Genetics Commission (HGC) with exploring ways to improve access to insurance for the genetically disadvantaged. Presently, they are considering four options for pooling the genetic risk of such individuals. The four pooling schemes proposed by the ABI are:[5]

[5] Report of the Chairman of the ABI Working Party on "Access to Insurance".

- The establishment of a new company which would issue insurance products at subsidised rates, while the losses would be met by a levy on member life companies;
- The 'Reinsurance pool' mechanism which would issue policies at subsidised rates, while a central risk premium pool would reinsure policies at rates consistent with the premiums paid. Losses would be met by participating life companies.
- The 'Assessmentism' system which would issue policies at subsidised rates, while a central fund would reimburse the mortality/morbidity component of eligible claims. Funds would be recovered from member companies.
- The 'Reimbursement of extra premiums' scheme where policies would be issued directly by the companies at actuarially-determined rates. However, policyholders would pay a subsidised rate of premium and the life companies would be reimbursed by a central pool which would recharge the costs to its members.

The 'subsidised' rate of premium refers to the rate charged in the absence of any genetic testing information, i.e. rates based on family history. Thus, disclosure of genetic testing information would not be necessary in the setting of premium rates. However, since the cost of cover has to be met, reserves would have to be set up and these would require some disclosure of genetic information. And herein lies the conflict between the policymakers and the financial community; a conflict that may have to be resolved in order to implement any of the schemes.[6] For the 'reimbursement of extra premiums' scheme, full disclosure of genetic information would be required up front in order to ascertain the actuarially fair premium, which according to Bakker *et al.* (2000) is the insurance premium which equals the expected loss to that individual as covered by the insurance policy. However, any such disclosure requirement would raise serious political and social concerns relating to data protection issues, and could further accentuate fears of discrimination.

However, many events have transpired to bring us where we are today. Specifically, the assertion that (with access to genetic test results) insurers could now predict the future lifetime of individuals created some concern among legislators who believed that persons found to be

[6] The Financial Services Authority (FSA) may be willing to accept simplified reserves, for example a percentage of premiums and in this way genetic testing information may not be required.

genetically disadvantaged would be discriminated against.[7] The following gives a brief account of the events leading up to the present situation.[8]

2.2. Brief History of Genetics and Insurance in the United Kingdom (1995-present)

The discussions between government and the insurance community on genetics started in 1996 when the government rejected the advice given by the House of Commons Science and Technology Committee (HCSTC) on aspects of human genetics and immediately established the Human Genetics Advisory Commission (HGAC) which was later subsumed into the HGC. A year later, the HGAC (1997) recommended a two-year moratorium on the use of genetic information to allow for the relevant research to be conducted. At the same time, the ABI appointed a genetics advisor and imposed a voluntary moratorium on requesting genetic tests, the use of any existing DNA-based test result for life insurance up to £100,000 in connection with a mortgage and 'cherry-picking' (giving low premiums to those with 'good' genetic test results). The ABI also introduced a list of eight (later seven) single-gene disorders that it regarded as significant to the industry.

Later, the Government also set up the Genetics and Insurance Committee (GAIC) with the task of considering applications from insurers to be allowed to use genetic test results in some circumstances. However, the ABI advised its members to continue to use results (within the terms of the moratorium) until told to do otherwise. Finally, the HCSTC (2001) and HGC (2001) reports led to a voluntary five-year moratorium being agreed between the government and the ABI on the use of genetic testing for contracts of below £500,000 for life insurance and £300,000 for other types of insurance. In addition, the HGC stressed that they regarded family history as genetic information and while not extending the moratorium to this area, emphasised that this stance would be revisited after three years.

One can see that the path forward was mapped out with the recommendation based on discussions between government and the insurance industry and published in the HGC summary report (2002) that "……*during the period of the moratorium risk pooling and other models*

[7] A public opinion survey commissioned by the HGC revealed that about 80% of persons polled believe that genetic testing should not be used in setting premiums and should be restricted to police investigations [Australian Law Reform Commission Report, Section 2.9-2.10, 2001].

[8] This account of events from 1995 to present is based on Macdonald (1999).

should be explored further by independent experts from the actuarial profession, insurance industry and the genetics community". Specific suggestions from that HGC report (2002) include a reinsurance pool and an insurance-funded risk pool. The document prepared by McGleenan (2001) then formed the basis for the Report of the Chairman of the ABI Working Party on "Access to Insurance".

2.3. Analysis of ABI Options for Pooling Genetic Risk

The ABI Working Party highlighted some distinguishing features of the four schemes along the following lines: quantification of extra risk; data collection; carrier of mortality (morbidity) risk; product structure; independence of industry; costs; distribution and control of multiple applications.

For the first three schemes – the 'new company', the 'reinsurance pool' and 'assessmentism' – quantification of the premiums is not required and these schemes therefore have an immediate advantage over the 'reimbursement of extra premiums' arrangement where the actuarially fair premium would have to be ascertained. To set actuarially fair premium rates, insurers would require genetic testing information, which is not the case for setting premiums in the first three arrangements. In contrast, the subsidised premium rates (for the first three schemes) would be determined by family history through the normal underwriting process. However, in light of the HGC's stance on family history being regarded as genetic information, one must wonder why the proposed subsidised rates still include the use of such information. That being said, the ABI has determined that their discussions with government concern just a ban on genetic information (narrowly defined).

Nonetheless, as mentioned in Section 2.1, since reserves would still have to be set aside, normal prudential practice means that genetic information should be collected if any of the first three schemes were adopted, making this requirement of genetic information a necessity for any of the schemes to work effectively.

In addition, in the event that the actuarially determined premium under the fourth arrangement is insufficient to cover the cost of the benefits due to the policyholder, the original insurer must meet the cost. This is not the case with the first three arrangements, which are designed to pool the cost of the mortality or morbidity risk across participating companies.

In attempting to choose among different options for pooling genetic risk, the costs of each mechanism feature prominently in the consideration of the ABI Working Party. So far, they have suggested that the setting up of the 'new company' would be the most costly of the proposed pooling schemes. This stems from the start-up cost and the fact that the scheme would not be operating through existing channels. However, the possibility of being independent of the industry may give the scheme the flexibility to do things differently. But any advantage gained from its perceived independence may be lost through its basic product structure.

The 'reinsurance pool' with its flexibility in product range as well as lower cost projection by the ABI appears to be superior to the 'new company'. However, some concern may be raised over the effectiveness of this system given the insurers' discretion in setting their standard rates of premium. This could easily result in a situation where insurers purposely set premiums excessively low and simply recoup the losses from the reinsurance pool.

Of the first three schemes, the 'assessmentism' pooling scheme has the appeal of being the least disruptive. That is, there would be no need to form a new company or to establish any reinsurance pool mechanism and products would be distributed using existing channels. Furthermore, it meets the need for genetically disadvantaged persons to be absorbed into the present system and not to feel alienated by their more 'fortunate' counterparts.

It is clear that if any of the schemes were compulsory the cost to the industry would be passed on. The costs of some schemes may be borne primarily by shareholders through reduced dividends, while for others the costs would be carried by existing policyholders through increased premiums. The last possibility is where government funds the subsidisation of the scheme through increased taxes [McGleenan, 2001]. However, in the final analysis the policyholder will have to bear any increase in cost. For example, if the initial cost was borne by the shareholder via a reduction in dividends, this would cause a fall in share prices. This downturn in the company's performance would require a restructuring of operations which will more often than not involve an increase in premium rates for policyholders.

These costs can be divided into administrative and subsidised costs with the foregoing being largely administrative costs. However, in the absence of any expertise in quantifying

administrative costs, it was agreed that this project would concentrate on trying to quantify the subsidised cost using tools already available to actuaries.

If participation was not compulsory then the pool may not be large enough to support the demand without placing too heavy a financial burden on the participating companies (in the cases of the first three schemes). In reality though, were the schemes not compulsory genetic testing would remain a contentious issue and part of the purpose of the scheme would be lost. Therefore, one might expect that there would be strong pressure on all insurers to participate (including those who are not members of the ABI).

Turning to subsidised costs, one observes that based on the equivalence principle for calculating premiums all four schemes are essentially the same. In other words, from an actuarial point of view no differentiation will be made when undertaking the costing exercise. It is suggested that these differences will emerge mainly at the administrative level.

On closer examination of any of the four options, one realises that the exercise is equivalent to quantifying the cost of adverse selection in the system depending on the information set of the insurers. This is because persons will be insured at the premium rates they would be charged if there was simply no requirement to disclose genetic test information. That said, it must be noted that other costs will arise if family history information cannot be used.

3. DEVELOPMENT OF THE MODEL

3.1. Multi-state Models

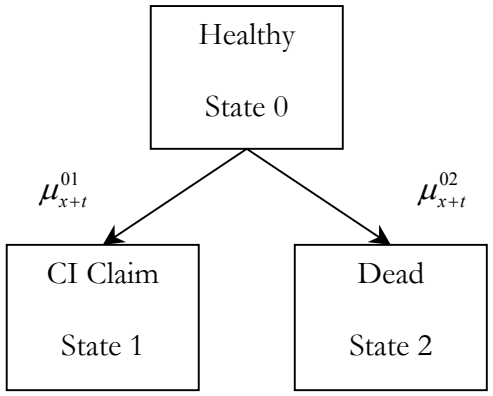
Quantifying the costs of adverse selection in the insurance industry has occupied actuaries for some time now. Most authors have utilised the multi-state model approach to capture the effect of withholding positive genetic test results in different insurance markets. In fact, Macdonald (2002) observed that "….*in particular the discreteness of the states* [of these multi-state models] *corresponds well with the small number of discrete genotypes that feature in the Mendelian single-gene disorders*". Modelling of markets for critical illness and life insurance have featured prominently in the literature largely because of the relative ease with which models may be constructed and the availability of data. This paper focuses on the critical illness insurance market.

3.2. Critical Illness Insurance

Critical illness insurance, unlike life insurance, can be viewed as a 'living benefit'. This is because the benefit is paid on diagnosis of a serious illness thereby allowing the patient to benefit financially while he/she is still alive. Under a 'stand-alone' contract, there is no benefit on death not related to a critical illness or death within a number of days of diagnosis of the critical illness (to be specified under the terms and conditions of each contract). On the other hand, under a life insurance contract, the survivors benefit on the death of the policyholder. Therefore, critical illness insurance is normally sold as a 'rider' to a life insurance contract. An exhaustive list of serious illnesses is also specified in each contract, which may include stroke, heart attack, cancer or kidney failure, etc.

Figure 1 shows how critical illness insurance can be modelled using a multi-state approach.

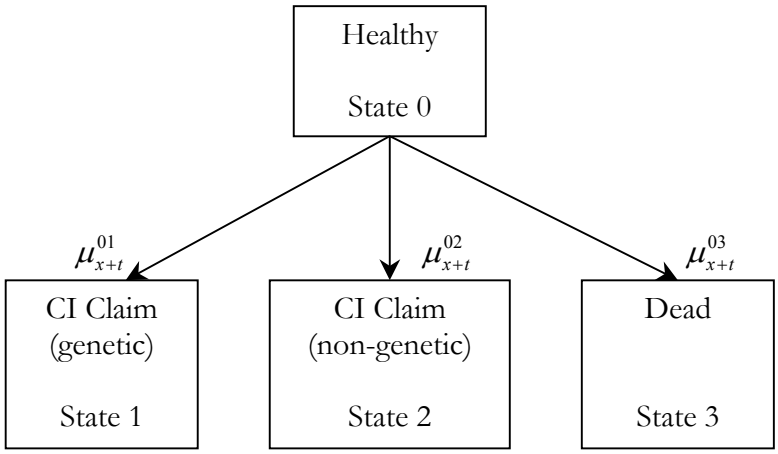
Figure 1: Multi-State Model applied to Critical Illness Insurance



There are three states – healthy, critical illness (CI) claim and dead – along with the associated age-dependent transition intensities μ_{x+t}^{0k}, k=1,2. Thus, a move from the healthy state to the claiming (critical illness) state suggests a diagnosis of a serious illness and the transition intensity μ_{x+t}^{01} captures the rate of onset of the illness. It is a Markov model because transition to state k depends only on the state being currently occupied and age and not how the person reached the present state. However, the validity of this assumption depends on the data and must be checked in each application. (Note the special case of decrement models however that are usually Markov by definition.)

The flexibility of the Markov multi-state model allows for an easy extension of the above model to encompass the possibility that the onset of a critical illness as a result of a genetic disorder, as illustrated below in Figure 2.

