ADULT POLYCYSTIC KIDNEY DISEASE AND INSURANCE: A CASE STUDY IN GENETIC HETEROGENEITY

By Cristina Gutiérrez and Angus Macdonald

ABSTRACT

Adult Polycystic Kidney Disease (APKD) is a single-gene autosomal dominant genetic disorder leading to end-stage renal disease (ESRD, meaning kidney failure). It is associated with mutations in either of two genes, APKD1 and APKD2, and although diagnosis is still mostly by ultrasonography rather than DNA-based tests, this may change in future. Recent studies have shown that the rates of onset of ESRD associated with APKD1 mutations are much greater than those associated with APKD2 mutations, a form of genetic heterogeneity that differs from (for example) familial breast cancer. In this paper, we model the the impact of mutations in APKD1 or APKD2 on critical illness (CI) insurance, extending the work of Gutiérrez & Macdonald (2003) which was based on studies pre-dating DNA-based tests. We then extend the model to life insurance, and show that the financial impact is strongly dependent on the availability of treatment (dialysis and transplant) but that if it is available, extra premiums for life insurance are modest. We show that genetic heterogeneity introduces a novel problem, because carrying an APKD2 mutation is less risky than having a family history of APKD. Thus, in jurisdictions where family history may be used in underwriting but genetic tests may not, it may be illegal to use knowledge that benefits the applicant.

KEYWORDS

Adult Polycystic Kidney Disease; Adverse Selection; APKD1 Gene; APKD2 Gene; Critical Illness Insurance; End-Stage Renal Disease; Life Insurance

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1. Introduction

1.1 *Heterogeneous Genetic Disorders and Insurance*

There is a growing literature on the actuarial implications of genetic disorders, mostly focussed on the small number of single-gene disorders that are dominantly inherited, severe, highly penetrant and have onset during adult ages. See Daykin *et al.* (2003) for a recent review. The development of DNA-based genetic tests for these disorders has had two consequences:

(a) It is possible to identify whether a person at risk of carrying a mutation because of their family history is or is not a mutation carrier. This, of course, is the origin of the debate on genetics and insurance.

(b) Some disorders previously identified on the basis of their symptoms are now known to be caused by mutations in any one of several genes. Examples are early-onset Alzheimer's disease, familial breast/ovarian cancer and adult polycystic kidney disease (APKD). Sometimes, mutations in different genes may lead to quite different outcomes. Thus, heterogeneous outcomes within a single disorder are resolved, by a genetic test, into different genetic causes.

Such genetic heterogeneity as in (b) above has particular implications for an insurance market in which there is a moratorium on the use of genetic information in underwriting. These are now common, but differ in whether they allow a family history of a genetic disorder to be used (as in the United Kingdom) or not (as in Sweden). In the U.K., the three moratoria that have been implemented by the Association of British Insurers (ABI) have banned the use of DNA-based test results except for very large amounts of cover. Strictly, this could mean that a person who is shown by such a test *not* to be a mutation carrier should still pay the premium appropriate for his or her family history, but in practice such a 'clear' test result will be used. This appears to be an unobjectionable use of genetic information where it is to the applicant's benefit. We will call this a 'lenient' moratorium.

Genetic heterogeneity, however, means that a genetic test often will not resolve a family history into a simple yes/no outcome, but place the tested individual somewhere within a broader spectrum of possibilities, including being a carrier of a mild or severe gene mutation. Then, it need not be the case that the premium rate appropriate for someone with a family history of overt symptoms of a disorder will be lower than that for carriers of a milder form of mutation. (Note that we refer here to mutations in different genes, but the same question could arise in respect of different mutations within the same gene.) A carrier of such a milder form of mutation, identified by a genetic test, could then apply the same logic and argue that, since the result would be to their benefit, their genetic test result should be used to allow them a lower premium rate, yet still higher than standard. Thus, just because insurers would be prepared to acknowledge 'clear' genetic tests, and that out of the best of intentions, the use of adverse test results in underwriting could appear through the back door. This would present significant problems for a 'lenient' moratorium.

We show in this paper that this is not just a theoretical possibility: APKD is an example.

1.2 *Treatable Genetic Disorders and Insurance*

The second theme of this paper, not previously allowed for in actuarial studies, is the treatability of a genetic disorder. Kidney failure (known as end-stage renal disease (ESRD)) is a standard cause of claim under most critical illness (CI) contracts, and there is little or nothing that can be done to affect the progression of APKD to ESRD. Then, however, survival depends on renal replacement therapy (RRT, meaning dialysis and/or a kidney transplant). The availability of RRT varies from country to country and from time to time; it is expensive, time-consuming, and transplants are critically dependent on a supply of kidneys from cadavers or living donors. The implications for life insurance, clearly, depend on what it is reasonable to assume about RRT. This feature has not

been too important in previous actuarial studies, usually because a disorder is currently untreatable (Huntington's disease, early-onset Alzheimer's disease) but it will increasingly matter as treatments are developed or because screening and prophylactic surgery may be possible (see Gui & Macdonald (2003)).

At first sight, the availability of treatment ought to alleviate any insurance problems caused by presymptomatic genetic testing, but this may not be true. Where the treatment is effective but drastic, such as double mastectomy for carriers of BRCA1 or BRCA2 mutations, many at-risk persons might not want the treatment, and hence might choose not to be tested. If the insurance industry signals that testing and treatment is a precondition for insurance at reasonable cost, this could be deemed to be interference in the person's medical autonomy. An even more extreme example would be a disorder so severe that persons with a family history would be declined: then a 'clear' test result, and a 'lenient' moratorium, would be the only route to obtaining insurance, and again signals from the insurance industry could be a factor in the decision to be tested. This is a possibility that the industry would perhaps be wise to avoid.

1.3 *Adult Polycystic Kidney Disease*

With a population frequency of about 1 per 1,000 (Dalgaard, 1957), APKD is one of the most common single-gene disorders in humans. As mentioned above, it leads to ESRD, after which survival depends on RRT.

It is inherited dominantly, meaning that a mutation from either parent is sufficient to lead to disease, and so far two genes have been identified, mutations in either of which on its own cause APKD: they are called APKD1 and APKD2 (or equivalently PKD1 and PKD2). The existence of APKD3 is suspected but not confirmed. APKD1 mutations are both more common that APKD2 mutations (they account for about 85% and 15% of APKD, respectively) and more severe, leading to ESRD at much earlier ages. Mutations in the two genes therefore have quite different implications for insurance.

APKD features cysts that proliferate in the kidneys, and these can be reliably detected by ultrasonography by about age 30 at the latest, and long before ESRD. Although the cysts are symptomatic of APKD, an affected person may be 'asymptomatic' in insurance terms because debilitation or death may be many years away. Therefore many of the issues that now surround DNA-based genetic testing have existed for APKD for a long time, but did not attract the intense scrutiny that genetics seems to bring. Gutiérrez & Macdonald (2003) modelled the impact on CI insurance of ultrasonic 'genetic tests' for APKD; one aim of this paper is to examine the impact of now being able to test for APKD1 and APKD2 mutations. Such testing is not yet in widespread use, except in a research setting, but since APKD1 and APKD2 mutations imply very different prognoses they may be used to help interpret the results of ultrasound tests.

Gutiérrez & Macdonald (2003) described the general epidemiology of APKD, and we refer the reader there for details. In Section 2, we describe recent studies estimating age at onset of ESRD associated with the APKD1 and APKD2 genes, including fitting suitable functions for actuarial modelling. Section 3.1 (and Appendix B) describe a model of CI insurance. Using this, and the rates of onset of ESRD, we model the costs arising either from using or from not using information about APKD1 and APKD2 risk in underwriting: (a) in Section 3.2, we estimate extra premiums appropriate if the presence of an APKD1

or APKD2 mutation is known; and

(b) in Section 3.4, we model the potential costs of adverse selection if insurers do not use information about APKD1 or APKD2 risk known to the applicant, because a moratorium on family histories and/or genetic test results may be in place.

In Section 4 we model survival after ESRD, based on the availability of RRT. We find that this depends on duration since ESRD as well as age, so this leads in Section 5 to a semi-Markov model for life insurance contracts. In Section 6 we show extra premiums based on available genetic information, and in Section 7 we give some sample figures for the costs of adverse selection based on undisclosed genetic information. Our conclusions are in Section 8.

2. Onset of ESRD Associated With APKD1 and APKD2 mutations

2.1 *Penetrance Estimates of APKD1 and APKD2 mutations*

At least three studies have published age-related penetrance estimates of APKD1 and APKD2 mutations: Johnson & Gabow (1997), Hateboer *et al.* (1999) and Ravine *et al.* (1992). 'Penetrance' means the probability that ESRD has occurred in a known mutation carrier, in the absence of any competing decrements: let the penetrance at age x be $q(x)$. All of these papers gave graphs of Kaplan-Meier estimates of the 'survival' probability $1 - q(x)$. It is very unusual, in the medical literature, for the numbers underlying such graphs to be published, although sometimes these are available from the authors. If not, then reading figures from these graphs is the only choice; in the case of Kaplan-Meier estimates, both the ages at which cases of onset occur, and the step-changes in the estimate, have to be so estimated. As 'unscientific' as this seems, it is a well-known problem; indeed, it is even expected:

> "The general quality of the actuarial and Kaplan-Meier curves varied across trials and extracting the relevant information from these survival curves can only be approximate. The main problems related to the size and scale of plots and the thickness of curves. Enlarging the graphs by using a photocopier may improve the accuracy." (Tudur *et al.*, 2001).

> "One rarely sees K-M tables reported because of their length. However, K-M curves are frequently seen. ... The cross hairs were added to the graphs for accurate straight-edge alignment." (Wesley, 2002).

It may also be remarked that this is far from being the greatest source of uncertainty in any application of a model parameterised using a small amount of data.

