

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

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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 the 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 insurance, extending the work of Gutiérrez and Macdonald (2003), which was based on studies predating 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.

1. INTRODUCTION

1.1 Heterogeneous Genetic Disorders and Insurance

There is a growing literature on the actuarial implications of genetic disorders, mostly focused on the small number of single-gene disorders that are dominantly inherited, severe, highly penetrant and have onset during adult ages. See Macdonald (2003a, 2004) for an introduction to the relevant genetical background and Daykin et al. (2003) for a recent review of the actuarial and social policy issues. Many of these issues involve the concept of “genetic exceptionalism”: namely, the idea that genes are so fundamental to a person’s definition as a human being that special considerations should apply to anything genetic.

The development of DNA-based genetic tests for inherited disorders has had two consequences:

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- 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, such as characteristic ages at onset. Thus, variability displayed by a single disease is resolved, by a genetic test, into different genetic causes.

The example we study is APKD, a progressive disease leading to kidney failure (known as end-stage renal disease [ESRD]). Mutations in either of two genes, APKD1 and APKD2, cause APKD, and carriers of APKD1 mutations tend to have much earlier ages at ESRD than do carriers of APKD2 mutations.

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. The information that might be available to an underwriter, concerning an applicant and his or her first-degree relatives (FDRs), is the following:

- a. Applicant has been tested and does not carry an APKD mutation
- b. Applicant has been tested and carries an APKD1 mutation
- c. Applicant has been tested and carries an APKD2 mutation
- d. Applicant has not been tested, but an FDR carries an APKD1 mutation
- e. Applicant has not been tested, but an FDR carries an APKD2 mutation
- f. Applicant has not been tested, but an FDR carries an APKD1 or APKD2 mutation.

Moratoria 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 United Kingdom, 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 coverage. Strictly implemented, this would confine the underwriter to knowing (f) above; they would be forbidden to ask questions from whose answers they could learn (a)–(e). As a consequence a person who had been tested and *proved* not to be a mutation carrier could not reveal this and would have to pay the premium appropriate for his or her family history. In practice this strict avoidance of using test results is not enforced, and a “clear” test result will be taken into account. 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 or 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. A carrier of such a milder form of mutation, identified by a genetic test, could then apply the same logic as is applied to “clear” tests in practice 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 the use of adverse test results in underwriting could appear through the back door. This would present significant problems for a “lenient” moratorium, but we will show in this paper that it is not just a theoretical possibility: APKD is an example.

APKD was previously studied by Gutiérrez and Macdonald (2003), and we will refer the reader to that paper for many details of the model. Their study, however, relied on epidemiology that did not distinguish between the two mutations that cause APKD; here we do.

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 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 over time; it is expensive and 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 and Macdonald 2003).

At first sight, the availability of treatment ought to alleviate any insurance problems caused by presymptomatic genetic testing, for individuals and insurers, 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 1000 (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 than 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 and Macdonald (2003) modeled 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 and 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 modeling. In Section 3 we model survival after ESRD, based on the availability of RRT. We find that this depends on duration since ESRD as well as age.

Section 4.1 (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. In Section 4.2 we estimate extra premiums appropriate if the presence of an APKD1 or APKD2 mutation is known. In Section 4.4 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 5 we describe a semi-Markov model allowing for survival and treatment after onset, applicable to life insurance. 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

The “penetrance” of an APKD mutation means the probability that ESRD has occurred in a known mutation carrier, in the absence of any competing decrements: let $q(x)$ denote the penetrance at age x . At least three studies have published penetrance estimates of APKD1 and APKD2 mutations: Johnson and Gabow (1997), Hateboer et al. (1999), and Ravine et al. (1992). All of these papers gave graphs of Kaplan-Meier estimates of the “survival” probability $1 - q(x)$.

In each case the event of interest was the first to occur 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

$$S(x) = \exp \left(- \int_0^x (\mu_t^{ESRD} + \mu_t^{DEAD}) dt \right), \quad (2.1)$$

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 and Gabow (1997)

Johnson and 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.

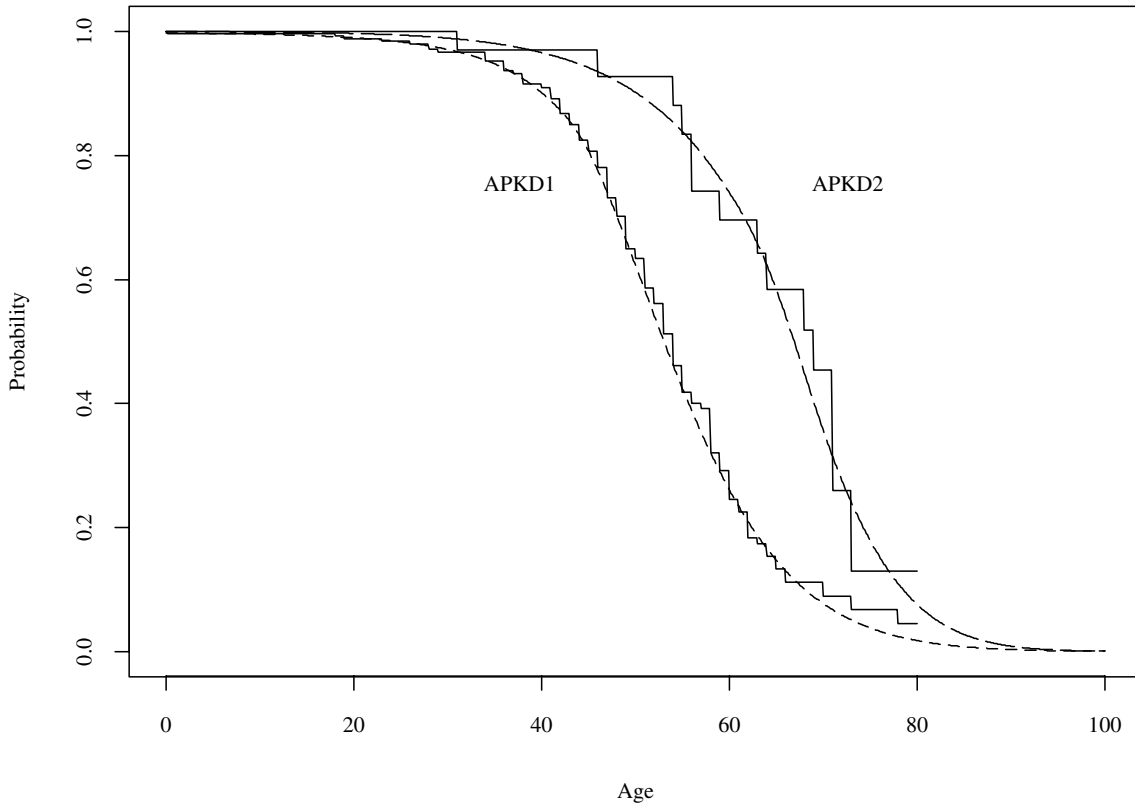
2.3 Hateboer et al. (1999)