Figure 2: Four-State Markov Model for Critical Illness

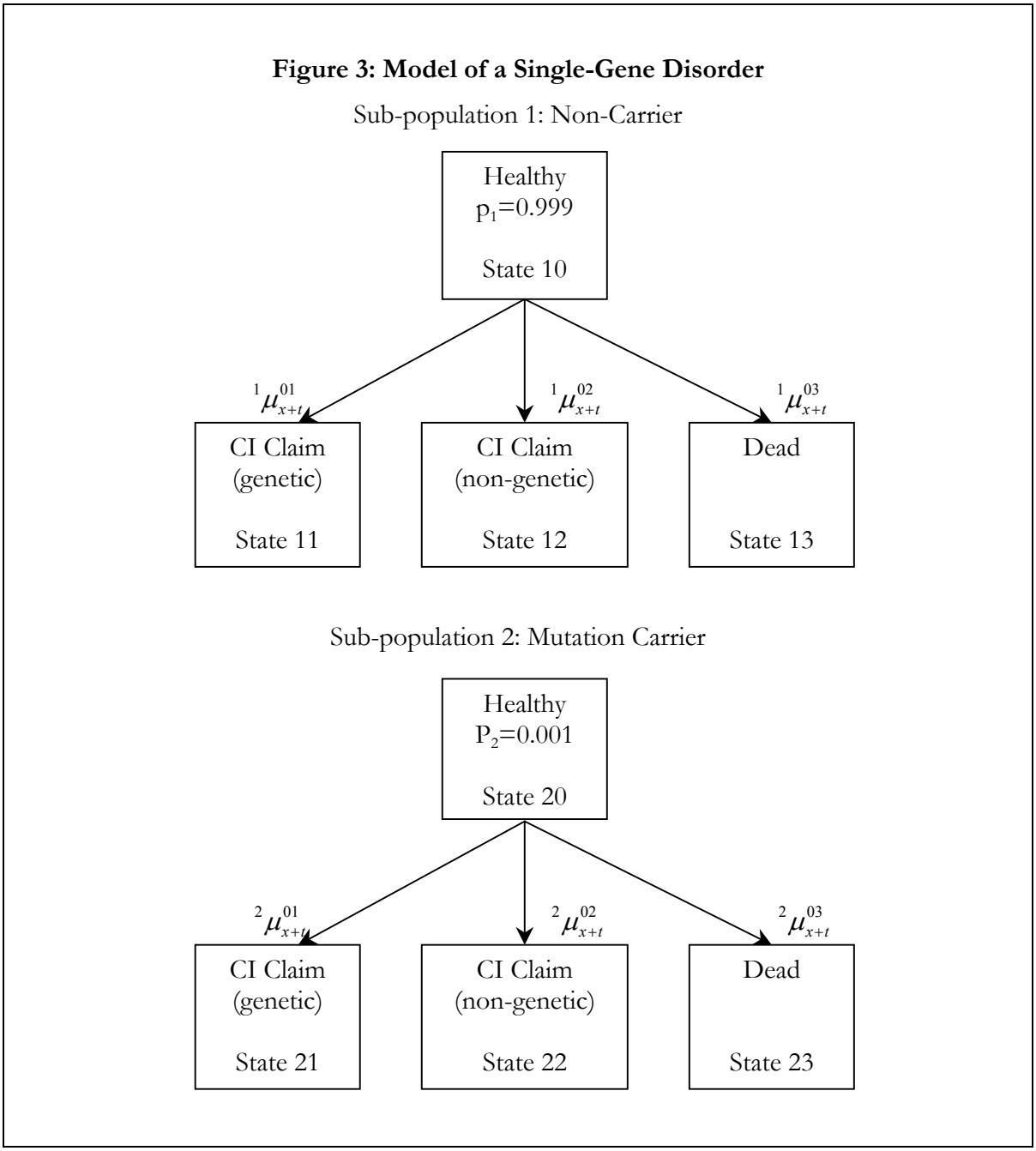


As the models in Figure 1 and 2 are presented, all persons start as healthy with probability one.

3.3. Genetic Heterogeneity

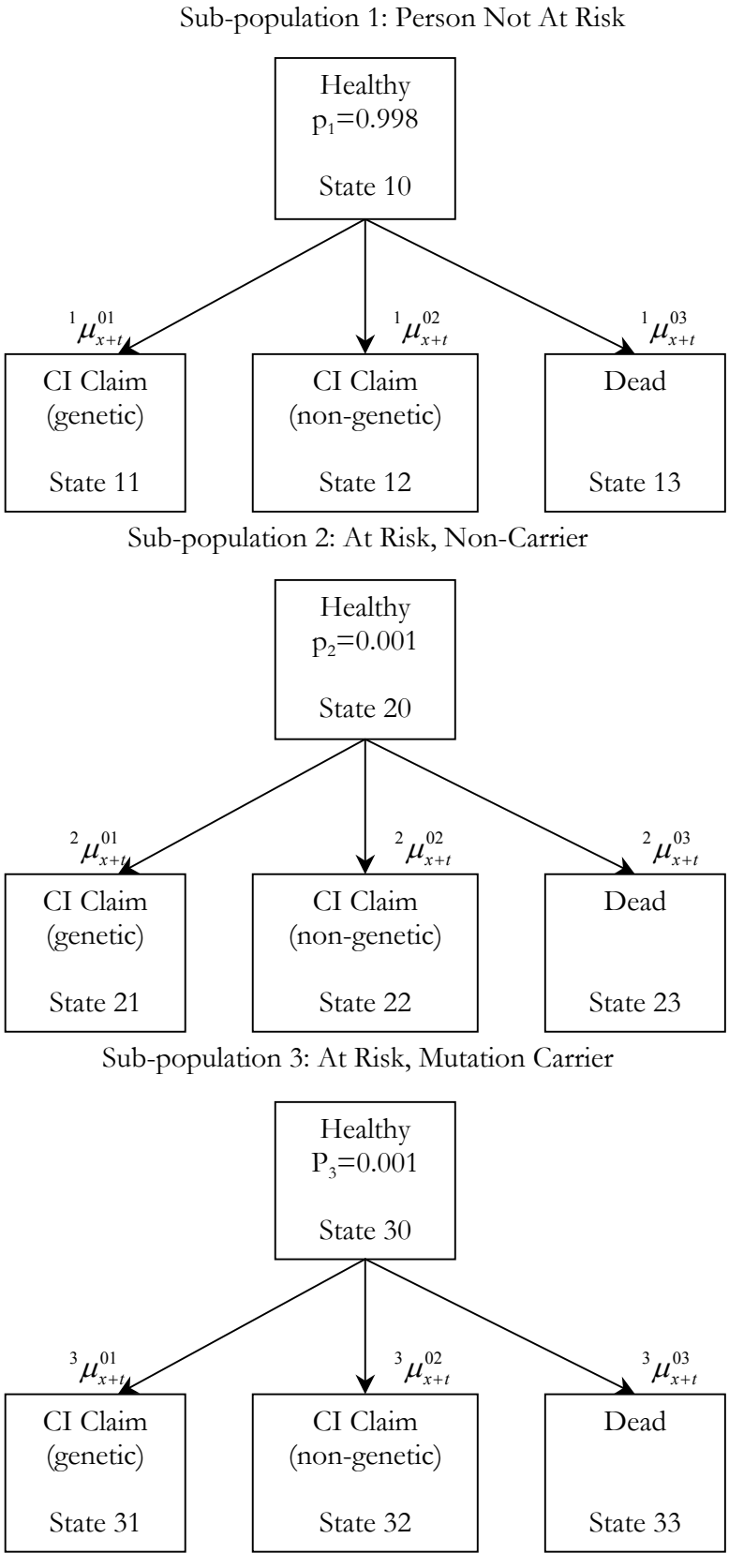
Genetic heterogeneity can be incorporated in the model in Figure 2 by defining separate models for each relevant sub-population. In the case of a single-gene dominant disorder, two sub-populations are evident - those who are non-carriers and those who are mutation carriers. Based on epidemiological research, one can hope to ascertain the proportion of the total population starting in state *i0*, where *i* is the sub-population (*i*=1,2 in this case). For example in the case of adult polycystic kidney disease (APKD), about 1 in every 1,000 are mutation carriers [Dalgaard, 1957]. Hence the proportion of persons carrying the mutation can be estimated as 0.001 ($=p_2$), while the $p_1=0.999$ represents the non-carriers in the population as highlighted in Figure 3.

Figure 3: Model of a Single-Gene Disorder



However, in the absence of genetic tests, family history information may be all that is available. Then the above model in Figure 3 can be extended to three sub-populations – those with no family history who are at no risk, those with a family history who are mutation carriers and those with a family history who are non-carriers. Based on the Mendelian laws of inheritance of dominant traits for rare diseases, 50% of those at risk are non-carriers and 50% are mutation carriers. Hence in the case of APKD, about 0.2% of the population have a family history of whom 0.1% are non-carriers and 0.1% are mutation carriers, leaving 99.8% at no risk. This model is presented in Figure 4 below.

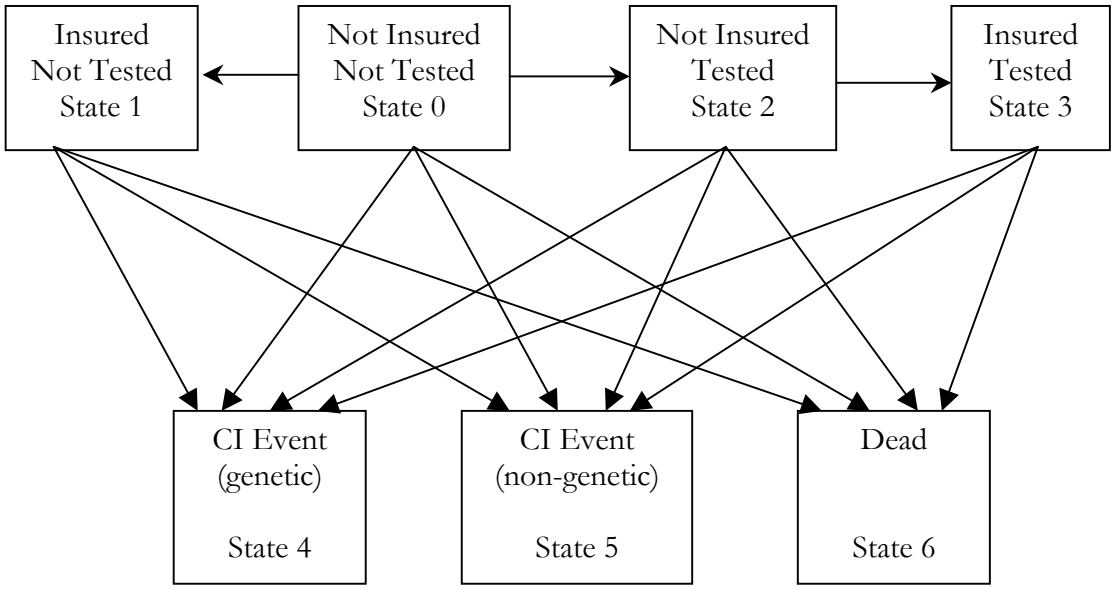
Figure 4: Model of a Single-Gene Disorder and Family History



3.4. Insurance Purchase and Genetic Testing

The question of adverse selection in the context of genetic testing needs a further extension of the model to incorporate both genetic testing and insurance purchases. Following Macdonald, Waters and Wekwete (2003a), the final extension to the model for critical illness insurance emerges and is illustrated in Figure 5 below.

Figure 5: Model for Insurance and Genetic Testing



From Figure 5, several scenarios can be considered in the process of purchasing insurance given the availability of genetic testing. Persons start out in state 0 where they are uninsured and have not had a genetic test. They may then either purchase insurance without having a test (state 1) or opt to get a genetic test without first seeking insurance (state 2). Movement to state 3 occurs when persons having had a genetic test choose to buy insurance. This is where the potential for adverse selection comes to the fore. The test previously done could have been negative in which case both the person and the insurer have the same information. However, in the event of an adverse test result, the potential insured may be allowed (or even compelled) to withhold this 'bad' news from the insurer and benefit from ordinary premiums or ordinary premiums adjusted for family history. Moreover, the insured may even choose to buy more insurance in an attempt to take advantage of the asymmetric information. Thus, the movement

from state 2 to state 3 captures persons' ability to 'select against the office' and this is of particular interest to the insurance industry.

3.5. Incorporating Genetic Heterogeneity, Genetic Testing and Insurance Purchasing

Bringing together the cases of genetic heterogeneity, genetic testing and insurance purchasing produces the model presented in Figure 6. This model now takes into account the following.