In each case, the event of interest was the first of ESRD, or death by any cause. That is, death was not treated as a type of censoring. The approach we adopt is to fit suitable curves to each Kaplan-Meier estimate, which we take to be estimates of:

$$S(x) = \exp\left(-\int_0^x \left(\mu_t^{ESRD} + \mu_t^{DEAD}\right)\, dt\right) \tag{1}$$

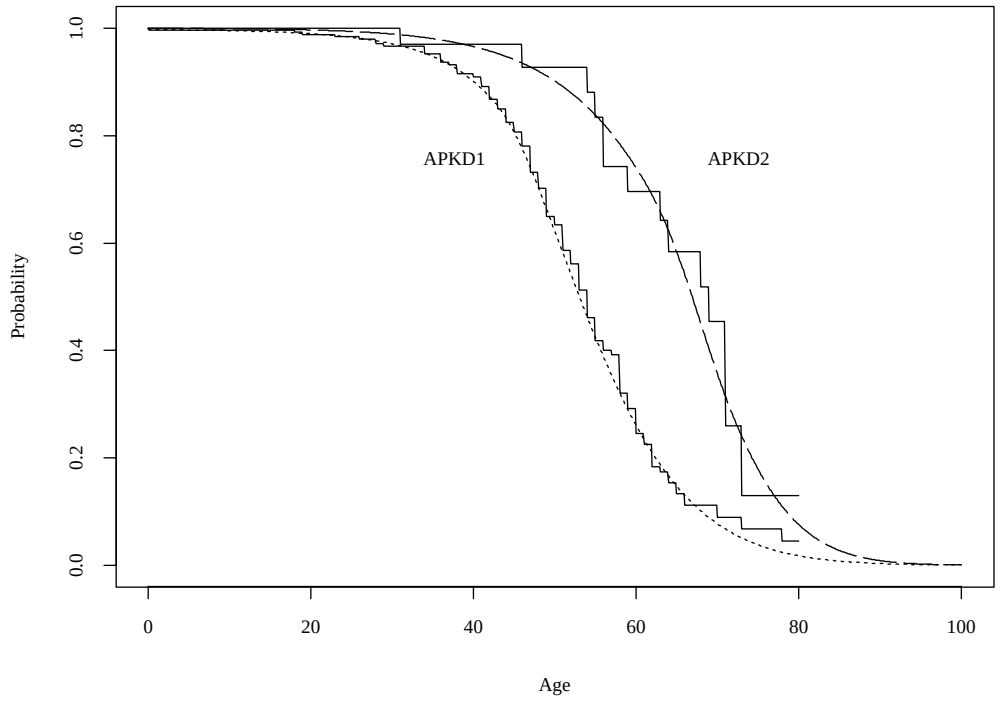

Figure 1: Kaplan-Meier estimates of survival to ESRD or death for APKD1 and APKD2 mutation carriers from Johnson & Gabow (1997), and fitted curves.

where μ_x^{ESRD} is the rate (force) of onset of ESRD and μ_x^{DEAD} is the force of mortality. Then μ_x^{ESRD} on its own can be found using a suitable population mortality table. The curve-fitting is done by unweighted least squares (no exposures or confidence intervals being available) and with one exception a blend of an exponential polynomial at low ages and a Gamma function at high ages was found to fit very well. Bear in mind that we are most interested in ages up to about 60 for actuarial applications.

2.2 *Johnson & Gabow (1997)*

Johnson & Gabow (1997) studied 287 subjects with APKD1 mutations from 44 families, and 34 subjects with APKD2 mutations from one family, drawn from patients at the University of Colorado Health Sciences Center and described in Gabow *et al.* (1992). APKD1 families were identified by linkage to markers close to the APKD1 locus, and families not showing such linkage were assumed to be APKD2 families. The survival time was defined as the time to dialysis, transplantation, or death, whichever came first. In subjects not reaching ESRD or death, the date of the last serum creatinine value obtained was taken as the time of censoring. The authors kindly provided us with the original data for their Kaplan-Meier estimates; these and our fitted functions are shown in Figure 1.

2.3 *Hateboer* et al. *(1999)*

Hateboer *et al.* (1999) studied APKD patients from centers in Bulgaria, Leiden, Santander, Barcelona, Madrid, Cardiff and London. Large APKD families, selected only because of their suitability for study by genetic linkage, were tested for evidence of linkage

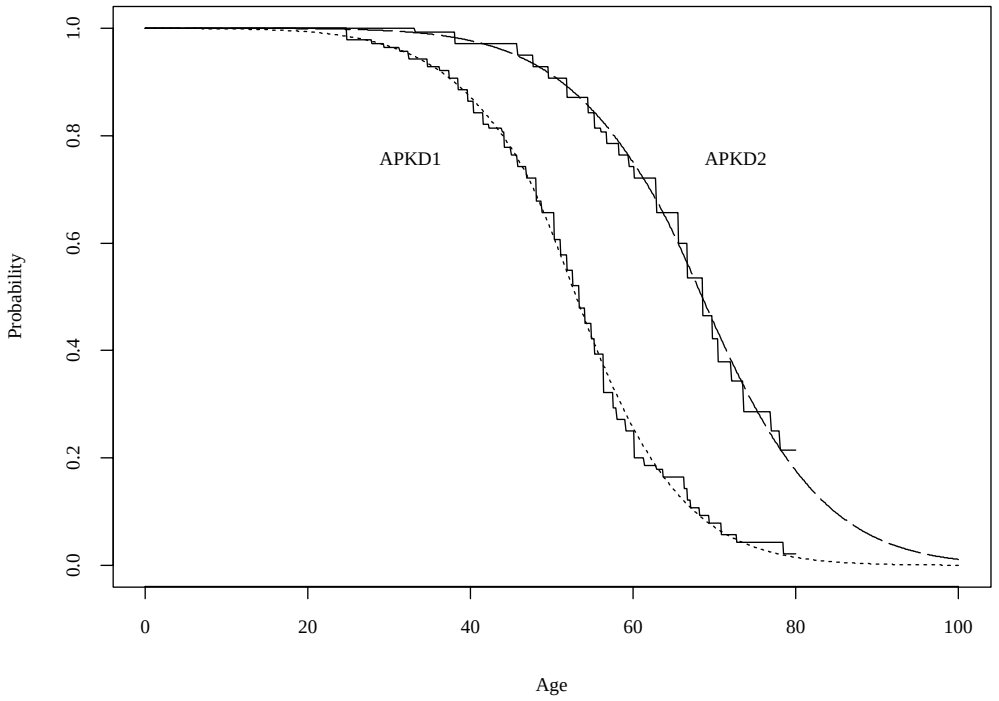

Figure 2: Kaplan-Meier estimates of survival to ESRD or death for APKD1 and APKD2 mutation carriers from Hateboer *et al.* (1999), and fitted curves.

to the APKD1 and APKD2 loci by means of polymorphisms flanking each locus. The sample included 333 subjects with APKD1 mutations from 31 families, and 291 subjects with APKD2 mutations from 31 families. The survival time was defined as the age at onset of ESRD (meaning the age at which RRT became necessary or, in people who died of renal failure, the age at death) or age at death, whichever was first. The Kaplan-Meier estimates of survival functions (our graph based on the published graph), and our fitted functions, are shown in Figure 2.

2.4 *Ravine* et al. *(1992)*

Ravine *et al.* (1992) studied APKD patients from centers in Melbourne and Victoria (Australia). After the family history had been recorded from each index patient, other known affected family members and those at 50% risk were asked to cooperate in the study. Families were tested for evidence of linkage to sites close to the APKD1 locus. Families with probability of linkage of greater than 0.95 were accepted as having APKD1 mutations. Families showing no such linkage were described simply as 'non-PKD1'. 18 APKD1 families (285 persons) were identified, and 5 non-APKD1 families (49 persons), all of European descent. The survival time was taken as the age at onset of ESRD (with the same definition as in Hateboer *et al.* (1999)) or death (whichever occurred first). The Kaplan-Meier estimates of survival functions (our graph based on the published graph), and our fitted functions, are shown in Figure 3.

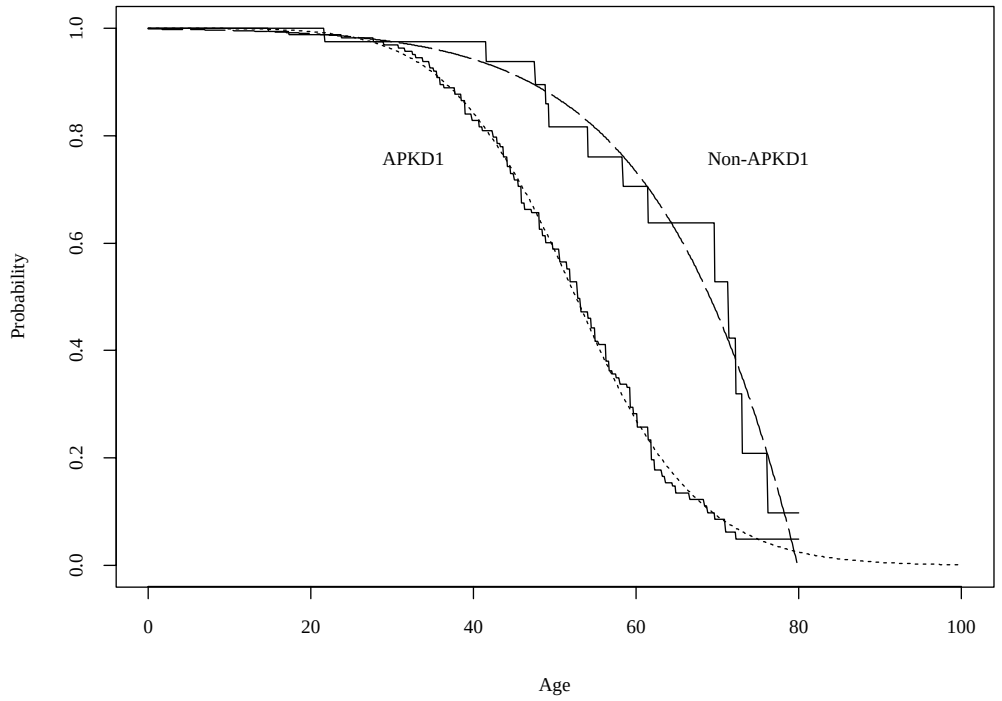

Figure 3: Kaplan-Meier estimates of survival to ESRD or death for APKD1 and putative APKD2 mutation carriers from Ravine *et al.* (1992), and fitted curves.

2.5 *Comparison of the Three Studies and Previous Studies*

Gutiérrez & Macdonald (2003) modelled APKD and CI insurance using studies of APKD that either predated the discoveries of, or did not distinguish between, the APKD1 and APKD2 genes. For brevity we refer to these as the 'aggregate experiences'. Churchill *et al.* (1984) gave a Kaplan-Meier estimate in respect of onset of ESRD or earlier death by uraemia (blood poisoning due to the failure of the kidneys to clear toxins); unusually they published details of the underlying events and exposures. The United States Renal Disease Survey (USRDS; USRDS, 1999) also supplied numbers of new cases of ESRD caused by APKD that were used in conjunction with US population data. Figure 4 shows the fitted survival functions based on all three studies, and also those based on the two aggregate experiences.

First, comparing the three studies described in Sections 2.2 to 2.4:

(a) The fitted functions seem very good for APKD1, and reasonable for APKD2 for which there are many fewer observations. The study by Hateboer *et al.* (1999) had the largest sample of APKD2 mutation carriers, and the fit there is very good.

(b) There is good agreement among the three studies at about age 60, but for both APKD1 and APKD2 there are marked differences at around age 40. This may be due to the different study protocols.