(1) mutation frequencies represented by the proportion p_i who start in each population;

(2) the size of the critical illness insurance market which is captured by the normal rate of purchase of critical illness insurance;

$$ {}^{i}\mu_{x+t}^{01},, \quad i = 1,2,3 $$

(3) the prevalence of genetic testing;

$$ {}^{i}\mu_{x+t}^{02}, \; i = 1,2,3 $$

which is assumed to be the same for all sub-populations but would be irrelevant in sub-population 1 since adverse selecting behaviour is assumed to be non-existent due to absence of 'risk factors'.

(4) the extent of adverse selection not only in terms of the act of insurance purchase given an adverse test result but also any increase in the amount of insurance purchased;

$$ {}^{i}\mu_{x+t}^{23}, \mathrm{i} = 1,2,3 $$

(5) rate of onset of critical illness due to the genetic disorder;

$$ {}^{i}\mu_{x+t}^{04}, \; {}^{i}\mu_{x+t}^{14}, \; {}^{i}\mu_{x+t}^{24} \; {}^{i}\mu_{x+t}^{34} \; i = 1,2,3 $$

which would be zero in sub-population 1 and 2.

(6) rate of onset of critical illness not related to the genetic disorder;

$$ {}^{i}\mu_{x+t}^{05}, \; {}^{i}\mu_{x+t}^{15}, \; {}^{i}\mu_{x+t}^{25} \; {}^{i}\mu_{x+t}^{35} \; i = 1,2,3 $$

which would be the same in each sub-population.

Figure 6: Model Incorporating Genetic Heterogeneity, Genetic Testing and Insurance Purchasing

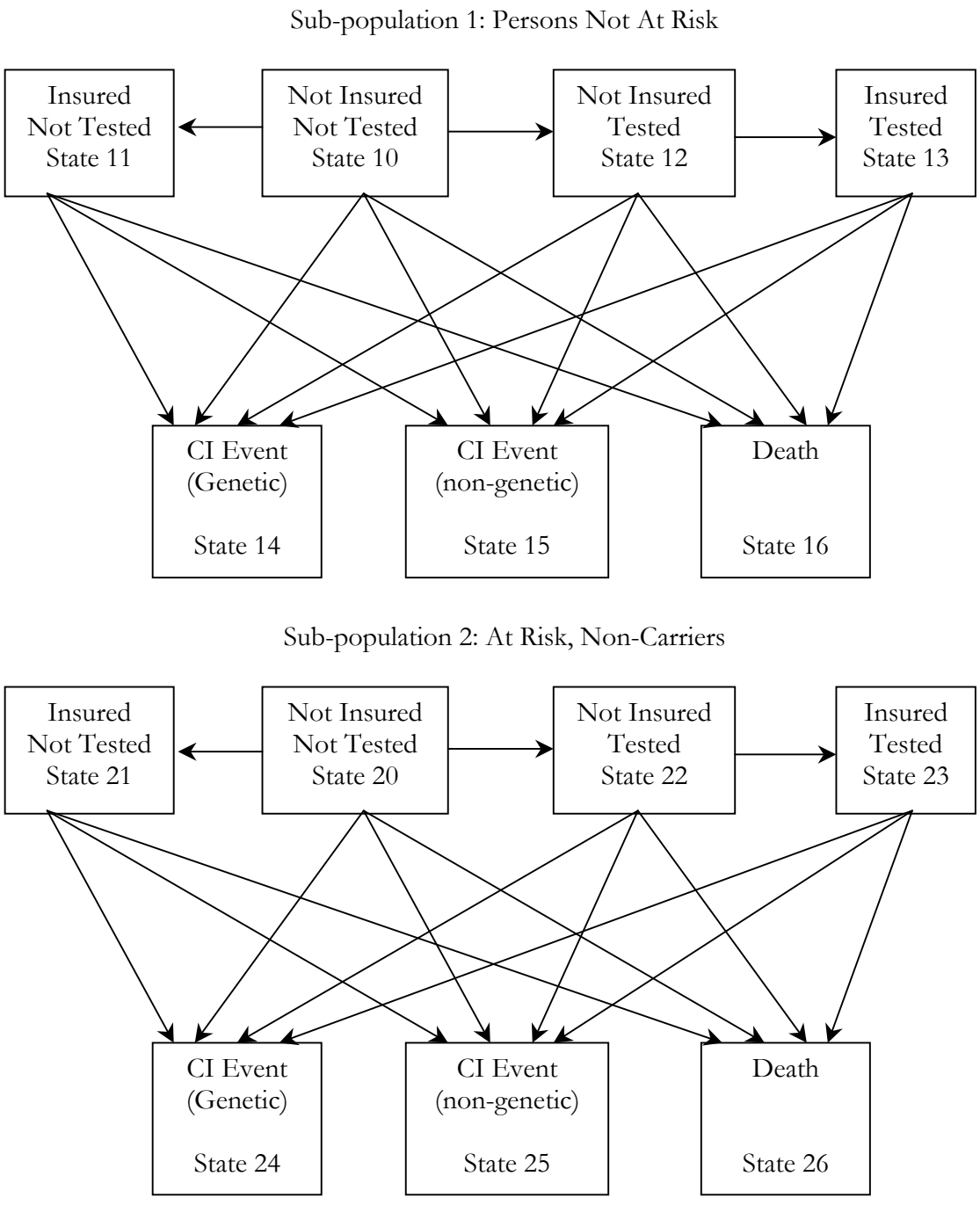
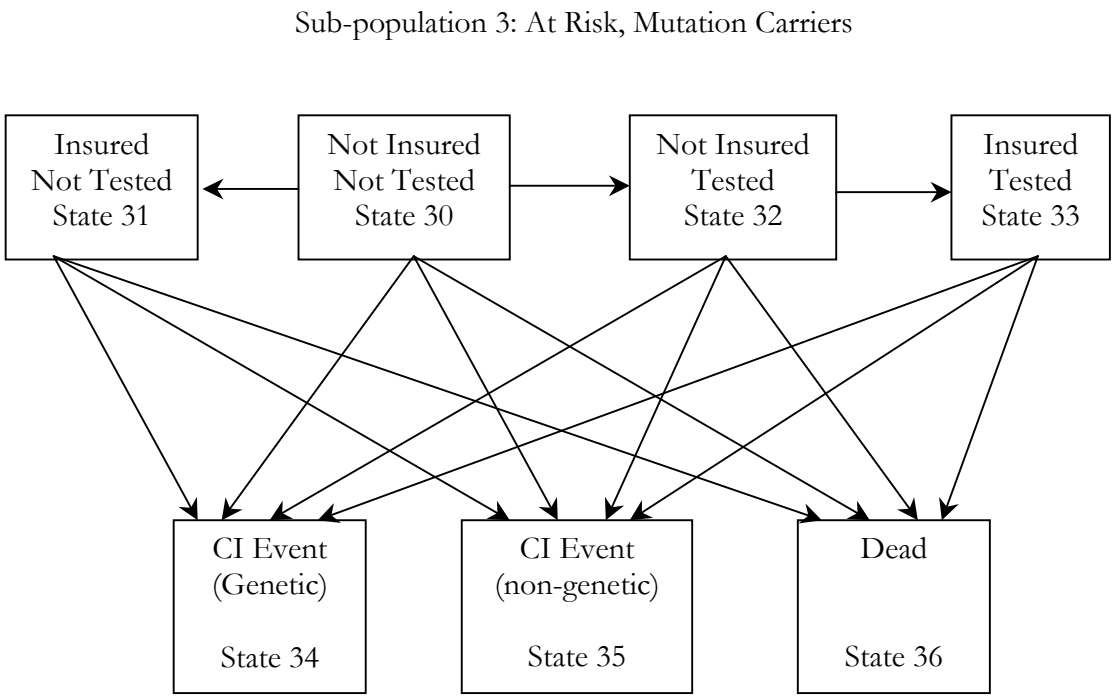


Figure 6 cont'd



(7) rate of mortality adjusted for the incidence of CI events;

$$ {}^{i}\mu_{x+t}^{06},\ {}^{i}\mu_{x+t}^{16},\ {}^{i}\mu_{x+t}^{26}\ {}^{i}\mu_{x+t}^{36}\ i=1,2,3 $$

which would be the same in each sub-population.

(8) the underwriting classes that may be used, defined as sets of insured states within each of which the same rates of premium will be charged.

3.6. Underwriting Classes and the Effect of a Moratorium

As mentioned earlier, the model presented in Figure 6 assumes that family history information is available to the insurer. Hence sub-population 1 comprises persons who are not at risk of the disorder based on the fact that there is no family history of the disease; these persons would pay the ordinary premium rate which forms one underwriting class. On the other hand, sub-populations 2 and 3 would face a premium adjusted upward for the risk due to family history since no differentiation could be made between the mutation carriers and non-carriers based on family history information alone. Thus, the risk is pooled for sub-populations 2 and 3,

resulting in another underwriting class. Therefore, for the case where family history is allowed to be used but not genetic test results, two different underwriting classes are apparent.

Of course, if insurers were allowed to use 'good' genetic test results then tested members of sub-population 2 which has the 'at risk' non-carriers would also benefit from ordinary premium rates. That is, with the moratorium lifted on the use of 'beneficial' genetic information, two different underwriting classes would emerge and at risk non-carriers would benefit, while insurers could better isolate the possibility of adverse selection. Finally, with a moratorium on the use of even family history, we would have just one underwriting class in which all persons pay the ordinary rate of premium.

3.7. Computation in the Model

Given the transition intensities outlined in Section 3.5, certain useful probabilities can be estimated using Kolmogorov equations, based on the following assumptions. If *i* denotes the sub-population and *j* represents the state occupied at age *x* and *k* the state to be occupied at age *x+t*, then the probability of moving from state *ij* to *ik* in a short interval of time *dt* is given by:

$$ {}^{i}_{dt}P^{jk}_{x+t} = {}^{i}\mu^{jk}_{x+t}\,dt + o(dt) \qquad (1) $$

Define the occupancy probability ${}^{i}_{t}P^{jk}_{x}$ as the probability that a person aged *x* who is currently occupying state *ij*, will be in state *ik* at age *x+t*. The Kolmogorov forward equations are then defined as:

$$ \frac{\partial}{\partial t}{}^{i}_{t}P^{jk}_{x} = \sum_{l\neq k} {}^{i}_{t}P^{jl}_{x}\,{}^{i}\mu^{lk}_{x+t} - \sum_{l\neq k} {}^{i}_{t}P^{jk}_{x}\,{}^{i}\mu^{kl}_{x+t} \qquad (2) $$

with the attaching boundary conditions ${}^{i}_{0}P^{jk}_{x} = \begin{cases} 1 & if\ j = k \\ 0 & otherwise \end{cases}$

Given the boundary conditions for the Kolmogorov forward equations and appropriate assumptions for the transition intensities, the occupancy probabilities can be obtained using a step-wise numerical approach. For our work, we solve the Kolmogorov equations (and Thiele's equations, see later) using a Runge-Kutta algorithm with step-size 0.0005 years.

3.8. Attaching Payments to the Model

To ascertain the cost of adverse selection, the issue of payments must be addressed. This is effected by making the following assumptions. Following Macdonald (2001), let ${}^{i}b_{x}^{j}$ be the rate at which the premium is paid to the insurer, while in the state *ij* and ${}^{i}b_{x}^{jk}$ be the benefit paid by the insurer on transition from state *ij* to state *ik*. Furthermore, define ${}_{t}^{i}V_{x}^{j}$ to be the prospective policy value (expected present value of future benefits less future premiums) in state *ij* at age *x* and δ the force of interest earned on assets. Then, Thiele's differential equations can be written as:

$$\frac{\partial}{\partial t}{}_{t}^{i}V_{x}^{j} = \delta {}_{t}^{i}V_{x}^{j} + {}^{i}b_{x}^{j} - \sum_{k \neq j} {}^{i}\mu_{x}^{jk}\left({}^{i}b_{x}^{jk} + {}_{t}^{i}V_{x}^{k} - {}_{t}^{i}V_{x}^{j} \right) \tag{3}$$

where the boundary conditions depend on the type of contract, normally a term assurance or CI policy expiring at age 60 resulting in a policy value of zero at expiry.

By solving equation (3) backwards, the policy value of the contract can then be determined. But first assumptions have to be made about ${}^{i}b_{x}^{j}$ and ${}^{i}b_{x}^{jk}$. For simplicity, ${}^{i}b_{x}^{jk}$ is assumed to be £1, while ${}^{i}b_{x}^{j}$ are assumed to be paid continuously.

Assuming further that persons seeking insurance are grouped into underwriting classes C (defined by a set of states as in Section 3.6) and persons within each class are charged the same premium rate, then the premium rate for the critical illness insurance market given genetic heterogeneity, genetic testing and insurance purchasing is given by:

$${}^{i}b_{x}^{j} = {}^{i}b_{x}^{jk} * \frac{\sum_{ij \in C} {}_{x}^{i}p_{0}^{0j}({}^{i}\mu_{x}^{j4} + {}^{i}\mu_{x}^{j5})}{\sum_{ij \in C} {}_{x}^{i}p_{0}^{0j}} \tag{4}$$

which is a weighted average of transition intensities to state 4 or state 5 where the weights are the occupancy probabilities for state *ij*, *i*=1..3, *j*=0..3. This approach avoids the complication that arises in the use of level premiums which depend on the age of insurance purchase. For instance, in a case of a group of 50 year-olds, *say*, the level premiums will not be the same for everyone in any of the insured states because they are determined by age of entry into the insured states and not solely on current age, making equation (3) inapplicable.

3.9. Quantifying the Cost of Adverse Selection

Since the prospective policy value is given by:

$$ {}^{i}_{t}V^{j}_{x} = EPV\,(future\,benefits) - EPV\,(future\,premiums) \tag{5} $$

which is equivalent to:

$$ {}^{i}_{t}V^{j}_{x} = EPV\,(future\ loss\,in\,the\,insurance\,market\ between\ ages\,x\ and\ 60) \tag{6} $$

then in the absence of adverse selection, the policy value in equation (6) should be zero at the outset and at expiry of the contract (for a term assurance). Hence, to capture the cost of adverse selection, Macdonald (2002) used the following measure:

$$ \frac{EPV\,(Insurance\,Loss\,with\,Adverse\,Selection) - EPV\,(Insurance\,Loss\,Without\,Adverse\,Selection)}{EPV\,(\text{Pr}\,emiums\,Payable\,with\,Adverse\,Selection)} \tag{7} $$

which illustrates the extent to which premiums would have to rise to cover the cost of adverse selection.

4. PARAMETERISATION OF THE MODEL I: GENETIC FACTORS

As mentioned previously, the ABI currently recognises seven single-gene disorders (inherited as dominant traits) as being relevant to the insurance industry, in general. Again these are Huntington's disease, familial adenomatous polyposis, myotonic dystrophy, Alzheimer's disease, multiple endocrine neoplasia, hereditary motor and sensory neuropathy and hereditary breast cancer. In addition, adult polycystic kidney disease will be included in this study although it was dropped from the ABI's list since the logic of defining a single-gene late onset disorder by the method of testing for it seems unconvincing.

What follows is an outline of the characteristics of the eight genetic disorders with the main focus on adult polycystic kidney disease, early-onset Alzheimer's disease, Huntington's disease and hereditary breast and ovarian cancer for which the epidemiological research and hence the actuarial work has advanced more rapidly. Particular attention is paid to the rates of onset of the illness(es) which are based on the mutation penetrance of the disease, the frequency in the population of the gene mutation(s) responsible for the disease, and rates of genetic testing, all of which are necessary in the parameterisation (genetic factors) of the model.

Any gaps left due to missing information will be filled by grouping all eight disorders into categories based on their mutation penetrance since the literature on the above-mentioned disorders revealed that penetrance estimates by age 60 ranged from approximately 25% for one gene associated with APKD to near complete penetrance for genes associated with Huntington's disease and early-onset Alzheimer's disease. This makes segmentation of the disorders along the lines of LOW or HIGH penetrance a pragmatic approach and disorders for which there is little information can be slotted into the appropriate group. Of course, while this approach facilitates the modelling of all eight (seven) disorders deemed relevant to the critical illness insurance industry, it also presents a modelling framework for later research. However, one must be aware that even where information is available from epidemiological research, some uncertainty still surrounds the penetrance estimates as well as the mutation frequencies and so caution should be exhibited in interpretations.

Section 5 will focus of non-genetic factors such as the rate of insurance purchase, the rate of onset of a serious illness caused by non-genetic factors and the rate of mortality.

4.1. Main Features of the Disorders

Adult Polycystic Kidney Disease (APKD) is characterised by large cysts in the kidneys and a gradual loss of the normal kidney tissues. It is caused by mutation of either of the two genes – APKD 1 or APKD 2 – which leads to end stage renal disease (or kidney failure) (ESRD).

Early-onset Alzheimer's disease (EOAD) is differentiated from Alzheimer's disease, which occurs in persons over 65 as a common part of the aging process, only in terms of age of onset of the illness. Therefore, the disease is characterised by the same decline in cognitive ability but occurring at earlier ages. While three genes – amyloid percursor protein (APP), presenilin-1 (PSEN–1) and presenilin-2 (PSEN-2) – have been confirmed as causing EOAD, PSEN-1 appears to be the main contributor to manifestations.[9] In addition, PSEN-1 mutations are associated with a very aggressive form of EOAD and a very high penetrance.

Familial adenomatous polyposis (FAP) is a colon cancer predisposition syndrome in which hundreds to thousands of pre-cancerous colonic polyps develop and is caused by mutations in the APC gene. *Gene Reviews*, formerly *Gene Clinics*, reports that by age 35 years, 95% of individuals with FAP have polyps. Interestingly enough though, these polyps in themselves are

[9] It is still unclear whether or not all cases of EOAD are of genetic origin.

not cancerous and can be removed through surgery called colectomy (removal of the colon); otherwise colon cancer is inevitable. Thus, the development of polyps is not currently a critical illness event making it irrelevant for that insurance industry and FAP is therefore dropped from the model. This is in contrast to APKD and EOAD which are clearly critical illness events. Furthermore, the possibility of 100% effective treatment could also make FAP irrelevant for the life insurance industry if an effective screening programme were in place.

Huntington's disease (HD), like AD or EOAD is a form of dementia. The disease can present itself as early as age 30 with survival thereafter ranging from 15 to 30 years. According to Gutiérrez & Macdonald (personal communication), the disease is a result of certain mutations of the huntingtin gene, which affects brain cells. It is often regarded as the clearest example of a late-onset monogenic disorder. The mutation penetrance is widely believed to be near 100% and hence any person confirmed as a mutation carrier is almost guaranteed to develop the disease.

HD results from an abnormally high number of repeats (normal being 10-34 times) in the huntingtin gene's DNA sequence called CAG (cytosine-adenine-guanine) resulting from expansion during the meiosis process. This duplication is called a "trinucleotide repeat". Furthermore, studies such as Brinkman *et al.* (1997) have confirmed that higher number of repeats is associated with earlier onset of HD.

Myotonic dystrophy (MyoD) is a disease in which the muscles have decreasing power to relax, becoming weak and wasting away. According to *Genes and Disease*, it can also result in mental deficiency, hair loss and cataracts. Onset of this rare disorder can occur at any age and is extremely variable in degree of severity. This variability in age and severity results in four different classifications of MyoD – late onset (mild), adult-onset (classical), childhood and congenital [Harley *et al*, 1993]. Furthermore, *Gene Reviews* reports that while patients diagnosed with mild MyoD may have a normal life span, sufferers of adult-onset MyoD become severely disabled and have a shortened life expectancy. Persons afflicted with congenital MyoD often die before adulthood. In addition, de Die-Smulders *et al.* (1998) report that the slow advancement of adult-onset MyoD makes survival for long (yet progressively debilitating) periods after onset of the disease very common. Thus, one might argue that only adult-onset MyoD may be important to critical illness insurance.

MyoD results from mutations of the myotonic dystrophy gene (myotonin dystrophy protein kinase (DMPK) gene), and like HD, becomes more severe in successive generations but in this case as a result of amplifications in the length of the trinucleotide CTG (cytosine-thymine-guanine) repeats. Unaffected individuals have between 5 and 36 CTG trinucleotide repeats, while the number for MyoD patients ranges from at least 50 repeats (mild) to several thousand repeats (severe).

Multiple Endocrine Neoplasia (MEN) is a group of rare diseases caused by genetic defects that lead to, *inter alia,* hyperplasia and hyperfunction. The former is an increase in the number of normal cells in the normal arrangement in a tissue, while the latter refers to excessive functioning of two or more components of the endocrine system.[10] When a person has MEN, specific endocrine glands such as the parathyroid glands, the pancreas gland and the pituitary gland, tend to become overactive. This overactivity may result in kidney stones or kidney damage, fatigue, weakness; muscle or bone pain, constipation, indigestion and thinning of bones [*Genes and Disease*].

There are two forms of MEN: MEN type I and MEN type II. While MEN I is associated with benign tumours and would not impact on critical illness or life insurance, MEN II is a little more complicated. In fact, according to *Gene Reviews* there are three subtypes of MEN II - MEN IIA, familial medullary thyroid carcinoma (FMTC) and MEN IIB - which all have a high risk for development of medullary carcinoma of the thyroid (MTC). There is also an increased risk for pheochromocytoma associated with MEN IIA and MEN IIB, while MEN IIA has an additional risk for parathyroid adenoma or hyperplasia. However, according to www.endocrineweb.com, while the cure rates for MTC are much lower than other thyroid cancers such as papillary and follicular, they are higher than for anaplastic thyroid cancer. Furthermore, there is a 90% (ten-year) survival rate if the cancer remains localised in the thyroid gland but these rates drop drastically when the disease begins to spread. This finding puts MEN into the same category as FAP, where given an effective screening programme in place, the near 100% effectiveness of the treatment would eliminate it from the list of critical illness events and so it is likewise dropped from the model.

[10] The endocrine system works analogously to a communications network containing hormone producing cells (transmitters), hormones (signals) and receptors (receivers).

Hereditary motor and sensory neuropathy (HMSN) is the commonest cause of the peroneal muscular atrophy syndrome consisting of distal leg muscle wasting and weakness, usually with a pes cavus foot deformity. In general, the presenting symptoms are due to difficulty walking. The inheritance is usually autosomal dominant, but recessive forms also occur [Department of Clinical Neurosciences]. However, HMSN is regarded of little relevance to the critical illness industry [Guidance from the ABI's Genetic Advisor].

Cancer is a household name affecting most persons in some form or fashion. Although, mutations in the genes BRCA1 and BRCA2 have been associated with the onset of breast and ovarian cancer (BC and OC), unlike the other disorders discussed previously (with the exception of EOAD), they need not be the only cause.[11] Furthermore, the mutation penetrance may be affected by other genes or indeed environmental factors placing this disorder in a category by itself. For this reason, the rates of onset are not zero in the case of non-carriers and different rates have to be calculated for each sub-population, i.e. mutation carriers and non-carriers.

4.2. Rate of Onset and Mutation Penetrance

Functional forms for the rate of onset and mutation penetrance are available only for APKD, some EOAD, HD and BC and OC. These will be dealt with in some detail while some guesstimates will be made for the other disorders using the limited information available. Current information for HMSN puts its mutation penetrance at around 50% by age 60 [Prof. J. A. Raeburn, personal communication].

4.2.1. MyoD

Connor & Ferguson-Smith (1997) report that all of the 50% of DMPK mutation carriers develop complications related to MyoD. In particular, they report that "*29% will be affected in later life, 12% neonatal deaths and 9% severe neonatal hypotonia and mental handicap*", which implies a mutation penetrance of 100% (possibly by age 60).

4.2.2. APKD

In the estimation of rates of onset for APKD, studies by Johnson & Gabow (1997), Hateboer *et al.* (1999) and Ravine *et al.* (1992) gave Kaplan-Meier estimates of the survival to ESRD or

[11] In fact, BRCA1 and BRCA2 are responsible for only a small proportion of cases.

death for both APKD1 and APKD2 gene mutations. This survival function takes the following form.

$$S(t) = \exp\left(- \int_0^x (\mu_t^{ESRD} + \mu_t^{DEAD})\, dt \right) \tag{8}$$

where μ^{ESRD} and μ^{DEAD} represent the rate of onset of ESRD and the rate of mortality, respectively.

However, of primary interest to critical illness insurers is the rate of onset of the illness. Thus, the rate of mortality has to be somehow removed from equation (8). Gutiérrez & Macdonald (personal communication) effect this transformation by subtracting the force of mortality of the English Life Table No.15 from the combined rates based on Hateboer *et al.* (1999) and Ravine *et al.* (1992) and the 1989-91 Colorado life table from the combined rates based on Johnson & Gabow (1997).

From Figure 8, page 9 of Gutiérrez & Macdonald (personal communication), the estimates of rate of onset for the APKD 1 ranged from 0.05 to 0.06 by age 50 and 0.08 to 0.1 by age 60. As one would expect based on the low penetrance of APKD 2, the estimated rates of onset were much lower than those of APKD1, reaching 0.03 at age 55 and falling back around 0.02 at age 60.