In view of the very small samples of APKD2 subjects in Johnson & Gabow (1997) and Ravine *et al.* (1992), the estimates will be unreliable at older ages and possibly before age 60 as well; for that reason we will treat Hateboer *et al.* (1999) as the most reliable

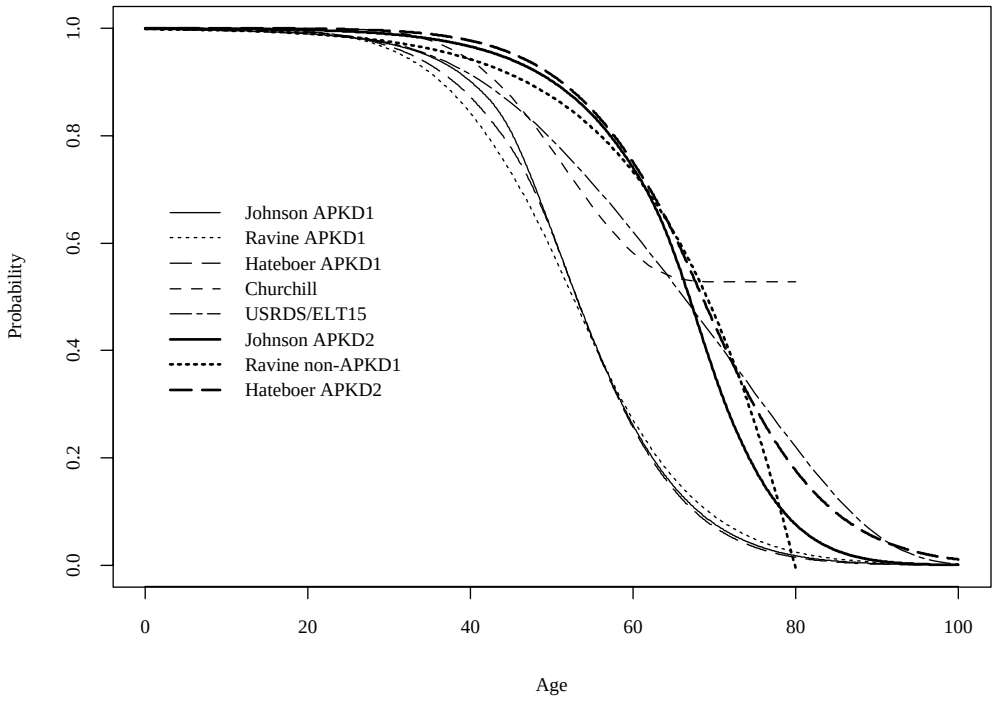

Figure 4: Survival probabilities to ESRD compared with estimates based on Churchill *et al.* (1984) and the USRDS (1999) (see Gutiérrez & Macdonald (2001)).

study of APKD2. Next, comparing the three studies with the aggregate experiences:

(a) The aggregate experiences lie more or less between those for APKD1 and APKD2 as we expect, at least up to age 70.

(b) Churchill *et al.* (1984) treated death (except by uraemia) as censoring. Adjusting the survival function to include other deaths as an event would move it closer to the survival functions for APKD1.

(c) The USRDS experience has here been adjusted to include deaths according to the English Life Tables No.15.

2.6 *Rates (Intensities) of Onset*

Figure 5 shows rates (intensities) of onset (to the first of ESRD or death) calculated from the fitted survival curves by numerical differentiation. The differences at around age 40 are particularly marked for APKD1. These rates have to be adjusted to remove non-APKD related mortality, by subtracting the force of mortality of a suitable life table (see Equation (1)): we used English Life Tables No. 15 with the rates based on Hateboer *et al.* (1999) and Ravine *et al.* (1992), and the 1989–91 Colorado life tables with the rates based on Johnson & Gabow (1997); the results are shown in Figure 6.

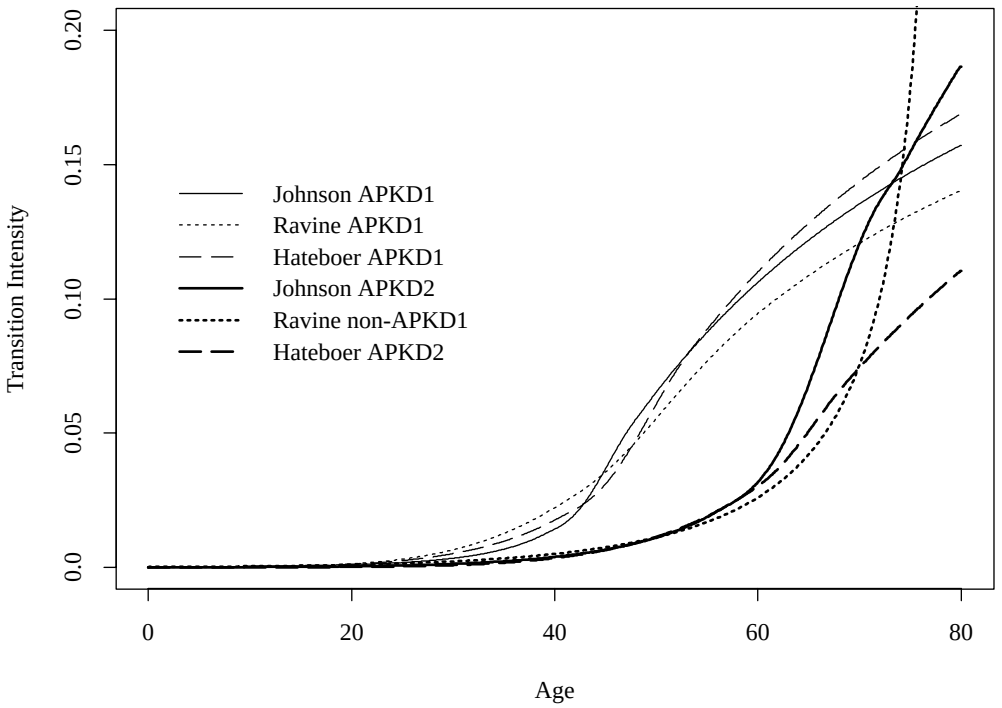

Figure 5: Fitted rates (equivalently forces or intensities) of onset (to the first of ESRD or death).

3. APKD1, APKD2 and Critical Illness Insurance

For brevity, in this section we refer whenever possible to methods and assumptions used in Gutiérrez & Macdonald (2003), and just highlight important differences revealed by knowledge of the individual genes.

3.1 *Model Specification*

We propose the model in Figure 7 for APKD and critical illness (CI) insurance. This assumes that effective dialysis is available, so that death by uraemia is not an endpoint, which seems appropriate for modelling future insurance risk. The model is parameterised by age-dependent intensities μ_x^{ijk}, where i labels the genotype and j, k are states. We need to estimate:

(a) the transition intensity μ_x^{i01} for each genotype (see Section 2); and
(b) the intensities μ_x^{i02} and μ_x^{i03}, assumed to be the same for all genotypes. These follow the model of Gutiérrez & Macdonald (2003), described briefly in Appendix B.

3.2 *CI Premiums if the APKD1 or APKD2 Genotype is Known*

Table 1 shows the level net premium for level CI cover for persons with a known APKD mutation, expressed as a percentage of the premium for standard risks (taken to be non-mutation carriers), for a range of terms and entry ages. All expected present values (EPVs) were found by numerical solution of Thiele's equations (Hoem, 1988) for prospective

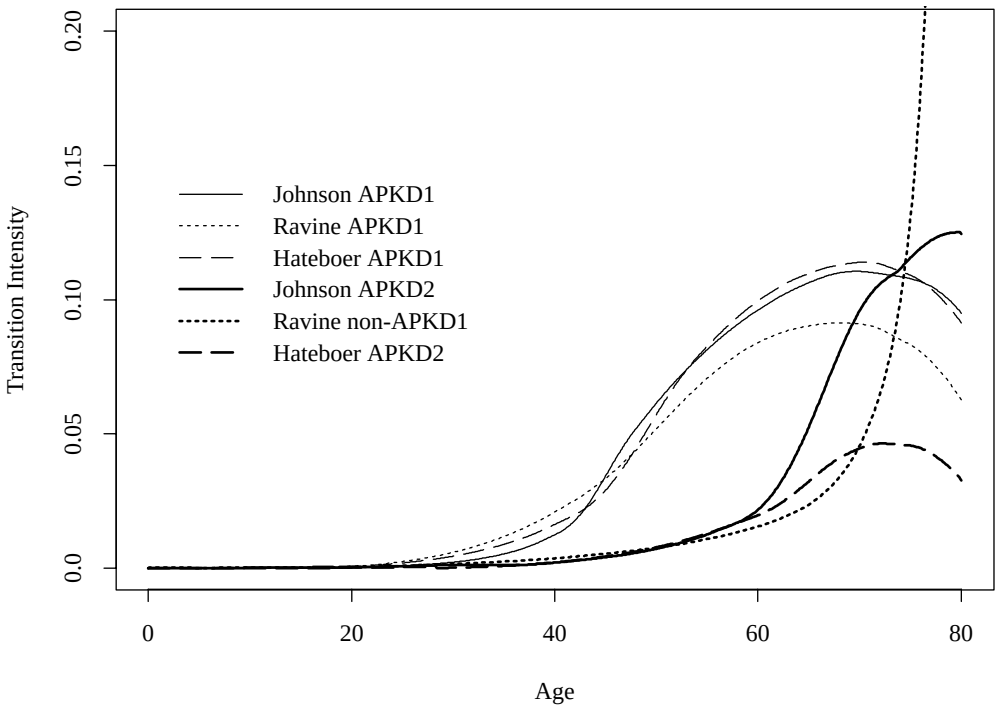

Figure 6: Fitted rates (equivalently forces or intensities) of onset of ESRD based on Figure 5 adjusted using the mortality of English Life Tables No. 15 (Hateboer *et al.* (1999) and Ravine *et al.* (1992)) or the 1989–91 Colorado life tables (Johnson & Gabow (1997)).

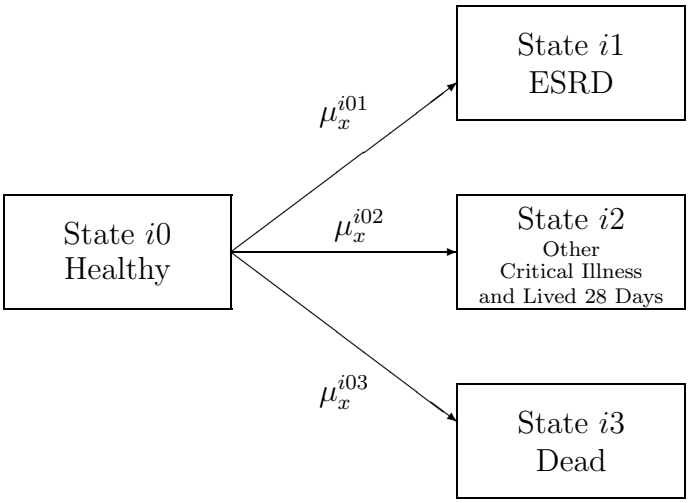

Figure 7: A model for APKD and critical illness insurance, in respect of the i^{th} of several genotypes.

Table 1: Level net premium for level CI cover for persons with a known APKD mutation, as a percentage of the premium for standard risks.

Sex of Applicant	Age at Entry (Years)	Policy Term (Years)	Premiums as Percentage of Standard					
				APKD1			APKD2	
			Ravine	Hateboer	Johnson	Ravine	Hateboer	Johnson
			%	%	%	%	%	%
Female	20	10	563	463	252	255	157	233
		20	743	596	385	259	157	201
		30	757	659	579	242	180	199
		40	658	619	567	226	196	207
	30	10	878	692	472	263	158	182
		20	852	740	682	242	186	192
		30	736	695	657	226	203	206
	40	10	909	829	879	232	207	200
		20	801	800	821	221	221	217
	50	10	840	954	954	218	239	237
Male	20	10	896	724	362	366	199	328
		20	1,031	818	513	330	183	246
		30	875	760	665	268	194	217
		40	653	614	561	225	194	205
	30	10	1,128	882	592	315	176	208
		20	927	803	739	256	194	201
		30	698	659	621	219	195	199
	40	10	905	825	875	231	205	200
		20	711	709	728	205	202	201
	50	10	690	780	781	194	206	209

reserves and Kolmogorov's equations for occupancy probabilities (Runge-Kutta algorithm, step-size 0.0005 years). The force of interest was 0.05 per annum.

We see the very significant difference between APKD1 and APKD2 mutations; the former would probably be uninsurable for almost all of these ages and terms, while the latter would all be insurable based on Hateboer *et al.* (1999). These premiums bear the expected relationship to those in Gutiérrez & Macdonald (2003, Table 5), based on aggregate data.