Recall that mutation penetrance refers to the probability that defective genes will lead to a manifestation of the illness. Therefore, penetrance can be viewed as the complement of the probability of survival without onset of the disorder as follows:

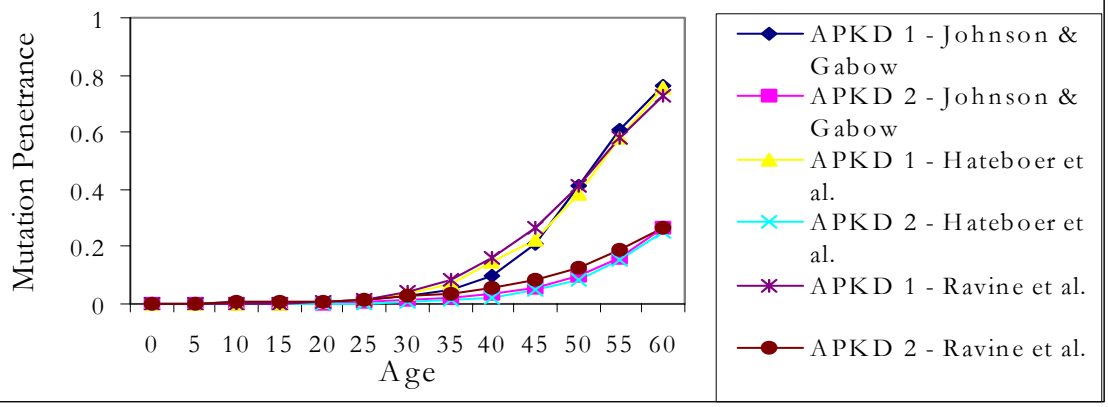
$$P(x) = 1 - S(x) = 1 - \exp\left(- \int_0^x \mu_t dt \right) \tag{9}$$

where μ_t represents the transition intensity from the healthy state to the critical illness state.[12]

[12] This formulation will be used throughout this section to transform the rate of onset transition intensities into mutation penetrance estimates.

Given the respective survival functions (for details refer to Gutiérrez & Macdonald (personal communication)) from Johnson & Gabow (1997), Hateboer *et al.* (1999) and Ravine *et al.* (1992), the mutation penetrance of APKD1 and APKD2 were estimated and presented in Figure 7.

Figure 7: Mutation Penetrance of APKD 1 and APKD2 resulting in APKD



All three graphs for APKD1 confirm its high mutation penetrance by age 60, reaching as high as 76% based on Johnson & Gabow (1997). The lower mutation penetrance of APKD2 averages around 26% by age 60.

4.2.3. EOAD

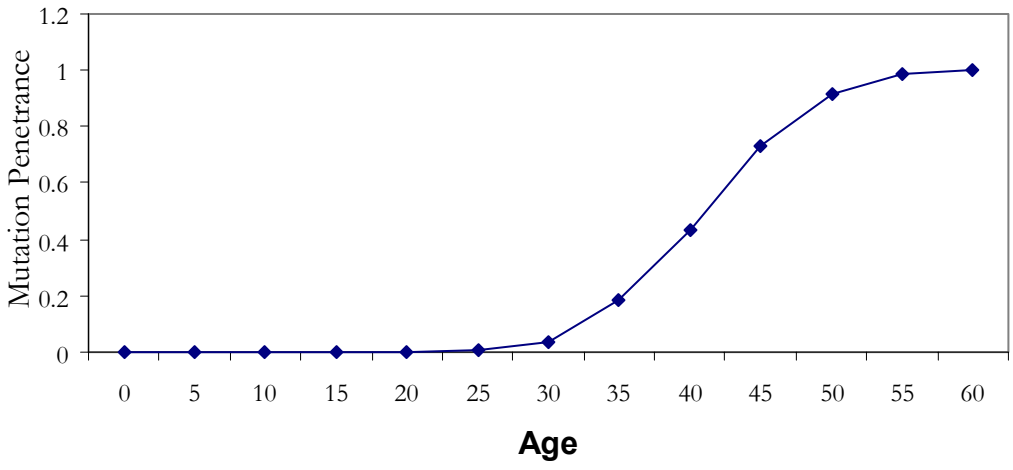
Rogaeva *et al.* (2001) argue that some 90% of mutation carriers will develop EOAD by age 60, while Wisniewski *et al.* (1998) report that onset of the disease was seen as early as age 24. Furthermore, Gui & Macdonald (2002a) estimated that 80% of PSEN-1 mutation carriers will be affected by age 46, which appears to be consistent with Rogaeva *et al.* (2001).

Using a Nelson-Aalen estimate, Gui & Macdonald (2002a) fitted age-dependent rates of onset of EOAD based on mutations of PSEN-1, as follows.

$$\mu_x = \begin{cases} 0 & \text{if } x < 20.0 \\ -0.0112324 + 0.000553792x & \text{if } 20 \le x < 28 \\ (29-x)*(-0.0112324 + 0.000553792x) + (x-28)*(-0.205248 + 0.00735054x) & \text{if } 28 \le x < 29 \\ -0.205248 + 0.00735054\,x & \text{if } 29 \le x < 38 \\ (39-x)*(-0.205248 + 0.00735054x) + (x-38)*(-0.602651 + 0.0177141x) & \text{if } 38 \le x < 39 \\ -0.602651 + 0.0177141x & \text{if } x \ge 39 \end{cases} \quad (10)$$

The estimates of the mutation penetrance obtained by substituting equation (10) into equation (9) are presented in Figure 8.

Figure 8: Mutation Penetrance of PSEN-1 resulting in EOAD



Here it is clear that by age 60 the onset of EOAD is nearly 100%. Furthermore, the age of earliest onset is around 30, which is not surprising given the function that was fitted.

4.2.4. HD

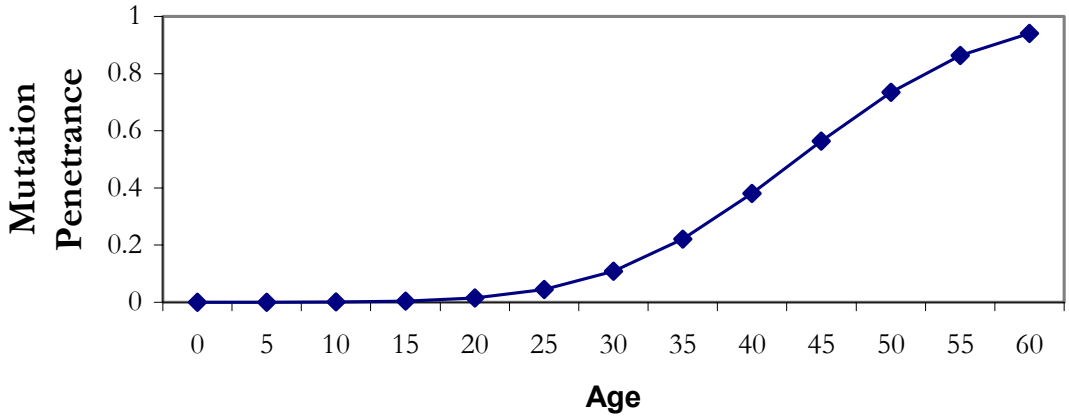
From studies which observed at least 100 subjects, Gutiérrez & Macdonald (personal communication) found that the mean age of onset of HD ranged from 33.8 years (Brackenridge, 1971) to 43.97 years (Wendt *et al.*, 1959) - even though by the authors' own admission, the rate of onset of a neurological disorder such as HD could be imprecise.

Because of the strong inverse relationship found between the number of repeats and the age of onset of HD, the rate of onset of HD is modelled by Gutiérrez and Macdonald (personal communication) as a function of CAG repeat lengths rather than the aggregate rates used by Smith (1998).[13] On the other hand, Brandt *et al.* (1996) found no correlation between the CAG repeat lengths and the rate of the progression of the disease after onset.

[13]As the number of repeats is likely to expand in each successive generation, the age of onset in families is likely to fall – a concept known as 'anticipation'.

However, many authors have found that the Normal model works quite well in modelling the penetrance of HD mutations (ignoring CAG repeat lengths)[Bell, 1934, Roos *et al.*, 1991, Wendt & Drohm, 1972 and Wilkie, 2000]. This is demonstrated in Figure 9 which shows these penetrance estimates for the ages 0 to 60 using the parameter estimates of Wilkie (2000).

Figure 9: Mutation Penetrance of huntingtin gene resulting in HD



The earliest age of onset of HD was around 25, which appears very likely for HD. Moreover, the probability of near complete penetrance of the disease by age 60 is supported by the genetic literature.

4.2.5. Hereditary BC and OC

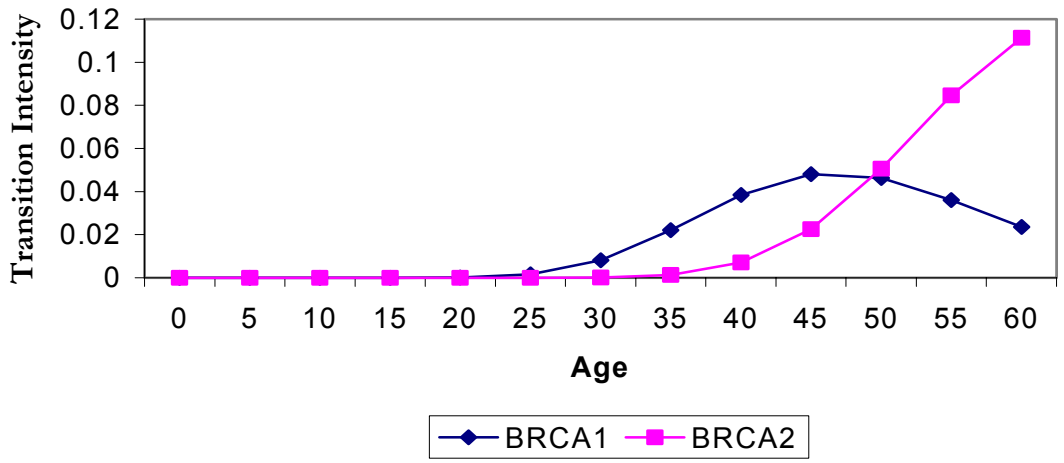
The estimated penetrances of mutations of the two genes BRCA1 and BRCA2 range between 40% or less (Hopper *et al.* 1999) and 80% (Easton *et al.*, 1993 and Easton *et al.*, 1995). Macdonald *et al.* (2003b) modelled the rates of onset of BC and OC based on Ford *et al.* (1998).

For mutation carriers, the following transition intensities were found firstly for BC.

$$\mu_x^{BC,BRCA1} = \frac{1.25}{\Gamma(22)}(0.45^{22} e^{-0.45x} x^{21}) \qquad \mu_x^{BC,BRCA2} = \frac{3.60}{\Gamma(30)}(0.45^{30} e^{-0.45x} x^{29}) \qquad (11)$$

Figure 10 below shows that the incidence rates of BC associated with mutations in BRCA1 are higher than those of BRCA2 for the age range 25 to 50. Thereafter, BRCA2 has higher incidence rates.