At older ages the premiums for carriers of either mutation based on the three studies are reasonably, sometimes remarkably, similar. At younger ages, however, those based on Johnson & Gabow (1997) are much lower for APKD1 mutation carriers, while those based on Hateboer *et al.* (1999) are much lower for APKD2 mutation carriers. The reasons could include differences in the study protocols, or simple stochastic variation between samples that, at the earliest possible onset ages, are inevitably small.

3.3 *CI Premiums if Only Family History is Known*

Because APKD is rare, dominantly inherited, and has no known cause other than single-gene mutations, each child of a mutation carrier is born a carrier with probability 1/2. However, the longer an at-risk person survives unaffected, the more likely it is that they are not a mutation carrier. Although there are only three genotypes (APKD1 mutation carriers, APKD2 mutation carriers, and everyone else) it is convenient to define five sub-populations labelled $i = 1, \ldots, 5$, as follows:

$i = 1$	persons with no family history, who are not at risk
$i = 2$	members of families affected by APKD1, but who do not carry a mutation
$i = 3$	members of families affected by APKD1, who do carry a mutation
$i = 4$	members of families affected by APKD2, but who do not carry a mutation
$i = 5$	members of families affected by APKD2, who do carry a mutation.

Only people in sub-populations 2–5 would be considered at risk and possibly charged an extra premium for their family history. Within this group, we can estimate that at birth 42.5% (= 85/2) will be in each of sub-populations 2 and 3, and 7.5% (= 15/2) in each of sub-populations 4 and 5. Let these proportions be denoted p^i, so that $p^2 = p^3 = 0.425$ and $p^4 = p^5 = 0.075$. Let p_x^{i0k} be the probability that a person in sub-population i is found in state ik at age x, conditional on being in state $i0$ (healthy) at birth. Then the proportion of all those in sub-populations 2–5 who are in subpopulation i, conditional on being healthy at age x, is:

$$\frac{p^i \; p_x^{i00}}{p^2 \; p_x^{200} + p^3 \; p_x^{300} + p^4 \; p_x^{400} + p^5 \; p_x^{500}}. \tag{2}$$

The probabilities p_x^{i0k} may all be found by solving the Kolmogorov forward equations, since all the necessary intensities have been estimated. Since an applicant for CI insurance aged x must be healthy, we can apply these weights to the expected present values (EPVs) of benefits and premiums in each sub-population, and hence find level premiums in respect of an applicant with a family history. The resulting premiums (as a percentage of the standard rate) are shown in Table 2.

Table 2: Level net premium for level CI cover for persons with a family history of APKD (50% risk at birth), as a percentage of the premium for standard risks.

Age at Entry (Years)	Policy Term (Years)	Premiums as Percentage of Standard					
		Females			Males		
		Ravine	Hateboer	Johnson	Ravine	Hateboer	Johnson
		%	%	%	%	%	%
20	10	307	258	174	457	372	228
	20	380	312	228	506	407	285
	30	379	336	307	429	378	344
	40	331	315	297	330	313	295
30	10	430	348	262	536	428	314
	20	405	361	343	436	387	367
	30	347	334	323	332	319	309
40	10	402	380	406	401	378	405
	20	340	346	359	309	314	326
50	10	311	348	349	269	298	299

As indicated in Section 1.1, these lie between the premiums for known APKD1 and APKD2 mutation carriers in Table 1. This is not just because APKD1 is more severe than APKD2, but also because APKD1 is so much more common. For example, based on Hateboer *et al.* (1999), a female age 20 seeking cover for 40 years would be charged a very high extra premium of +519% (or more likely, be declined) if she carried an APKD1 mutation; or a modest extra premium of +96% if she carried an APKD2 mutation; but +215% on the basis of family history. Clearly, when a 'lenient' moratorium permits the use of family history, an APKD2 mutation carrier could claim the benefit of an *adverse* test result, which still gives a lower premium than that based on a family history of APKD. Or, they might argue that the insurer should calculate a lower premium based on their family history *given* the information that it is APKD2 and not APKD1 that segregates in their family. Such 'lenient' moratoria do exist but have not been in operation for very long, so such questions may have to be faced in future. (Note that in the U.K., the ABI in 1997 listed eight (later seven) disorders of significance for insurance. APKD was not on the list, because it is most often detected by ultrasonography rather than by DNA-based tests. The logic of this distinction may be a little unclear, but in effect it means that APKD risk is expected to be underwritten solely on the basis of family history, possibly with leniency shown towards those with 'clear' test results. Therefore, the question we have raised here is very relevant.)

3.4 *Adverse Selection Associated With APKD1 and APKD2 Mutation Testing*

To measure the potential costs of adverse selection, we must introduce insurance purchasing behaviour to the model. This is illustrated by Figure 8, based on the five sub-populations defined in Section 3.3. It represents the life history of a person participating in an insurance market, rather than one who has just bought insurance. A person in the i^{th} sub-population starts in State $i0$, uninsured and not having had a genetic test. From

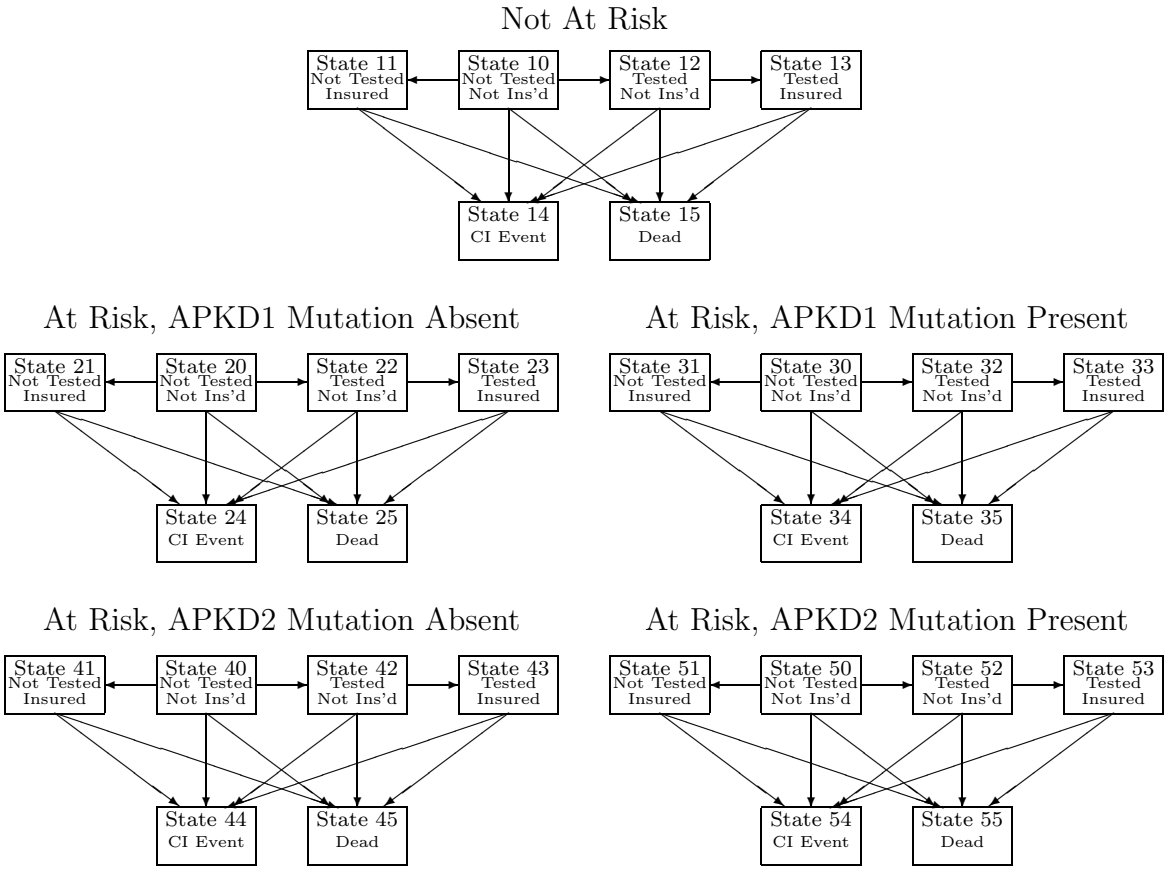

Figure 8: A Markov model of a critical illness insurance market, allowing for family history of APKD and insurance purchasing behaviour.

Table 3: Percentage increases in premium rates arising from severe adverse selection. Moratorium on the use of genetic test results, but family history underwriting still allowed. CI insurance market operating between ages 20–60. Rate of genetic testing 0.035 per annum.

Market Size	Insurance Purchasing of At-Risk Persons	Source of Data	Moratorium on Using All Test Results Females %	Males %	Adverse Test Results Females %	Males %
Large	Normal	Ravine	0.022	0.021	0.019	0.018
		Hateboer	0.020	0.019	0.018	0.017
		Johnson	0.019	0.018	0.017	0.016
	Half	Ravine	0.042	0.039	0.036	0.034
		Hateboer	0.040	0.037	0.034	0.032
		Johnson	0.038	0.036	0.032	0.030
	Nil	Ravine	0.080	0.075	0.067	0.063
		Hateboer	0.079	0.074	0.066	0.062
		Johnson	0.078	0.073	0.064	0.060
Small	Nil	Ravine	0.247	0.227	0.208	0.190
		Hateboer	0.243	0.222	0.203	0.186
		Johnson	0.239	0.219	0.198	0.181

there they may buy insurance (State $i1$) or have a genetic test (State $i2$) and perhaps then buy insurance (State $i3$). At any time, they may die or suffer a 'CI event' (onset of an illness leading to a CI insurance claim, if they are then insured). The intensities of these transitions in the various sub-populations represent the market size, the level of genetic testing among at-risk groups or in the population, and adverse selection. The proportions in each sub-population represent the mutation frequencies in the population. Moreover, the underwriting classes used by an insurer (possibly constrained by a moratorium on using genetic information) can be represented by a suitable partitioning of the states. A fuller description of this type of model is given in Macdonald (2003) or Gutiérrez & Macdonald (2003).

Table 3 shows the costs of a moratorium on genetic test results, with the use of family history still being allowed for underwriting. Its main features are explained as follows, and we refer to Gutiérrez & Macdonald (2003) for full details:

(a) Large and small markets are represented by 'normal' insurance purchase (by persons not rated-up) at rate 0.05 or 0.01 per annum, respectively, between ages 20 and 60.

(b) In the large market, persons at risk because of their family history, charged a higher rate of premium, respond by buying insurance at the 'normal' rate, half the 'normal' rate or not at all. In the small market they do not buy insurance.

(c) Genetic testing of at-risk persons takes place at rate 0.035 per annum, between ages 20 and 40 (when most decisions that may persuade someone to be tested must be

made).

(d) We take 'severe adverse selection' to mean that mutation carriers, after a test, will buy insurance at rate 0.25 per annum, regardless of the family history premium rating. We do not show the effect of them also buying above-average amounts of insurance, but note that this is proportionate to the figures in the table.

(e) The calculation proceeds by finding the rate of premium that would be charged within each underwriting class, in the absence of adverse selection, then finding the EPV of the loss if the same rates were charged when there is adverse selection. This quantity is spread over the EPV of all premiums received, and the resulting percentage increase in premiums is the result shown in the table. The numerical methods used were the same as for level premiums in Section 3.2.