Figure 10: Incidence Rates of BC arising from Mutations of BRCA1 and BRCA2

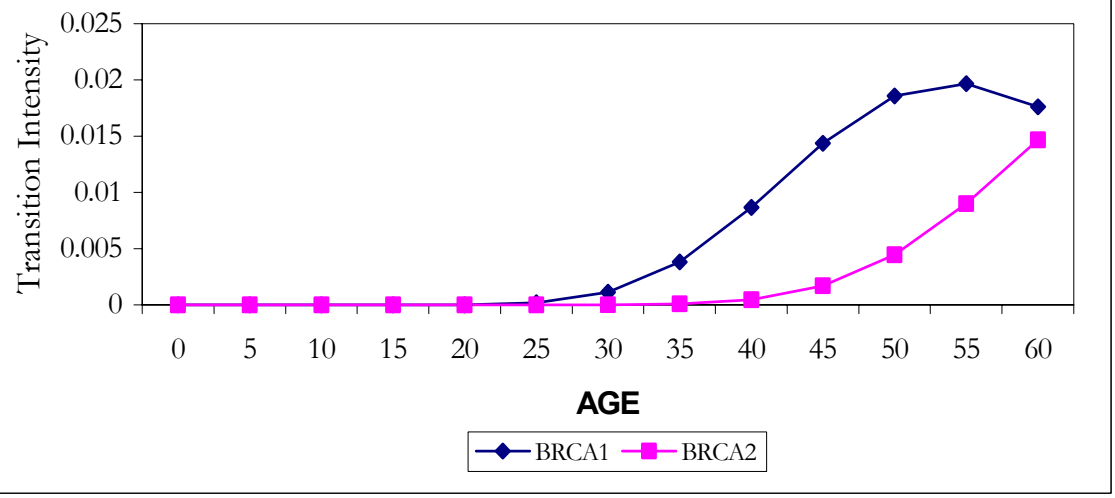


The incidence rates of OC were also estimated by Gamma functions and reproduced in Figure 11 for illustration.

$$\mu_x^{OC,BRCA1} = \frac{0.60}{\Gamma(21)}(0.37^{21} e^{-0.37x} x^{20}) \qquad \mu_x^{OC,BRCA2} = \frac{0.86}{\Gamma(27)}(0.355^{27} e^{-0.355x} x^{26}) \qquad (12)$$

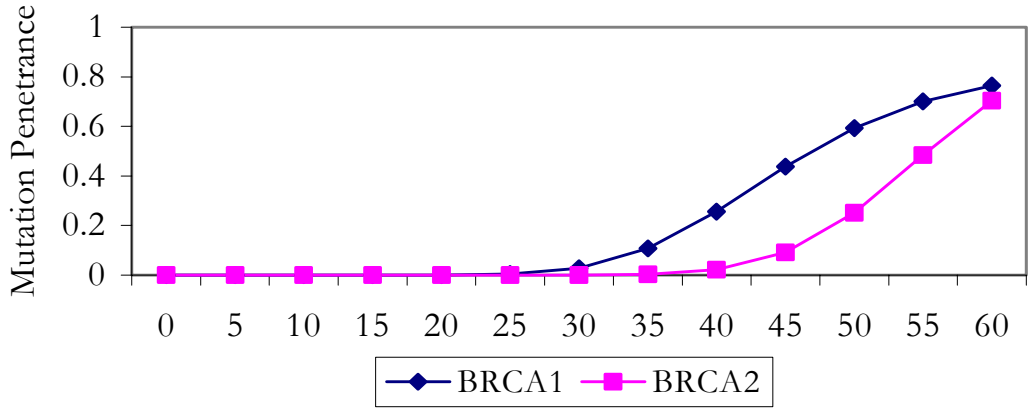
In contrast to Figure 10, the rate of onset of OC is dominated completely by mutations in the BRCA1 gene over the entire age range presented.

Figure 11: Incidence Rates of OC arising from Mutations in BRCA1 AND BRCA2



Estimates of the mutation penetrances of BRCA1 and BRCA2 where the endpoint may be BC or OC were found by summing the transition intensities across the respective disorders for each gene and substituting into equation (9). The results of this exercise are presented in Figure 12.

Figure 12: Mutation Penetrance of BRCA1 and BRCA2 resulting in either BC or OC



As expected the penetrance of BRCA1 mutations is higher than that of BRCA2 in most of the relevant age range. Penetrance by age 60 is around 77% for BRCA1 and 70% for BRCA2.

4.2.6. Implications for Rate of Onset in the Model

The foregoing discussion suggests a possible categorisation of disorders along the lines of mutation penetrances, which are now defined as follows:

- Let LOW denote disorders having penetrance of 0% to 25% by age 60, which we represent by a mean penetrance of 12.5%.
- Let LOW-MEDIUM denote disorders having penetrance of 25% to 50% by age 60, which we represent by a mean penetrance of 37.5%;
- Let MEDIUM-HIGH denote disorders having penetrance of 50% to 75% by age 60, which we represent by a mean penetrance of 62.5%;
- Let HIGH denote disorders having penetrance of 75% to 100% by age 60, which we represent by a mean penetrance of 87.5%;

With an estimated penetrance of between 25% and 27% by age 60 and 9% to 13% by age 50, APKD2 can be regarded as having LOW penetrance. HMSN was put into category LOW-

MEDIUM because of its mutation penetrance of around 50% by age 60. HD, EOAD and MyoD with almost 100% penetrance by age 60 will naturally fall into category HIGH. In addition, BRCA1 associated with either BC or OC which has an estimated penetrance of 77% by age 60 will also be included in this category. Although APKD1 has a mutation penetrance ranging from 72% to 76%, its penetrance by age 50 is significantly lower than those in the HIGH category and hence it will be treated as a MEDIUM-HIGH penetrance disorder (see Table 1).

In searching for a functional form to model the rate of onset of a genetic condition across the various categories, a number of options are available. From Section 4.2.3 to 4.2.5, one can observe the Gamma or even a Normal distribution being utilised for specific disorders. While the Normal distribution has been widely used to model the mutation penetrance of HD, the negative age range is cited as its main disadvantage even though authors such as Bell (1934), Roos *et al.* (1991), Wendt & Drohm (1972) and Wilkie (2000) all found this drawback to be negligible. The Gamma function used in Section 4.2.5 to model the rates of onset of BC and OC does have a positive age range, albeit an infinite one.

The Beta distribution, which closely follows the symmetric property of the Normal, but also possesses a positive finite range, has none of the potential drawbacks of the Normal and Gamma distributions. However, the age ranges must be standardised in every application of the Beta distribution so that 0 maps to the lowest age at onset and 1 maps to the age at which the maximum penetrance is reached. Here we assume that this is age 60. One drawback to this approach is that the mutation penetrance at ages below 60 will be overestimated. This should therefore be borne in mind when interpreting the results in Section 6.

In order to adapt the Cumulative Beta distribution to each category, define m_i to be the mean penetrance by age 60 for category i= LOW, LOW-MEDIUM, MEDIUM-HIGH and HIGH. Then the specification used in the model is given by:

$$P(x) = m_i * \int_0^x \frac{\Gamma(\alpha+\beta)}{\Gamma(\alpha)\Gamma(\beta)} t^{\alpha-1}(1-t)^{\beta-1}\,dt \qquad 0<t<1 \qquad (13)$$

where α=5 and β=5, resulting in a symmetric distribution [Yang, personal communication]. The rate of onset is then determined by substituting equation (13) into equation (9).

4.3. Mutation Frequency

The estimates of mutation frequencies in the population range far and wide. Therefore, at some junctures a range of frequencies is reported. For the purpose of the model, only one number can be used and hence it was decided to go with the upper limit rather than an average, as this has the advantage of giving a ceiling on the cost of adverse selection.

APKD is one of the most common single-gene disorders. From the late 1950s, Dalgaard (1957) reported a mutation frequency of 1 per 1,000. Moreover, mutations in the APKD 1 gene are more frequent (perhaps accounting for 85% of mutations) and are more severe resulting in earlier onset of ESRD.

Gui & Macdonald (2002b) estimate mutation frequencies for PSEN–1 gene leading to EOAD at 15 per 100,000. This was based on Campion *et al.* (1999) which found the prevalence rate for EOAD to be about 25.4 per 100,000 at risk (from all genes involved) and that 58.8% of those affected carried the PSEN-1 gene mutation. Campion *et al.* (1999) more or less supported the earlier studies done by Kokmen *et al.* (1989), Schoenberg *et al.* (1985) and Sulkava *et al.* (1985), which found 26.9, 45.5 and 18.2, per 100,000 respectively, to be at risk (from all genes involved). Hence, for all EOAD a mutation frequency of 30 per 100,000 will be used, assuming that half of the total mutations are associated with the PSEN-1 gene.

Based on HD prevalence of 3-5 per 100,000 and 7.5 per 100,000 in Western Europe and the United Kingdom, respectively, Harper (1996) and Harper, Lim and Craufurd (2000) estimated the HD mutation frequencies as 7.5-12.5 per 100,000 and 18.75 per 100,000, respectively. The latter will be used in the model because it is directly applicable to the UK.

Following Macdonald *et al.* (2003b), this study will restrict the range of frequencies of BRCA1 and BRCA2 mutations to the more recent studies of Parmigiani *et al.* (1998). Hence, the frequency of mutations of BRCA1 in the population ranges from 0.00045 to 0.0008, while the range for BRCA2 mutations is 0.000165 to 0.0002.

Finally, one in every 10,000 persons is born with the gene mutation leading to HMSN. The corresponding mutation frequency for MyoD is 1 per 20,000 (Prof. J. A. Raeburn, personal communication), which lies in the middle of the 1-10 per 100,000 range cited by Emery (1991).

4.3.1. Implications for Mutation Frequencies in the Model

Summing the mutation frequency within each category, one can ascertain the total mutation frequency for each. To simplify this process, Table 1 presents the mutation penetrance of the disorders by age 50 and 60, appropriately categorised, which then allows for summing of mutation frequencies in the final column. Thus with only APKD2 in category LOW, the mutation frequency for that category would by 0.00015. Similarly, the mutation frequency for categories LOW-MEDIUM, MEDIUM-HIGH and HIGH are 0.0001, 0.00105 and 0.0013375, respectively.

Table 1: Categorisation of the Disorders

Category	Disorder	Gene	Mutation Penetrance		Mutation Frequency (p_i)	$\sum p_i$
			By age 50	By age 60		
LOW	APKD	APKD2	9% to 13%	25% to 27%	0.00015	0.00015
LOW-MEDIUM	HMSN		--	50%	0.0001	0.0001
MEDIUM-HIGH	BC/OC	BRCA2	25%	70%	0.000165 to 0.0002	0.00105
	APKD	APKD1	38% to 41%	73% to 76%	0.00085	
HIGH	HD	Huntingtin gene	73%	94%	0.0001875	0.0013375
	EOAD	PSEN-1	92%	100%	0.00015	
		All			0.00030	
	BC/OC	BRCA1	59%	77%	0.00045 to 0.00080	
	MyoD	DMKP		100%	0.00005	

From Table 1, one can observe that only 0.0026375 of the population is likely to carry a mutation in the genes leading to the specified disorders considered as critical illness events. This implies that the cost of adverse selection should be minimal as the proportion of the population (0.9973625) who are non-carriers or not at risk at all is overwhelming.

4.4. Rate of Genetic Testing

Genetic testing, broadly defined, covers not only tests on an individual's DNA in search of alterations – molecular genetics (as expounded in Section 1.1) - but also includes the examination of chromosomes and the use of techniques based on enzymology, biochemistry or immunology to test the functioning of genes that may lead to an inherited disease [*Laboratory Services for Genetics*, 2000]. However, molecular genetics is the basis of most of the testing carried out for single-gene disorders.

APKD was dropped from the ABI's list because it can be accurately detected quite early with the use of ultrasound technology. However, there is no cure, and the only treatment is dialysis or kidney replacement after ESRD. Therefore, it should still be classified as a critical illness event. On the other hand, the possibility for prolonging life after onset of the illness may imply a rate of testing somewhat higher than disorders where there is no treatment and death from the disorder is certain.

EOAD is a hereditary disease involving the gradual and progressive loss of one's mental faculties eventually leading to death. It is not considered treatable and hence although genetic testing is available many persons with a family history are not willing to be tested for fear of being handed a 'death sentence'.

Because HD is a hereditary disease, it is certain that, based on current National Heath Service (NHS) practice in the United Kingdom, only persons with a family history will be tested. However, the lack of treatment of HD implies that persons may be reluctant to get tested. Based on these assertions, the cumulative incidence of testing for HD among persons at risk has been estimated as between 10-20% by Meiser & Dunn (2000) and 18% by Harper, Lim & Craufurd (2000).

In addition, *Laboratory Services for Genetics* (2000) reports that 1196 samples were tested for mutations in the huntingtin gene in 1998-99, while the number tested for myotonic dystrophy mutations was 1275.

For BC there are methods of early detection that can be used by the patient, with screening programmes for menopausal women. According to Macdonald *et al.* (2003b) if genetic testing is carried out, the results need to be carefully interpreted largely because of a lack of knowledge

surrounding the mutations of the genes in question and the functions of the proteins with which they are associated. In 1998-99, a total of 2,279 samples were tested for BC/OC cancer-causing genes [*Laboratory Services for Genetics*, 2000].

Testing for MyoD is done through direct analysis of the CTG repeats in the DMPK gene with 100% effectiveness [*Gene Reviews*].

4.4.1. Implications for Rates of Genetic Testing in the Model

Recall that in Section 4.4, estimates of the rate of genetic testing were largely unavailable with Meiser & Dunn (2000), Harper *et al.* (2000) and the *Laboratory Services for Genetics* (2000) being the only source of hard numbers. Other studies such as Macdonald (2001) used a range of rates of testing (0.02 for moderate testing to 0.1 for high testing).

Using the information from *Laboratory Services for Genetics* (2000) on the number of samples tested along with population at risk figures, one can first obtain estimates similar to Meiser & Dunn (2000) and Harper *et al.* (2000); of course the population at risk figures are simply the whole population times the probability of being at risk of the disorder times the years of exposure to risk. Hence, approximately,

$$p_g = \frac{Number\ of\ Samples\ Tested}{Population * 2 * Mutation\ Frequency * years\ \exp osed\ to\ risk} \tag{14}$$

which represents the prevalence of genetic testing among families at risk.