(f) The number of decimal places shown is not meant to imply that degree of accuracy, but to show the magnitude of some very small percentages that would otherwise be rounded to zero.

(g) The moratorium may be imposed on the use of all test results (so an at-risk person who voluntarily discloses a 'clear' result will still be rated on the basis of family history) or it may be a 'lenient' moratorium on the use of adverse test results only. The difference is small.

(h) It is theoretically possible, since APKD is a heterogeneous disorder, that an underwriter could know that there was a family history, and whether it was APKD1 or APKD2 that was inherited (for example if a relative of the applicant had had a test and that result were disclosed). This seems quite a remote possibility, but we did rerun the figures in Table 3 on that basis and found it made a negligible difference.

The costs are all very small (bearing in mind that APKD is one of the more common single-gene disorders). Moreover, it makes little difference which of the three sources of data we use. Comparing these with the corresponding results in Gutiérrez & Macdonald (2003, Table 8), which were based on aggregate data, we find that the costs in this study are all a little higher, but reasonably close. They seem quite consistent with Figure 4, bearing in mind that APKD1 is so much more common than APKD2.

Table 4 shows the corresponding premium increases, were a moratorium to be extended to family histories as well as genetic test results. They are shown in two stages:

(a) Because there is now only one underwriting class, by default the new 'standard rates' class, the standard rate of premium will increase just because at-risk persons may now buy insurance at the 'normal' rate, just like everyone else. We do not regard this as adverse selection.

(b) Further premium increases may be caused if there is severe adverse selection, on the part of tested mutation carriers *and* untested at-risk persons (the most extreme possibility).

Just expanding the 'standard' underwriting class is usually much more costly than adverse selection under either of the previous moratoria, and further (severe) adverse selection could imply total premium increases of about 0.3% or 1.0%, at worst, in the large and small markets, respectively. Again, these are somewhat higher than the results in Gutiérrez & Macdonald (2003, Table 9) but consistent with Figure 4.

Table 4: Percentage increases in standard CI premium rates arising from new underwriting classes and severe adverse selection following a moratorium on the use of adverse genetic test results and family history. CI insurance market operating between ages 20–60. Rate of genetic testing 0.035.

Market Size	Source of Data	OR Premium Increases Arising from New Underwriting Classes		Premium Increases Arising from Severe Adverse Selection	
		Females	Males	Females	Males
		%	%	%	%
Large	Ravine	0.205	0.190	0.109	0.103
	Hateboer	0.201	0.186	0.096	0.090
	Johnson	0.196	0.181	0.082	0.077
Small	Ravine	0.196	0.176	0.803	0.739
	Hateboer	0.197	0.177	0.747	0.686
	Johnson	0.195	0.176	0.690	0.633

4. Survival After Onset of ESRD

4.1 *General Features*

APKD subjects who develop ESRD (called ESRD-APKD patients) require RRT, meaning dialysis (haemodialysis or peritoneal dialysis) or renal transplantation. In most countries with developed health services, almost all subjects will initially be accepted into a dialysis program. What may vary much more from country to country and from time to time, is the availability of kidneys for transplantation. Very few people have renal transplantation immediately, generally from a living donor (known as preemptive transplantation). Therefore, while we can estimate mortality rates during dialysis and after transplantation, the rate at which people are removed from dialysis by receiving transplants is not easily estimated from past data, nor would such estimates apply beyond the time and place of any particular study. For this part of the model, we will develop a sensitivity analysis.

There is a large literature on survival after ESRD for general populations, and several studies of ESRD-APKD populations. These studies are based either on single centre experiences (Gabel & Brynger, 1980; Fitzpatrick *et al.*, 1990; Florijn *et al.*, 1994; Hadimeri *et al.*, 1997); on data from national registries (Abbot & Agodoa, 2002a, 2002b; McDonald & Russ, 2002; Meier-Kriesche *et al.*, 2001; Perrone *et al.*, 2001; Rabbat *et al.*, 2000) or on international collaborations (the ERA-EDTA Registry for example).

ESRD-APKD patients appear to have better short-term survival (Tsakiris *et al.*, 1999; Abbot & Agodoa, 2002a) and long-term survival than the general ESRD populations (Wolfe *et al.*, 1999). Possible reasons are the earlier follow-up to progression to ESRD, and the younger age and better general health of APKD patients at ESRD. The same reasons make ESRD-APKD patients more likely to be placed on a waiting list for transplantation.

Table 5: Parameterisation of Gamma functions (Equation (3)) fitted to cumulative probability functions of duration of death following onset of dialysis or kidney transplant.

Ages at Onset	State	a	b
20–44	Dialysis	0.0442787	1.36159
20–24	Transplant	0.0746419	2.54771
45–59	Dialysis	0.0902674	1.61700
45–59	Transplant	0.0249060	1.26870

Studies comparing survival after a transplant with survival while on dialysis or on a waiting list (McDonald & Russ, 2002; Meier-Kriesche *et al.*, 2001; Rabbat *et al.*, 2000) agree that transplantation has the better outcome, conditional on surviving for 90 days, when the effects of the major surgery involved are overcome. We will consider this in Section 4.4.

4.2 *Short-Term Survival After Onset of ESRD*

Some studies focus on mortality in the first (usually three) months after starting RRT, and find it to be high. These deaths are not generally reported in national registries. However, Tsakiris *et al.*, (1999), in a study based on data from the ERA-EDTA registry, report that ESRD-APKD patients are less likely to die within 90 days of starting dialysis, compared with most other ESRD patients. From their sample of 6,792 ESRD-APKD patients, 1.4% died within 90 days. We will use this figure to adjust the post-onset mortality rates presented in Section 4.4.

4.3 *Long-Term Survival After Onset of ESRD*

We will base post-onset survival in our model on a survival analysis of the 1981 ESRD-APKD cohort in Canada, carried out at our request by the Canadian Organ Replacement Register (CORR) and the Canadian Institute of Health Information (CIHI). The calculations were made by the senior consultant of CORR using the LIFTEST (life table) procedure in SAS. The resulting Kaplan-Meier estimates (and standard errors) are shown in Tables 6 and 7.

Table 6 shows the survival probabilities for all 2,688 patients who started dialysis (of all kinds) and who survived at least 90 days. Transplantation is treated as a censoring event. Table 7 shows the survival probabilities for 1,128 patients after transplantation (of all kinds). The survival time after transplantation is counted from the day of the surgery with no time gaps.

We will concentrate on the first two age groups (20–44 and 45–59) which are most relevant for insurance. We use Gamma graduations (shown in Figures 9 and 10) of the probability $1 - S(d)$ of dying by duration d years of the form:

$$1 - S(d) = \frac{a^b}{\Gamma(b)} \int_0^d t^{b-1} e^{-at} dt \tag{3}$$

with the parameters shown in Table 5.

Table 6: Kaplan-Meier survival probabilities (and standard errors) since start of dialysis, conditional on surviving for 90 days, of the 1981 cohort of ESRD-APKD patients in Canada. Sample sizes are denoted n. Source: CORR-CIHI.

	Ages 20–44 ($n = 518$)		Ages 45–59 ($n = 1,252$)		Ages 60–74 ($n = 752$)		Ages 75+ ($n = 166$)		All ages ($n = 2,688$)	
Duration (Yrs)	Survival	S.E.	Survival	S.E.	Survival	S.E.	Survival	S.E.	Survival	S.E.
1	0.976	0.00677	0.998	0.00478	0.885	0.0118	0.874	0.0293	0.941	0.00463
2	0.968	0.00792	0.972	0.00735	0.802	0.0151	0.607	0.0408	0.884	0.00638
3	0.950	0.0101	0.933	0.00942	0.708	0.0177	0.396	0.0434	0.825	0.00777
4	0.935	0.0116	0.887	0.0111	0.633	0.0193	0.267	0.0422	0.773	0.00874
5	0.916	0.0132	0.843	0.0127	0.551	0.0205	0.215	0.0393	0.721	0.00961
6	0.877	0.0164	0.796	0.0138	0.457	0.0214	0.126	0.0345	0.667	0.0104
7	0.857	0.0179	0.759	0.0147	0.375	0.0219	0.069	0.0283	0.624	0.011
8	0.839	0.0193	0.728	0.0157	0.307	0.0218	0.056	0.0258	0.585	0.0115
9	0.822	0.0206	0.693	0.017	0.281	0.0218	0.042	0.0228	0.551	0.012
10	0.799	0.022	0.645	0.0179	0.248	0.0219	0.042	0.0228	0.524	0.0124
11	0.778	0.0243	0.615	0.0179	0.210	0.0219	0.025	0.0189	0.497	0.0129
12	0.748	0.0268	0.593	0.0186	0.199	0.022	–	–	0.474	0.0133
13	0.707	0.03	0.562	0.0196	0.177	0.0229	–	–	0.450	0.0139
14	0.699	0.03	0.539	0.0204	0.167	0.0237	–	–	0.425	0.0145
15	0.668	0.034	0.495	0.0221	0.150	0.0266	–	–	0.401	0.0152
16	0.621	0.041	0.444	0.0247	0.084	0.0382	–	–	0.384	0.0162
17	0.598	0.045	0.418	0.0247	0.084	0.0382	–	–	0.360	0.0179
18	0.552	0.061	0.386	0.0332	–	–	–	–	0.332	0.0213

Table 7: Kaplan-Meier survival probabilities (and standard errors) since transplantation, of the 1981 cohort of ESRD-APKD patients in Canada. Sample sizes are denoted n. Source: CORR-CIHI.

	Ages 20–44 ($n = 211$)		Ages 45–59 ($n = 669$)		Ages 60–74 ($n = 244$)		Ages 75+ ($n = 4$)		All ages ($n = 1,128$)	
Duration (Yrs)	Survival	S.E.	Survival	S.E.	Survival	S.E.	Survival	S.E.	Survival	S.E.
1	0.995	0.0048	0.984	0.00491	0.955	0.0139	1.00	0.0	0.980	0.00424
2	0.995	0.0048	0.977	0.00598	0.950	0.0147	1.00	0.0	0.975	0.00481
3	0.990	0.00726	0.977	0.00701	0.945	0.0156	1.00	0.0	0.969	0.00549
4	0.990	0.00726	0.952	0.00913	0.919	0.0196	1.00	0.0	0.953	0.0069
5	0.983	0.00969	0.943	0.0101	0.912	0.0207	0.667	0.2722	0.944	0.00768
6	0.976	0.0121	0.933	0.011	0.880	0.0256	0.667	0.2722	0.930	0.00873
7	0.968	0.0145	0.925	0.0118	0.842	0.0306	0.667	0.2722	0.917	0.00976
8	0.958	0.0172	0.904	0.014	0.842	0.0306	0.667	0.2722	0.902	0.0109
9	0.937	0.0225	0.894	0.015	0.816	0.0306	–	–	0.887	0.0121
10	0.912	0.0279	0.874	0.0172	0.816	0.0306	–	–	0.870	0.0136
11	0.882	0.0341	0.864	0.0183	0.794	0.206	–	–	0.850	0.0153
12	0.882	0.0341	0.836	0.0217	0.794	0.206	–	–	0.832	0.0171
13	0.882	0.0341	0.815	0.0242	0.794	0.206	–	–	0.819	0.0185
14	0.830	0.0479	0.806	0.0257	0.794	0.206	–	–	0.800	0.0208
15	0.789	0.0609	0.773	0.0334	0.794	0.206	–	–	0.784	0.0236
16	0.701	0.0988	0.692	0.0621	0.794	0.206	–	–	0.770	0.0269
17	0.701	0.0988	0.692	0.0621	0.794	0.206	–	–	0.694	0.0481

Because they are based on the 1981 cohort of patients, the data do not extend beyond duration 18 years. We need mortality rates up to age 60, so for ages 20–44 at onset we extrapolate the fitted functions to duration 40 years, as shown in Figure 9. This is unnecessary for ages 45–59 at onset.