It was decided that in the model, testing should be confined to ages 20 to 40. This assertion is based on the assumption that most persons are tested for genetic disorders during child-bearing ages, which seems logical. Hence of an estimated population of 59 million in the United Kingdom at mid-2001, approximately 18,179,800 were reported to be between ages 20 and 40 [*National Statistics*]. Thus, given the number of samples tested in 1998-99, population of around 18.2 million and the previously estimated mutation frequencies for HD and MyoD, the rate of genetic testing can be estimated by equation (15) below.

$$\mu_x = -\ln(1 - p_g) \tag{15}$$

The results of this exercise are presented on Table 2.[14]

Table 2: Estimates of the Rate of Genetic Testing

Disorder	Number of Samples	Mutation Frequency	P_g	μ
MyoD	1275	0.00005	0.70	1.204
HD	1196	0.0001875	0.175	0.193
Estimate for HD	--	--	0.1 to 0.2 Meiser & Dunn (2000) for a 8-year period	0.0126 to 0.025

Assuming that the Meiser & Dunn (2000) estimate of the prevalence of genetic testing for HD is based on an eight-year period, then the testing rate per annum would be between 0.0125 and 0.025, which is significantly less than the one-year estimate of 0.175. More weight will be given to Meiser & Dunn (2000) because of the longer assessment period. Hence, using the formula in equation (15), the rate of testing was estimated at between 0.0126 and 0.025. These are significantly lower than the rate calculated from the one-year sample data. The estimate for MyoD seems too high given its high penetrance and the lack of effective treatment. The apparent discrepancy remains to be explained.

On the last point, we justify using a low rate of testing of 0.01 in the model since a higher rate assumes that treatment is available. Thus, while disorders such as FAP and MEN may have higher rates of testing than HD and EOAD, the 'treatability' of the complications would not allow it to be classified as a critical illness event and hence it would be dropped from a model of critical illness insurance. In general, we suppose that higher rates of genetic testing might be associated with new or improved treatment that would, as a first approximation, change the definition of a critical illness and so offset any increased costs caused by more people entering the pooling arrangement.

The flipside of this argument, however, comes with the observation that this positive correlation between testing and treatment does not always hold within the NHS. For example,

[14] Because the incidence of testing not related to gene mutation, the same exercise could not be undertaken for BC/OC.

it has been noticed that while the uptake for testing for prostrate cancer is on the rise, the effectiveness of existing treatments has not improved.

5. PARAMETERISATION OF THE MODEL II: NON-GENETIC FACTORS

The last estimates needed to fully parameterise the model are the rate of insurance purchase, rate of onset of critical illness not related to a genetic disorder and the rate of mortality, each of which will now be dealt with in turn.

5.1. Rate of Insurance Purchase

Most studies have utilised a constant rate of insurance purchase when employing the Markov modelling approach to address questions such as the costs of adverse selection. For example, Macdonald, Waters and Wekwete (2003a) used annual rates of 0.1%, 1% and 5% to represent small, medium and large, respectively, critical illness insurance markets, while Macdonald (2001) assumed the normal rate of purchase to be between 1% for a small market and 5% for a large market for the life insurance industry.

Yang (2000) attempted to improve on these level rates of insurance purchase (force of new insurance business) by treating it as an age-dependent transition intensity. She undertook this objective for life insurance purchases of whole life, endowment and term assurances by using CMIB duration-0 in-force data for 'occurrences' and population statistics for 'exposures'.

The study showed that the force of insurance generally rises from age 0 to 27 and generally declines thereafter for whole life and endowment assurances. For term assurances, the peak came later at around ages 35 to 39.

The age-dependent force of insurance was then estimated for ages 25-70 using linear, quadratic and cubic graduations, of which the cubic formulation produced the best results. From the investigation, Yang (2000) concludes that the rate of purchase for the three life contracts can be modelled as follows:

$$\mu_x = -0.10048281 + 0.013038339x - 2.738625116*10^{-4}x^2 + 1.587800935*10^{-6}x^3 \qquad (19)$$

When compared with equation (19), the constant of 0.05 used by Macdonald (2001) underestimated the rate of purchase in the early years and overestimated it in the later years, the latter implying that a somewhat higher rate could be used by Macdonald (2001). However, the present study follows Macdonald, Waters and Wekwete (2003a) and assumes a rate of normal purchase of insurance as 0.05, 0.01 and 0.001 for a large, medium and small critical insurance market, respectively. In later research, a different specification may be found to model this market better but this is beyond the scope of this paper.

Persons with adverse test results are expected to buy insurance at a higher rate than those who possess no knowledge of a genetic disorder. This assertion is based on the view that these persons will seek to gain financially from their misfortune. Given a normal rate of insurance purchase of 5%, previous work such as Macdonald (2001) has assumed a rate of insurance purchase by adverse selectors of up to five times the normal rate of purchase. This can be considered an extreme assumption since it was used primarily to get upper limits on the costs of adverse selection in the life insurance industry.

However, it is plausible that not all uninsured persons with knowledge of a genetic condition will seek to benefit from insurers. Hence, a more modest estimate of around 2 to 4 times the normal rate will be used, which is again held constant over a twenty-year span starting at age 20. The latter is based on the trend of insurance purchasing being confined generally to persons in this age range who are about to enter the mortgage market.

5.2. Rate of Onset of Critical Illness not related to the Genetic Condition

These estimates are taken from Gutiérrez & Macdonald (2001) for a critical illness insurance model based on medical studies and population data. As the name suggests, it encompasses all other disorders not resulting from the specific genetic condition. These were confined to cancer (excluding non-malignant skin cancer), heart attack, stroke and other minor causes of critical illness insurance claims. The aggregate rate of critical illness claims due to these causes was then estimated as follows:

$$\mu_x^{CI} = 1.15(\mu_x^c + p_x^h * \mu_x^h + p_x^s * \mu_x^s) \qquad (20)$$

where μ^c, μ^h and μ^s are the age-dependent transition intensities for cancer (excluding non-malignant skin cancer), heart attack, and stroke, respectively, while p^h and p^s are the 28-day survival probabilities after the first-ever heart attack or stroke, respectively. These are taken

together with the other minor causes which amount to 15% of critical illness claims due to cancer, heart attack and stroke.

The reader is referred to Gutiérrez & Macdonald (2001) for a full specification of the transition intensities outlined in equation (20).

5.3. Rate of Mortality

Once again following Gutiérrez & Macdonald (2001), the rate of mortality was taken from the English Life Tables No.15 adjusted to exclude deaths which followed a critical illness claim.

6. RESULTS

The model presented in Figure 6 in Section 3 was modified in light of the discussion in Section 4 and 5. The modified model contains 9 sub-populations as follows: persons not at risk; and non-carriers and mutation carriers in each of the four categories i=LOW, LOW-MEDIUM, MEDIUM-HIGH, HIGH, where the estimates of mutation frequencies 0.00015, 0.0001, 0.00105 and 0.001334 (with rounding), respectively, were taken from Table 1 in Section 4.3.1. Accordingly, a computer programme by Macdonald (personal communication) originally for modelling EOAD was modified using programming code developed by Yang (personal communication) for the Beta functions used to model the rate of onset.

In the first instance, two cases were considered in the modelling exercise. The first case represents the present situation of a moratorium on the use of adverse test results only. Secondly, consideration was given to an outright ban on the use of any genetic test results, i.e. a moratorium on all tests. The analysis was conducted under a number of different assumptions about the size of the critical illness insurance market in the UK. This investigation was then extended to consider a moratorium on the use of family history. Note that all results are for females as time did not permit the modelling of males.

6.1. Baseline Scenario

Consider the baseline scenario where the rate of purchase for individuals with a family history of some genetic disorder is the same as the normal rate of insurance. As in Section 5.1, the latter is proxied by the size of the insurance market. Hence, for the large, medium and small

market, the normal rate of purchase of insurance is assumed to be 0.05, 0.01 and 0.001 per annum, respectively. In addition, assuming that there is no adverse selection in the market, then the rate at which persons who receive an adverse test result purchase insurance would be the same as those with a family history. At this stage, the rate of genetic testing is assumed to be 1% per annum.

Based on these assumptions, the expected present value (EPV) of benefits and losses in the whole market can be calculated as the weighted averages of the EPV of benefits and losses in each sub-population at outset. The EPVs are found by solving Thiele's equations, with premiums of zero in the case of benefits (*B*) or as in equation (4) in the case of losses (*L*). These EPVs represent an insurance market operating between ages 20 and 60 which includes those who are uninsured as well as those who are insured. Because the rates of premium in equation (4) are based on rates of insurance purchased in the supposed absence of adverse selection, if adverse selection is absent in fact, the EPV of losses are zero (allowing for rounding errors from the numerical algorithm used to solve Kolmogorov's and Thiele's equations). Therefore, only the EPV of benefits, for a large, medium and small critical illness insurance market, are presented in Table 3.

Table 3: Expected Present Value of Benefits

Market Size	EPV of Benefits
Small	0.00065767
Medium	0.006041793
Large	0.021383169

6.2. Introducing Adverse Selection in the Model

Taking the baseline scenario developed above, one can introduce adverse selecting behaviour into the model. This is done by assuming a rate of insurance purchase higher than the rate at which persons normally buy insurance in respect of persons receiving an adverse test result. A number of scenarios for the large, medium and small insurance market were examined.

Three scenarios were run for each market size, with each scenario consisting of three different assumptions about the degree of adverse selection taking place. Let *insrate* and *famrate* denote the rate at which persons normally buy insurance and the rate at which persons with a family history buy insurance, respectively. Then scenario A examines the case where *famrate=insrate,*

which represents the extreme case where the demand for insurance is assumed to be perfectly price inelastic. Also let *advrate* denote the rate at which adverse selectors purchase insurance. Then, *advrate* is assumed to be equal to 2, 3 or 4 times the *insrate,* so the latter is the most severe case of adverse selection. Under scenarios B and C *famrate=1/2 insrate* or *famrate=0*, respectively, reflecting different assumptions about the elasticity of demand for insurance.

Recall from Section 3.6. that different underwriting classes exist under a moratorium on adverse test results only and under a moratorium on all tests. Letting 0 denote the ordinary rate of premium payment and 1 denote the ordinary rate adjusted for family history, the underwriting classes are illustrated in Table 4.

Table 4 shows that 'at risk' non-carriers who benefit from ordinary premiums under a moratorium on adverse test results only, now have to pay this premium adjusted upward for a family history of the genetic disorder when there is a ban on the use of any test results. They therefore pay the same premium as those who have not been tested because test results regardless of their outcome are not admissible under a moratorium on all tests.

6.2.1. Moratorium on Adverse Test Results Only

Let B_1 and L_1 be the EPV of benefits and losses, respectively, under a moratorium on adverse test results only in the presence of adverse selection. Then, following equation (7) in Section 3, the percentage increase in ordinary premium required to cover the cost of adverse selection within each market can be estimated as:

$$\frac{L_1 - L}{B_1 - L_1} * 100 \qquad (21)$$

where $L=0$ as above. The increase in premium is based on the premium being paid with adverse selection present because premiums naturally rise to reflect the increase in purchasing behaviour.

Table 4: Underwriting Classes Under Different Types of Moratoria

	Moratorium on Adverse Test Results Only				Moratorium on All Tests			
	States				States			
Sub-population	Untested, Uninsured State 0	Untested, Insured State 1	Tested, Uninsured State 2	Tested, Insured State 3	Untested, Uninsured State 0	Untested, Insured State 1	Tested, Uninsured State 2	Tested, Insured State 3
Persons Not At Risk	0	0	0	0	0	0	0	0
LOW								
Non-Carrier	1	1	0	0	1	1	1	1
Mutation Carrier	1	1	1	1	1	1	1	1
LOW-MEDIUM								
Non-Carrier	1	1	0	0	1	1	1	1
Mutation Carrier	1	1	1	1	1	1	1	1
MEDIUM-HIGH								
Non-Carrier	1	1	0	0	1	1	1	1
Mutation Carrier	1	1	1	1	1	1	1	1
HIGH								
Non-Carrier	1	1	0	0	1	1	1	1
Mutation Carrier	1	1	1	1	1	1	1	1

The results, presented in Table 5 below, range from 0.041% to 0.218% in the large market and 0.085% to 0.345% in the small market. Thus, one can observe that the cost of adverse selection in the large market is lower than in the small or medium-sized market. In fact, as one would expect, the larger market which generates significantly more business than a small market is able to spread more of the risk. This makes it more able to cope with adverse selection than a smaller market. From the magnitude the costs obtained, one can observe that disallowing information for adverse test results would cause only a small increase in premiums.

Table 5: Summary of the Results of the Cost of Adverse Selection

(proxied by the % increase in premiums)

	Moratorium on Adverse Test Results Only			Moratorium on All Tests		
	Small	Medium	Large	Small	Medium	Large
Scenario A						
Insrate^=Famrate; Advrate=2*Insrate	0.085	0.074	0.041	0.088	0.077	0.042
Insrate=Famrate; advrate=3*Insrate	0.168	0.140	0.065	0.174	0.144	0.066
Insrate=Famrate; Advrate=4*Insrate	0.251	0.198	0.079	0.259	0.204	0.081
Scenario B						
Insrate; Famrate=1/2 Insrate; Advrate=2*Insrate	0.129	0.119	0.085	0.134	0.123	0.088
Insrate; Famrate=1/2 Insrate; Advrate=3*Insrate	0.214	0.188	0.114	0.221	0.194	0.117
Insrate; Famrate=1/2 Insrate; Advrate=4*Insrate	0.297	0.248	0.131	0.307	0.257	0.136
Scenario C						
Insrate; Famrate=0; Advrate=2*Insrate	0.175	0.171	0.161	0.181	0.177	0.166
Insrate; Famrate=0; Advrate=3*Insrate	0261	0.242	0.195	0.270	0.251	0.202
Insrate; Famrate=0; Advrate=4*Insrate	0.345	0.305	0.218	0.357	0.316	0.225

Note: Insrate=market size, i.e. 0.05-large market; 0.01-medium market; 0.001-small market.

6.2.2. Moratorium on All Test Results

Similarly, let B_2 and L_2 denote the EPV of benefits and losses with respect to a moratorium on all test results with adverse selection assumed to be taking place in the market. The cost of adverse selection is estimated by:

$$\frac{L_2}{B_2 - L_2} * 100 \tag{22}$$

From Table 5, one can see that the costs under this moratorium are larger than under a moratorium on adverse test results alone. These marginal differences are a result of the smaller family rates underwriting class for the moratorium on adverse test results only (Refer back to Table 4). If those who have tested 'clear' can remove themselves to the standard rates underwriting class, the family history underwriting class will contain a higher proportion of mutation carriers, and the premium rates charged within that underwriting class will rise, hence reducing the cost of adverse selection.

Nonetheless, the results under this moratorium are still quite small and these obtain across market sizes with the small market again facing the highest cost of adverse selection.

6.2.3. General Observations

Note that as the rate of purchase by those with a family history declines, the cost of adverse selection rises. While one can assume that some law of demand holds for insurance purchasing, it is still unclear whether demand for insurance responds more or less than proportionately to increases in premiums (elasticity of demand for insurance). Thus, the assumption that a person buys half as much insurance with an increase in premiums suggests a possible inelastic demand for insurance. In this case, the buffer previously created by 'overcharging' the non-carriers in each sub-population is eroded. Therefore, premiums have to be increased by a higher percentage to recoup the losses. On the other hand, if among persons with a family history, only adverse selectors purchase insurance (implying an elastic demand for insurance) then the insurer is no longer shielded from the cost of adverse selection. Premiums then have to rise commensurately. This trend is seen clearly from Table 5 where under the assumption of a large market, and adverse selecting behaviour of 2 times the normal rate and moratorium on adverse test results only, the premiums rise from 0.041% to 0.085% and 0.161% under the assumption that persons facing the premiums adjusted for family history will buy insurance at half the rate of normal purchase or will not buy at all.

Overall the results imply that cost of adverse selection within the critical illness insurance market is small under a moratorium on adverse test results only as well as on all tests. Furthermore, this conclusion holds across all market sizes. However, it is important to note that the results may be sensitive to the rate of genetic testing which has been held constant in all scenarios, an assumption which will be relaxed in Section 6.4.

6.3. Extending the Moratorium to include Family History

In a situation where insurers cannot even use family history information in the underwriting process then all sub-populations will be pooled and everyone faces the same ordinary premium rate. Macdonald (2001) reports that under this type of moratorium, the costs to the insurer are no longer simply the costs of adverse selection, but are in fact two-fold. Firstly, the ordinary premium is calculated assuming that genetic disorders did not exist. That is, nobody is at risk and everyone buys insurance normally. Letting B_3 represent the EPV of benefits in the programme with nobody at risk buying insurance, then the EPV of premiums payable is given by B_3/p_1 where p_1 is the proportion of the population that is not at risk. In reality though, this underwriting class is also made up of individuals at risk of genetic disorders of varying degrees of penetrance. Assuming that everybody in this heterogeneous population buys insurance at the normal rate then this cannot be regarded as adverse selection. Thus, the EPV of premiums is equal to the EPV of benefits with no adverse selection, which is the same as the baseline scenario. The required increase in premium to cover the liabilities arising from the diverse risk is:

$$\frac{B - B_3/p_1}{B_3/p_1} \tag{23}$$

The second reason that premiums may have to rise is due to adverse selection. Recall in Section 6.2 that adverse selection was confined to the sub-population of tested mutation carriers. With the moratorium extended to family history, a new set of possible adverse selectors emerges. This class now includes all the mutation carriers and the untested non-carriers since they too are benefiting from premiums below their risk. The cost of adverse selection is calculated in exactly the same way as for the other two moratoria but with different scenarios to address the widening of adverse selecting 'class'. The increases in premiums arising within each situation are presented in Table 6.

Again the small market is the most affected by the moratorium. However, this time the increases are significantly larger than under the previous two moratoria. For the large market, the increase in premium due to the new underwriting class is even larger than the cost of adverse selection. Thus, legislators must be mindful that pooling heterogeneous risks and charging the same premium will lead to increases in premiums without even considering the action of adverse selectors. On the other hand, the cost of adverse selection remains the biggest cost concern for the small market.

Table 6: Increase in Premiums Under a Moratorium on Family History and Genetic Information

	New Underwriting Class	Adverse Selection	New Underwriting Class	Adverse Selection	New Underwriting Class	Adverse Selection
	Small		Medium		Large	
Scenarios	1.598	--	1.612	--	1.667	--
Insrate=Market size; Famrate=Advrate=2*Insrate		1.704		1.470		0.777
Insrate=Market size; Famrate=Advrate=3*Insrate		3.367		2.701		1.123
Insrate=Market size; Famrate-Advrate=4*Insrate		4.991		3.735		1.285

6.4. Sensitivity Analysis

As mentioned before, all the scenarios were run using a rate of genetic testing of 0.01. When this assumption was relaxed and higher rates were tested the cost of adverse selection increased but less than proportionately to the increase in the rate of testing. Therefore, the results are (as one would expect) sensitive to the rate of testing parameter employed. Table 7 gives a synopsis of this exercise using a rate of testing of 0.02 in a small market. Again it is felt that even higher rates of testing will be associated with improved medical outcomes, and may result in disorders being dropped from the model and so this estimate appears reasonable.

Table 7: Increase in Premiums Using Rate of Testing of 0.02

	Moratorium on Adverse Test Results	Moratorium on All Tests
Scenario A		
Insrate^=Famrate; Advrate=2*Insrate	0.154	0.165
Insrate=famrate; advrate=3*Insrate	0.306	0.328
Insrate=Famrate; Advrate=4*Insrate	0.456	0.488
Scenario B		
Insrate; Famrate=1/2Insrate; Advrate=2*Insrate	0.235	0.252
Insrate; Famrate=1/2Insrate; Advrate=3*Insrate	0.389	0.416
Insrate; Famrate=1/2Insrate; Advrate=4*Insrate	0.540	0.579
Scenario C		
Insrate; Famrate=0; Advrate=2*Insrate	0.319	0.341
Insrate; Famrate=0; Advrate=3*Insrate	0.474	0.508
Insrate; Famrate=0; Advrate=4*Insrate	0.627	0.672

Time does not permit us to perform sensitivity tests on the mutation penetrance function employed in the paper; no doubt a different specification will result in different cost outcomes. On the other hand, the positive correlation between mutation frequency and cost of adverse

selection makes it intuitively clear what will be the result of changing the frequencies employed in the model.

6.5. Discussion

The cost of subsidising the pooling schemes will be small under any moratoria on the use of genetic testing information. Furthermore, given that upper limits were used in some of the assumptions in the model, the actual costs should be even lower. However, this may be offset by the relatively low rate of testing used in this modelling exercise. Hence, given the ABI's focus on this type of moratorium, the actuarial costs of such a moratorium are clearly not prohibitive.

The moratorium on family history is beyond the scope of the current discussions between the ABI and government and therefore this extension tries to address questions of whether family history is genetic information (HGC's concern) and how this view will change the cost of subsidising genetically disadvantaged individuals. The results showed that any pooling scheme which did not allow the use family history information would incur higher costs. Although the cost of adverse selection alone is higher than in the case of a ban on genetic test information due to the bigger group of adverse selectors, the ordinary premiums must also rise even if there were no adverse selection because of the heterogeneity that would exist in the pool. Of course, these costs could be even higher depending on the mutation frequencies of the disorders in this model.

Of concern is the relationship between the rate of testing and the cost of adverse selection. As more persons get tested for genetic disorders relevant to the critical illness insurance industry in the UK, the scope for adverse selection will increase. Therefore, the possibility of adverse selection will remain a worry to insurers as long as genetic tests are available and there exist moratoria on the use of such information. Analogously, the cost of subsidising the pooling schemes could rise with increased rates of genetic testing. However, as Section 4.4.1 highlighted, higher rates of testing may be indicative of improved treatments which implies less likelihood of the disorder remaining a critical illness event. The latter also has implications for the life insurance industry since the rates of survival should be greatly improved with more effective treatments.

6.6. Suggestions For Refinement of the Paper

The scope of the project was quite large and hence many of the ideas envisaged could not be pursued in the limited time available. The following is a list of suggestions for improvements that can be made to the study.

Firstly, time permitted modelling for only females. Hence, the most obvious extension is to include males in the study.

Secondly, the paper relied heavily on estimates of penetrances and frequencies from epidemiological research. In the case of rate of onset or penetrance estimates, these are usually estimated from a relatively small sample of patients and hence the confidence intervals surrounding the estimates are very wide. In other cases, no estimates are available. Hence, the study would benefit from more accurate penetrance estimates as they become available. In addition, the mutation frequencies quoted by authors are usually from different parts of the world and so a better assessment of the frequencies within the population being studied would be useful (in this case the UK).

Thirdly, the definition and the rate of progression of neurological disorders such as EOAD and HD is a contentious issue. Indeed, the immediate onset of symptoms relating to these disorders may not be classified as a critical illness event. Hence, the study could perhaps make some allowance for the occurrence of critical illness claims in these cases being some time after the time of clinical onset.

Fourthly, the rate of genetic testing still needs some research. While the constant rate was used for all levels of penetrance in the model, perhaps a more rational approach would be to differentiate the mutation testing based on treatment as done here in the extreme case of FAP and MEN.

Fifthly, better estimates of the rate of purchase of insurance could be obtained from industry data. This would be moving in the direction of an age-dependent estimate as done by Yang (2000). It would perhaps require analysing the output under different scenarios over the relevant age ranges. In addition, the scenarios used under the moratoria on genetic information could greatly benefit from information on the price elasticity of demand for insurance. This

information would give modellers more intuition into the buying behaviour of persons subject to the family history rating and thus help to refine the number of scenarios examined.

The final refinement of the paper is to extend it to cover the life insurance market. This is especially relevant for the UK where life insurance is a very important industry. Moreover, since critical illness insurance is sold as a 'rider' to life insurance policies, one should consider modelling both markets together.

7. CONCLUSION

Notwithstanding the shortcomings of the paper, the results showed that the subsidised cost of pooling genetic risks under the moratorium on adverse test results or the moratorium on all tests are minimal. However, the costs are higher when the moratorium is extended to include family history but we note that these findings lie outside the scope of the ABI's current considerations.

However, one issue still remains unresolved. More specifically, a potential conflict between policymakers, who may wish to implement a system where no disclosure of genetic information is necessary, and the insurance community, who may require this information in order to set up reserves, could arise. Given the low cost of the pooling schemes under the moratoria on genetic testing information, the FSA may show some lenience in requiring such information for the setting up of reserves under these circumstances. However, in the case of a ban on the use of family history information, the costs are larger and hence a stricter treatment of reserve calculations may be warranted.

However, the final outcome of this situation may be political. Thus, one can foresee a situation where subsidising the schemes may be feasible but the political will necessary to address this contentious issue of disclosure of genetic testing information may be lacking.

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