4.4 *Forces of Mortality While In Renal Replacement Therapy*

We obtain forces of mortality based on the graduated survival functions in Section 4.3. However, the CORR-CIHI data excluded the first 90 days of RRT (almost all dialysis). Based on Tsakiris *et al.* (1999) (see Section 4.2) we assume a constant force of mortality of 0.05814 during the first 90 days of RRT, equivalent to mortality of about 1.4% over that period. The fitted forces of mortality specified in Table 5 are used thereafter.

For the life insurance model in the following sections, we represent ESRD and RRT by passage into 'Dialysis' and 'Transplant' states. The forces of mortality out of these states are taken to be the greater of the duration-dependent forces described above, and that of English Life Tables No.15. Thus mortality during RRT depends on both age and duration, and ESRD never results in mortality lower than normal at any age.

4.5 *The Rate of Transition from Dialysis to Transplantation*

Based on reported waiting times to transplantation from the U.K. Transplant Registry 2002 (506 days), the U.S. Renal Data System (USRDS, 1999) (818 days) and the Australia and New Zealand Data Registry (ANZDATA, 2002) (31 months for blood group O, 28 months for blood group A); and on Harris & Brown (1998) who reported that complications, morbidity and mortality are higher after 10 years of dialysis, we assume a maximum of five years on a waiting list for transplantation. After this time we assume that no transplantation is available and the ESRD-APKD subjects will continue on dialysis. Apart from this assumption, we do not attempt to estimate the rate of transition from dialysis to transplantation from data, as the results would be very localised in space and time, but we use four possible scenarios as follows:

(a) Only dialysis is available, and the intensity to transplantation is zero. This sets one boundary for the sensitivity analysis.
(b) There is a low intensity to transplantation, and about 22% of ESRD-APKD patients on dialysis will receive a transplant within five years (an intensity of 0.05 per year). This is consistent with the UK Transplant 2002 report for the whole cadaveric kidney programme, and it represents the situation where the number of transplants depends entirely on the number of cadaveric donors given that there is no encouragement for living donor transplantation.
(c) There is a moderate intensity to transplantation, and about 53% of ESRD-APKD patients on dialysis will receive a transplant within five years (an intensity of 0.15 per year). This represents the fact that ESRD-APKD patients are more likely to be wait-listed and more likely to receive a kidney transplant.
(d) All patients receive preemptive transplantation, and pass straight from 'Healthy' to 'Transplant' states. Although very unlikely, this sets the other boundary for the sensitivity analysis.

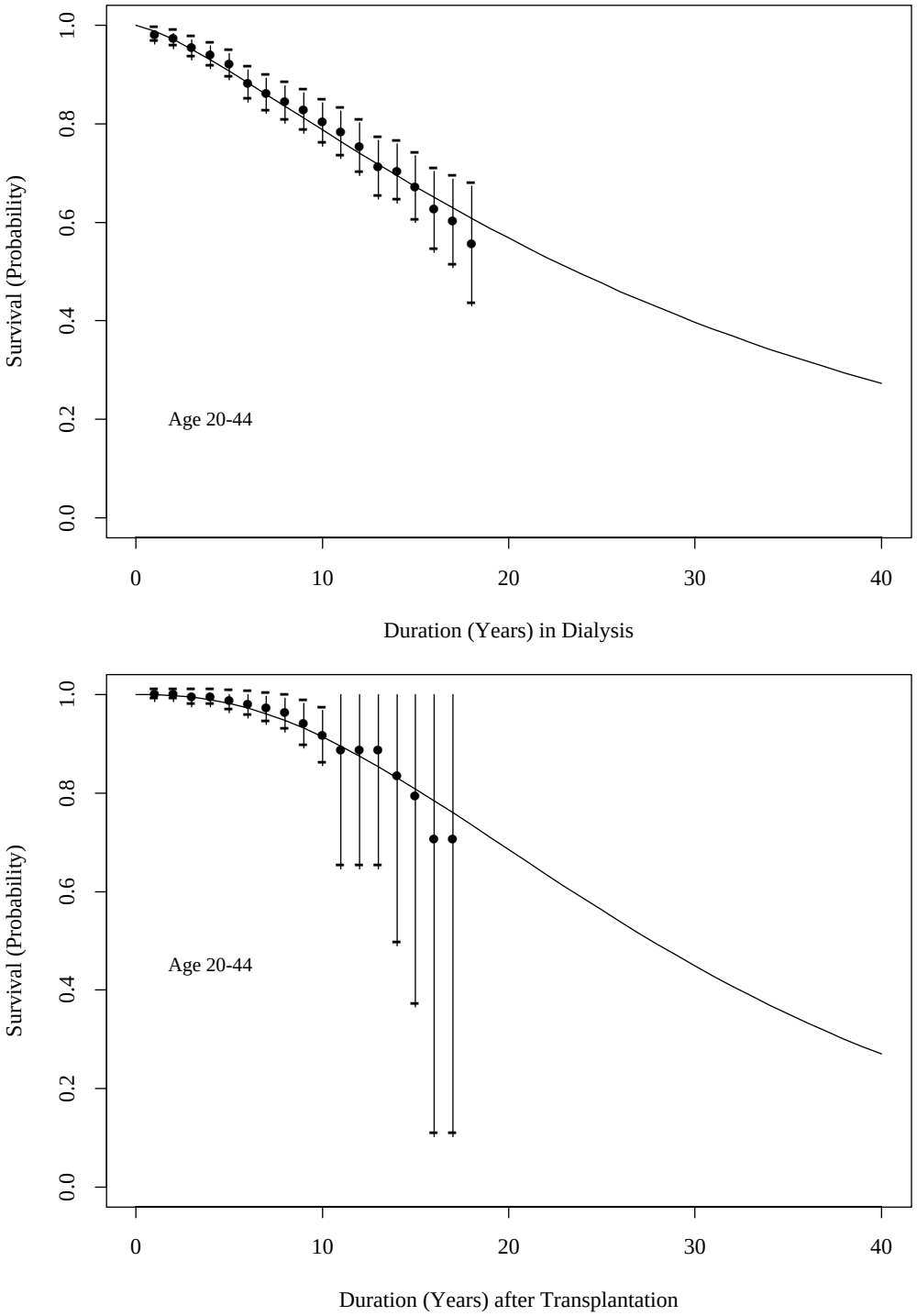

Figure 9: Probability of survival as a function of duration since onset of dialysis, conditional on surviving 90 days (top) or since renal transplantation (bottom), at ages 20–44, based on CORR-CIHI data. We show Kaplan-Meier estimates, with approximate 95% confidence intervals and our fitted curves (extrapolated for 20 years).

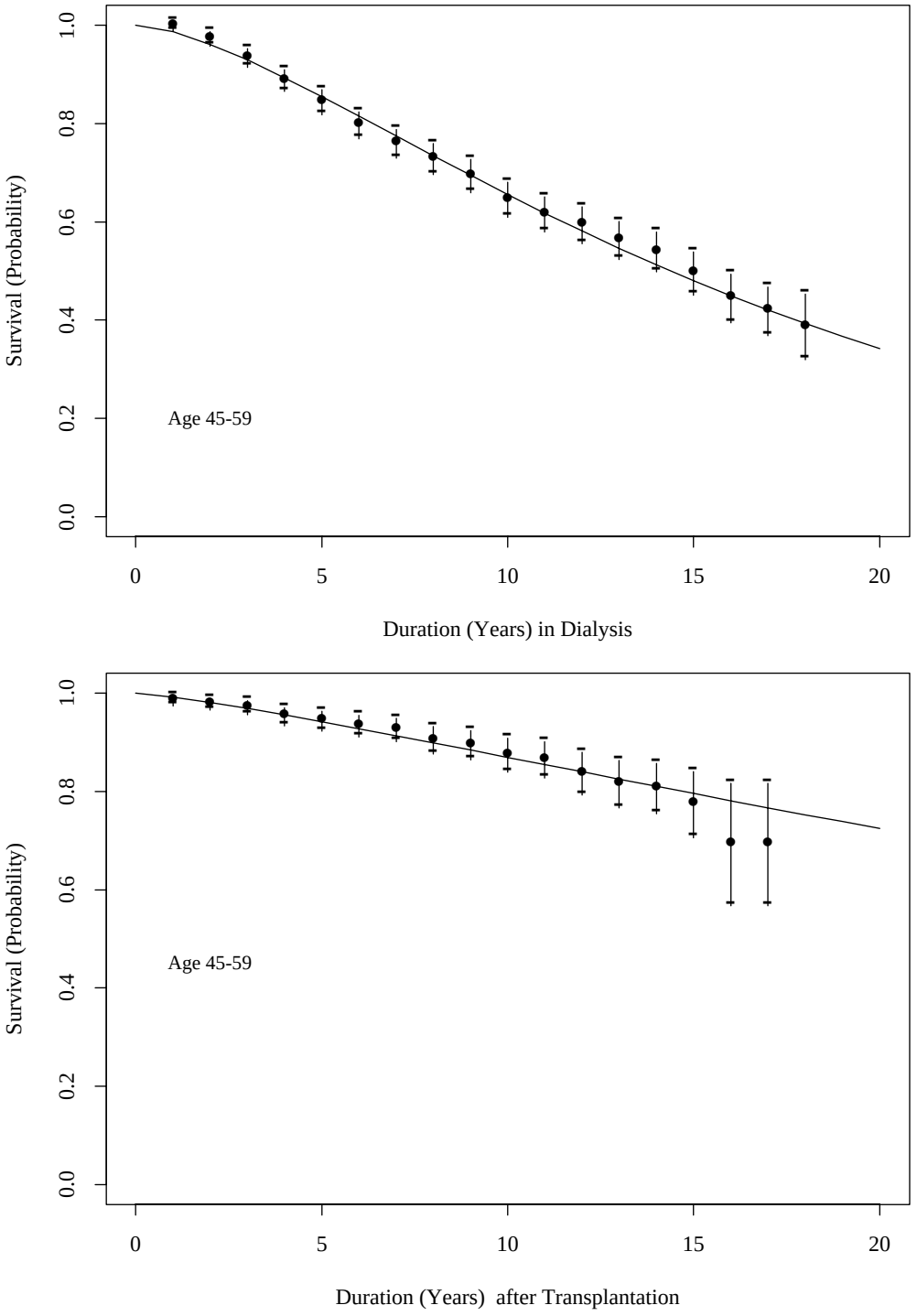

Figure 10: Probability of survival as a function of duration since onset of dialysis, conditional on surviving 90 days (top) or since renal transplantation (bottom), at ages 45–59, based on CORR-CIHI data. We show Kaplan-Meier estimates, with approximate 95% confidence intervals and our fitted curves.

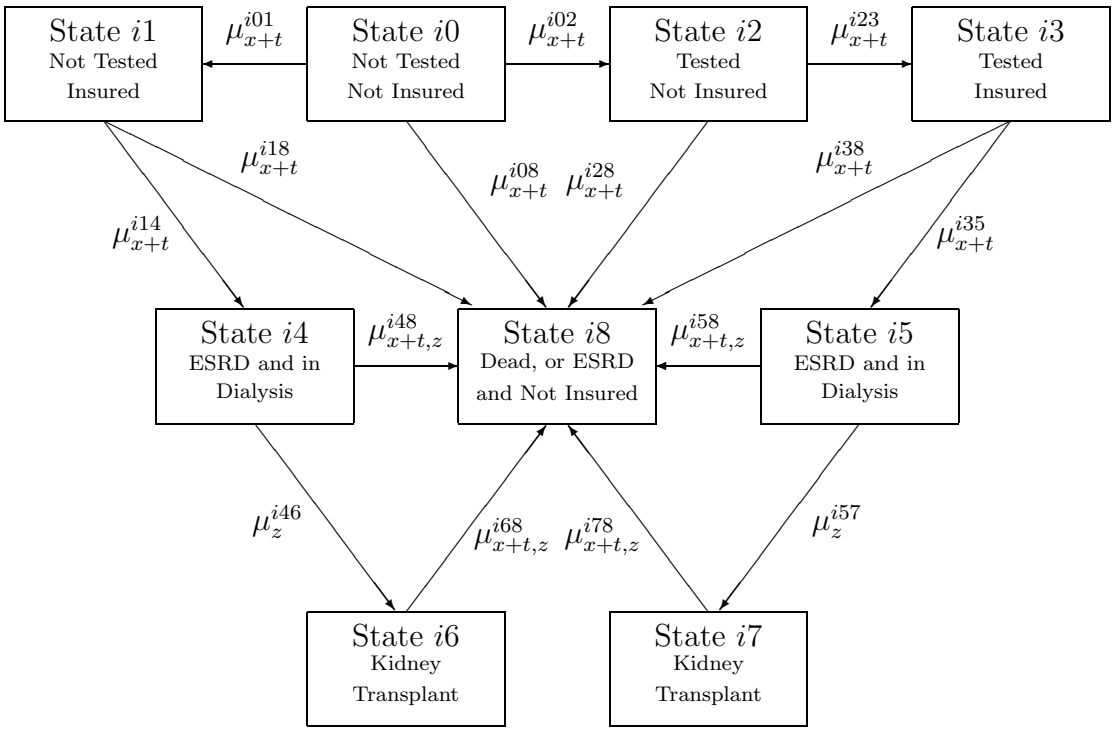

Figure 11: A semi-Markov model of genetic testing, life insurance purchase and clinical history of APKD, for a person in the i^{th} subpopulation. The duration since entering the current state is denoted z.

5. The Life Insurance Model

Figure 11 shows a semi-Markov model of a life insurance market. The intensities $\mu^{i48}_{x+t,z}$, $\mu^{i58}_{x+t,z}$, $\mu^{i68}_{x+t,z}$, $\mu^{i78}_{x+t,z}$, represent mortality after ESRD, and depend on both age $x+t$ and duration z. The intensities μ^{i46}_{z} and μ^{i57}_{z} represent the rate of transplantation, and depend on duration since ESRD alone. (In the fourth scenario in Section 4.5, in which everyone with ESRD receives an immediate transplant, we omit states $i4$ and $i5$ from the model, but we leave out the details.)

We make the same assumptions about rates of insurance purchase and of genetic testing as we did in the CI insurance model. No new principles are involved in computing EPVs in this model, although the introduction of duration dependence means that Thiele's differential equations become integro-differential equations which take longer to solve. We used the device (valid for first moments only) mentioned in Gutiérrez & Macdonald (2004), of splitting the calculations into two parts:

(a) for every state which has a duration-dependent intensity into any other state, compute the EPV on entry into that state, as a function of age; and
(b) treat that EPV as a sum assured payable upon entry into that state in a Markov model.

6. Level Premiums for Life Insurance

6.1 *Extra Premiums if the APKD Genotype is Known*

Tables 8 to 11 show the level premium for level life insurance cover, as a percentage of the standard (non-carrier's) premium, under each of the four transplantation scenarios outlined in Section 4.5.

The most relevant comparisons are between CI insurance and life insurance, and between the different levels of RRT.

(a) Even taking the worst case in respect of life insurance (no transplants, Table 8) the picture painted by CI insurance is changed entirely; every single case is within the limits of insurability (typically represented by premiums of about 500% of the standard). The differences between premiums based on the three studies that were noted in Section 3.2 are present here as well, because survival after onset was estimated independently of the rates of onset.

(b) As the availability of transplants improves, so do the premiums, so that if immediate transplantation was always possible (Table 11):
   (1) extra life insurance premiums for APKD1 mutations would hardly ever exceed +100%, and for many terms and ages it is likely that no extra premium would be charged; and
   (2) APKD2 would be almost eliminated as a relevant rating factor, with extra premiums rarely exceeding +25%.

This is striking evidence of the significant impact that treatment can have, even in respect of otherwise severe disorders.

6.2 *Extra Premiums Based on Family History Only*

Tables 12 and 13 show the level premium for level life insurance cover, as a percentage of the standard (non-carrier's) premium, for applicants with a family history of APKD. For brevity, since the effect of the intermediate treatment scenarios was made clear in Section 6, we show only the extreme scenarios of no transplantation and immediate transplantation.

Once again, our most significant result is the potentially awkward ranking of premium ratings based on different levels of genetic information. For example, in the case of no transplantation, and based on Hateboer *et al.* (1999), a female age 20 seeking life cover for 40 years would be charged a high extra premium of +224% if she carried an APKD1 mutation; or (possibly) a small extra premium of +37% if she carried an APKD2 mutation; but +97% on the basis of family history.

7. Life Insurance and Adverse Selection

Since it is already evident from the previous comparison between CI and life insurance that the costs of APKD risk in respect of the latter are much lower, we will not show adverse selection costs in every scenario. Also, we noted from Tables 3 and 4 that there was very little difference in the CI adverse selection costs based on the three different studies. Therefore, here we only show adverse selection costs based on one treatment

Table 8: Level net premium for level life insurance cover for persons with a known APKD mutation, as a percentage of the premium for standard risks. Dialysis only, no transplants available.

Sex of Applicant	Age at Entry (Years)	Policy Term (Years)	Premiums as Percentage of Standard					
				APKD1			APKD2	
			Ravine	Hateboer	Johnson	Ravine	Hateboer	Johnson
			%	%	%	%	%	%
Female	20	10	150	140	115	118	107	117
		20	241	209	154	141	114	130
		30	315	274	224	152	123	136
		40	346	324	299	157	137	144
	30	10	232	201	159	130	108	116
		20	323	281	244	147	122	127
		30	359	338	325	155	139	141
	40	10	250	230	233	127	120	119
		20	333	329	341	144	141	139
	50	10	241	258	260	124	127	126
Male	20	10	119	115	106	107	103	106
		20	165	150	125	119	106	114
		30	212	190	164	127	112	119
		40	229	216	203	130	119	123
	30	10	173	156	133	117	105	109
		20	232	207	185	128	113	116
		30	246	234	225	131	122	123
	40	10	193	180	182	116	112	112
		20	232	230	236	125	123	122
	50	10	175	184	185	113	114	114

Table 9: Level net premium for level life insurance cover for persons with a known APKD mutation, as a percentage of the premium for standard risks. Low level of transplantation.

Sex of Applicant	Age at Entry (Years)	Policy Term (Years)	Premiums as Percentage of Standard					
			APKD1			APKD2		
			Ravine	Hateboer	Johnson	Ravine	Hateboer	Johnson
			%	%	%	%	%	%
Female	20	10	145	136	113	117	107	115
		20	221	194	147	134	112	125
		30	284	249	207	144	120	130
		40	311	291	269	148	132	137
	30	10	218	190	153	127	108	114
		20	295	258	227	140	120	123
		30	326	307	294	146	133	135
	40	10	239	220	224	124	118	117
		20	307	304	313	138	135	133
	50	10	229	245	247	122	124	124
Male	20	10	117	114	105	106	103	106
		20	156	143	122	116	105	112
		30	195	177	155	123	110	116
		40	210	199	186	125	116	119
	30	10	166	150	129	115	104	108
		20	215	193	175	124	112	114
		30	227	216	208	126	118	119
	40	10	186	174	176	115	111	111
		20	217	215	221	121	120	119
	50	10	169	177	178	111	113	112

Table 10: Level net premium for level life insurance cover for persons with a known APKD mutation, as a percentage of the premium for standard risks. Moderate level of transplantation.

Sex of Applicant	Age at Entry (Years)	Policy Term (Years)	Premiums as Percentage of Standard					
				APKD1			APKD2	
			Ravine	Hateboer	Johnson	Ravine	Hateboer	Johnson
			%	%	%	%	%	%
Female	20	10	138	130	111	114	105	112
		20	198	176	138	127	109	120
		30	252	223	189	136	117	125
		40	277	258	236	140	126	131
	30	10	198	175	144	122	106	111
		20	262	231	207	133	116	119
		30	292	274	260	138	127	128
	40	10	221	205	209	121	116	115
		20	277	272	280	131	129	127
	50	10	212	227	228	118	121	120
Male	20	10	114	112	104	105	102	105
		20	145	135	118	113	104	109
		30	179	164	146	119	109	113
		40	191	181	169	121	113	116
	30	10	155	142	125	112	104	106
		20	196	178	163	119	110	111
		30	208	197	188	121	115	115
	40	10	175	165	168	113	110	109
		20	200	197	202	117	116	115
	50	10	160	168	169	110	111	111

Table 11: Level net premium for level life insurance cover for persons with a known APKD mutation, as a percentage of the premium for standard risks. Immediate transplantation, no time spent on dialysis.

Sex of Applicant	Age at Entry (Years)	Policy Term (Years)	Premiums as Percentage of Standard					
			APKD1			APKD2		
			Ravine	Hateboer	Johnson	Ravine	Hateboer	Johnson
			%	%	%	%	%	%
Female	20	10	108	107	102	103	101	103
		20	143	134	115	114	105	111
		30	189	171	145	123	109	116
		40	211	196	176	127	115	120
	30	10	124	118	110	106	101	103
		20	179	163	146	117	107	110
		30	207	194	182	123	114	115
	40	10	136	131	133	106	105	105
		20	176	172	175	114	113	112
	50	10	135	140	140	106	107	106
Male	20	10	103	102	101	101	100	101
		20	119	115	106	106	102	105
		30	144	135	121	112	105	108
		40	153	144	134	113	106	109
	30	10	112	109	105	103	101	102
		20	144	135	125	109	104	105
		30	153	145	138	111	106	107
	40	10	119	117	117	103	103	102
		20	134	132	133	106	105	105
	50	10	111	112	112	102	102	102

Table 12: Level net premium for level life insurance cover based on family history of APKD, as a percentage of the premium for standard risks. Dialysis only, transplants unavailable.

Age at Entry (Years)	Policy Term (Years)	Premiums as Percentage of Standard					
		Females			Males		
		Ravine	Hateboer	Johnson	Ravine	Hateboer	Johnson
		%	%	%	%	%	%
20	10	122	117	108	110	107	103
	20	163	147	125	132	122	112
	30	195	175	155	153	139	128
	40	208	197	187	161	150	145
30	10	158	143	126	139	116	116
	20	196	177	163	169	132	141
	30	210	201	197	176	141	159
40	10	160	153	156	137	129	134
	20	192	192	199	152	147	156
50	10	145	153	154	134	137	129

Table 13: Level net premium for level life insurance cover based on family history of APKD, as a percentage of the premium for standard risks. Immediate transplantation, no time spent on dialysis.

Age at Entry (Years)	Policy Term (Years)	Premiums as Percentage of Standard					
		Females			Males		
		Ravine	Hateboer	Johnson	Ravine	Hateboer	Johnson
		%	%	%	%	%	%
20	10	104	103	101	101	101	100
	20	119	115	107	108	106	103
	30	139	131	120	117	115	110
	40	149	142	134	120	119	115
30	10	110	108	104	105	102	102
	20	134	127	120	118	110	109
	30	146	140	136	122	113	114
40	10	114	113	114	108	105	107
	20	130	130	131	114	110	114
50	10	111	113	114	104	104	104

Table 14: Percentage increases in premium rates arising from severe adverse selection. Moratorium on the use of genetic test results, but family history underwriting still allowed. Life insurance market operating between ages 20–60. Rate of genetic testing 0.035 per annum. Rates of onset based on Hateboer *et al.* (1999). Moderate rate of transplantation.

Market Size	Insurance Purchasing of At-Risk Persons	Moratorium on Using All Test Results		Moratorium on Using Adverse Test Results	
		Females	Males	Females	Males
		%	%	%	%
Large	Normal	0.021	0.010	0.020	0.009
	Half	0.022	0.011	0.020	0.009
	Nil	0.025	0.013	0.022	0.011
Small	Nil	0.076	0.039	0.066	0.033

Table 15: Percentage increases in standard premium rates arising from new underwriting classes and severe adverse selection following a moratorium on the use of adverse genetic test results and family history. Life insurance market operating between ages 20–60. Rate of genetic testing 0.035. Rates of onset based on Hateboer *et al.* (1999). Moderate rate of transplantation.

Market Size	OR Premium Increases Arising from New Underwriting Classes		Premium Increases Arising from Severe Adverse Selection	
	Females	Males	Females	Males
	%	%	%	%
Large	0.057	0.028	0.049	0.025
Small	0.051	0.025	0.241	0.129

scenario (a moderate rate of transplantation, which seems reasonably realistic for our purposes) and on one study, namely Hateboer *et al.* (1999), which we had already noted as being possibly the most reliable of the three in respect of APKD2.

Table 14 shows the results of severe adverse selection in the presence of a moratorium on genetic tests alone, while Table 15 shows the results of a moratorium extending to family history as well, in the same two stages as before to separate out genuine adverse selection from the creation of a broader underwriting class. In support of studies of other disorders, these tables show that only the removal of family history as a rating factor makes any possible difference, and we would remind the reader that we think our assumptions are extreme.

8. Conclusions

We have modelled the impact on insurance of a genetic disorder that is more complex than others studied to date, in several respects.

(a) It is heterogeneous, being caused by mutations in either of two genes. While this is also true of familial breast/ovarian cancer, for example, in the case of APKD the relative mutation frequencies and penetrances combine to make knowledge of family history a riskier piece of information than an *adverse* test result for an APKD2 mutation. This subverts our intuitive ranking of the 'strength' of genetic information, in which we would naturally suppose family history to carry less risk than a known mutation. Since it is clear that some such intuitive ranking may have influenced the form of moratoria currently in use, this may call for some rethinking. Perhaps the basic conflict to which it points is the extra moral, social or ethical weight that sometimes seems to be attached to genetic information, with more weight being attached to information that is seen as 'more genetic'. The relative ranking of the 'more genetic' APKD2 test result and the 'less genetic' family history of APKD does not support a pure form of genetic exceptionalism.

(b) The counterintuitive ranking of risks does lead to some practical difficulties in the application of a moratorium. It seems to be accepted in most jurisdictions that a 'lenient' moratorium is acceptable, so that genetic information that benefits the applicant may be used in underwriting. Now, it is possible that an *adverse* test result may benefit the applicant. However, such has been the desire of those involved in shaping the various moratoria to nail down the possibility of insurers using adverse genetic tests, that there might be no way to allow the applicant the benefit of a 'good' adverse result — surely a perverse outcome. We realise that this problem falls away if the moratorium extends to family history, but this would seem to us to be an over-reaction if it were introduced merely to get around this particular difficulty.

(c) The three studies used here did not give entirely consistent results; the earliest (Ravine *et al.*, 1992) gave much higher rates of onset at younger ages. It is impossible to establish the reason for this, but one possible cause would be the tendency for the earliest studies of a genetic disorder to be more affected by ascertainment bias; that is, the overstatement of rates of onset caused by the selection of families with unusually large numbers of cases. This has been observed in respect of many disorders. For actuaries, the chief implication is that quantitative studies of genetic disorders may have to be updated from time to time as the epidemiology improves. Had we written a paper in 1995 based on Ravine *et al.* (1992), it would by now be necessary to revise the results in the light of the later studies.

(d) The other complicating factor introduced here is treatment, and its variable effects. Because progression to ESRD is not treatable, this only affects life insurance. And, since the alternative is certain death, we may suppose that the issue is not whether individuals exercise any choice over being treated or not, but the extent to which the health services can deliver the treatment. We have assumed that dialysis is available to all, but that kidney transplants are scarce to varying degrees. This seems reasonably realistic in respect of countries with highly developed health services, perhaps with the additional assumption that those segments of the population that have access to

insurance are also those that have access to health care. Closer examination of this question would be so specific to particular countries that we leave it aside.

(e) The main impact that treatment has here is to create a very large difference between CI insurance and life insurance. The impact of APKD, and the various risk factors for APKD, do show why genetics and insurance has become an issue, whereas if genetic disorders always led to premiums like those shown in respect of life insurance, we may wonder if genetics would ever have become an insurance issue at all. We would argue that this also tends to undermine the pure position of genetic exceptionalism.

(f) In other cases, we would expect the possibility of prophylactic treatment to bring more difficult problems, especially in two respects. First, effective treatment may be drastic, as in double mastectomy to reduce the risk of breast cancer. Then many people would find it highly undesirable if insurance considerations should impinge on the medical autonomy of an at-risk person, either in deciding to be tested or in deciding to be treated. We suspect that many people might even see this as inherently less acceptable than the actual principle of charging different premium rates. Therefore, the possibility of such decisions being taken in the conscious belief that testing and/or treatment is the only way to obtain affordable insurance is one that the insurance industry should perhaps strive to avoid. In this case, there may a rational basis for genetic exceptionalism, because the ability of a genetic test (for a single-gene disorder) to deliver a firm 'yes' or 'no' in respect of a perfectly healthy individual is rather unusual. Second, surgery might sometimes be delayed until screening detects early symptoms; this is the basis for proposed screening programs for familial forms of bowel cancer, for example. It may be possible almost to normalise the mortality risk, but this depends on being enrolled in, and remaining in, a screening program. It is not clear how this can reasonably be made a condition for favorable premium rating, when there is a close association with sensitive genetic information.

(g) The costs of adverse selection shown here are small in absolute terms, although showing how much more serious a moratorium extending to family history might be in relative terms. This information should not be viewed in isolation however, since APKD is just one of several single-gene disorders. We view these results as part of an ongoing research program aimed at modelling enough of the major genetic disorders to be able to measure the potential for adverse selection on the basis of epidemiological evidence — the 'bottom-up' approach to this problem mentioned in Daykin *et al.* (2003).

Finally, we note that while this study has had genetic heterogeneity and treatment as its foci, it has remained within the relatively clear-cut area of severe, single-gene disorders. We should expect heterogeneity and treatments to be major features when we come to study complex, multifactorial disorders such as heart disease and many cancers.

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APPENDIX A

FITTED SURVIVAL FUNCTIONS BASED ON TIME TO ESRD OR DEATH

(a) *Johnson & Gabow (1997)*
For APKD1:

$$S(x) = 1 - \exp(-6.12251 + 0.058346x + 0.000921743x^2) \quad (x < 39) \tag{4}$$

$$S(x) = 25.6616 \left(\frac{0.310552^{13.2644} \exp(-0.310552x) x^{12.2644}}{\Gamma(13.2644)} \right) \quad (x > 49) \tag{5}$$

with blending by curve of sines (Benjamin & Pollard, 1980) between ages 39 and 49, and for APKD2:

$$S(x) = 1 - \exp(-8.51304 + 0.14592x - 0.000441722x^2) \quad (x < 56) \tag{6}$$

$$S(x) = 17.7985 \left(\frac{0.673076^{39.8749} \exp(-0.673076x) x^{38.8749}}{\Gamma(39.8749)} \right) \quad (x > 74) \tag{7}$$

with blending by curve of sines between ages 56 and 74.

(b) *Hateboer* et al. *(1999)*
For APKD1:

$$S(x) = 1 - \exp(-9.08371 + 0.231087x - 0.00138536x^2) \quad (x < 40) \tag{8}$$

$$S(x) = 23.0056 \left(\frac{0.345615^{15.1344} \exp(-0.345615x) x^{14.1344}}{\Gamma(15.1344)} \right) \quad (x > 55) \tag{9}$$

with blending by curve of sines between ages 40 and 55, and for APKD2:

$$S(x) = 1 - \exp(-11.8117 + 0.25559x - 0.00136435x^2) \quad (x < 58) \tag{10}$$

$$S(x) = 24.7781 \left(\frac{0.364067^{21.278} \exp(-0.364067x) x^{20.278}}{\Gamma(21.278)} \right) \quad (x > 70) \tag{11}$$

with blending by curve of sines between ages 58 and 70.

(c) *Ravine* et al. *(1992)*
For APKD1:

$$S(x) = 1 - \exp(-10.0993 + 0.294084x - 0.00219349x^2) \quad (x < 40) \tag{12}$$

$$S(x) = 24.4878 \left(\frac{0.277887^{12.0004} \exp(-0.277887x) x^{11.0004}}{\Gamma(12.0004)} \right) \quad (x > 60) \tag{13}$$

with blending by curve of sines between ages 40 and 60, and for APKD2:

$$S(x) = 1 - \exp(-6.53247 + 0.102286x - 0.000256903x^2) \quad (x < 80) \qquad (14)$$

APPENDIX B

THE CRITICAL ILLNESS INSURANCE MODEL

Gutiérrez & Macdonald (2003) obtained the following model for CI insurance based on medical studies and population data. Full references can be found in that paper.

(a) Rates of onset were found for:

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

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

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

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

(2) *Heart Attack*: For males:

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

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

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

(3) *Stroke*: For males:

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

and for females:

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

(b) 28-day survival factors for heart attack and stroke victims were taken from Dinani *et al.* (2000) (this relates to the common contractual condition, that payment depends on surviving for 28 days). Let p_x^h and p_x^s be the 28-day survival probabilities after the first-ever heart attack or stroke, respectively, and $q_x^h = 1 - p_x^h$, $q_x^s = 1 - p_x^s$ the corresponding mortality rates. From Dinani *et al.* (2000), $q_x^h = 0.21$ at ages 20–80 for females, and q_x^h for males is given in Table 16. From the same source, $p_x^s = (0.9 - 0.002x)/0.9$ for both males and females.

Table 16: 28-Day mortality rates ($q_x^h = 1 - p_x^h$) following heart attack. Based on Dinani *et al.* (2000).

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

(c) Other minor causes of CI insurance claims amount to about 15% of those arising from cancer, heart attack and stroke. Therefore the aggregate rate of CI claims is:

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

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