Hateboer et al. (1999) studied APKD patients from centers in Bulgaria, Leiden, Santander, Barcelona, Madrid, Cardiff, and London. The sample included 333 subjects with APKD1 mutations from 31 families, and 291 subjects with APKD2 mutations from 31 families. The survival time (since birth) 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 ac-

Figure 1
Kaplan-Meier Estimates of Survival to ESRD or death for APKD1 and APKD2 Mutation Carriers from Johnson and Gabow (1997) and Fitted Curves



cepted as having APKD1 mutations. Families showing no such linkage were described simply as “non-PKD1.” Eighteen APKD1 families (285 persons) were identified, and five non-APKD1 families (49 persons), all of European descent. The survival time (since birth) 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.

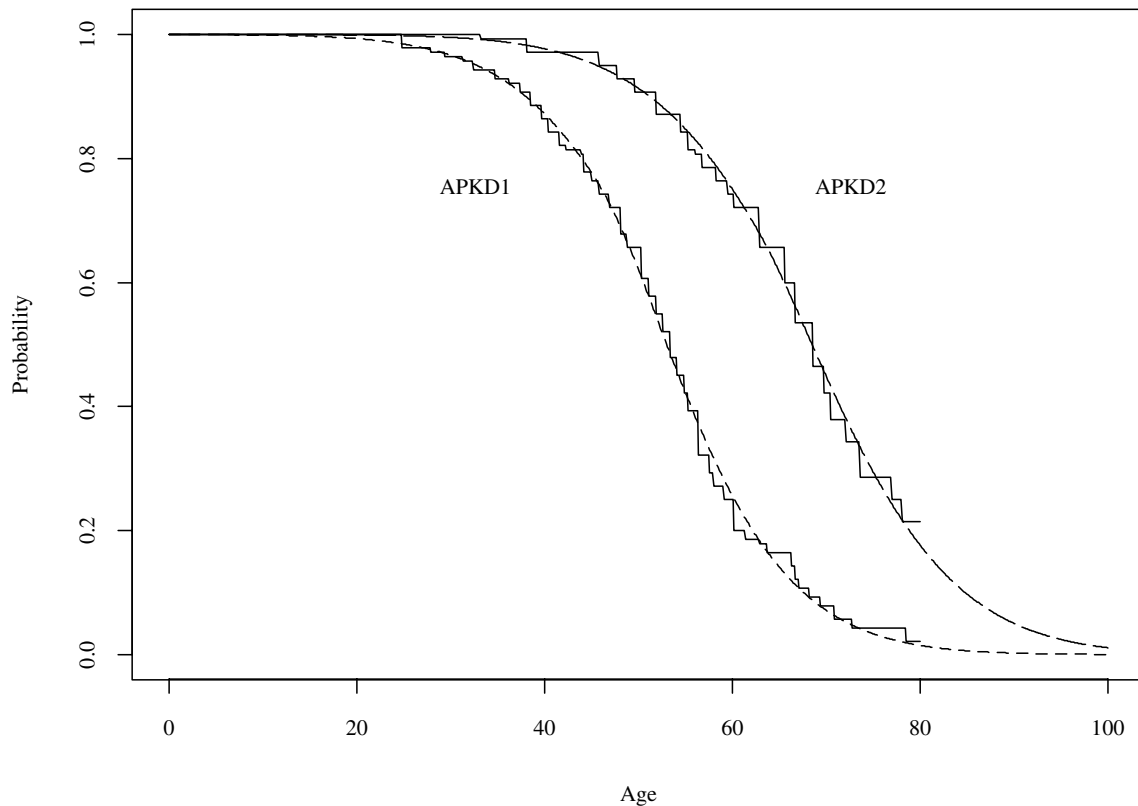
2.5 Comparison of the Three Studies and Previous Studies

Gutiérrez and Macdonald (2003) modeled 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 uremia (blood poisoning due to the failure of the kidneys to clear toxins). 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 U.S. population data. Figure 4 shows the fitted survival functions based on all three studies, as well as those based on the two aggregate experiences.

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

- 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.

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



- 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 because of the different study protocols.

In view of the very small samples of APKD2 subjects in Johnson and 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 study of APKD2. Next, comparing the three studies with the aggregate experiences:

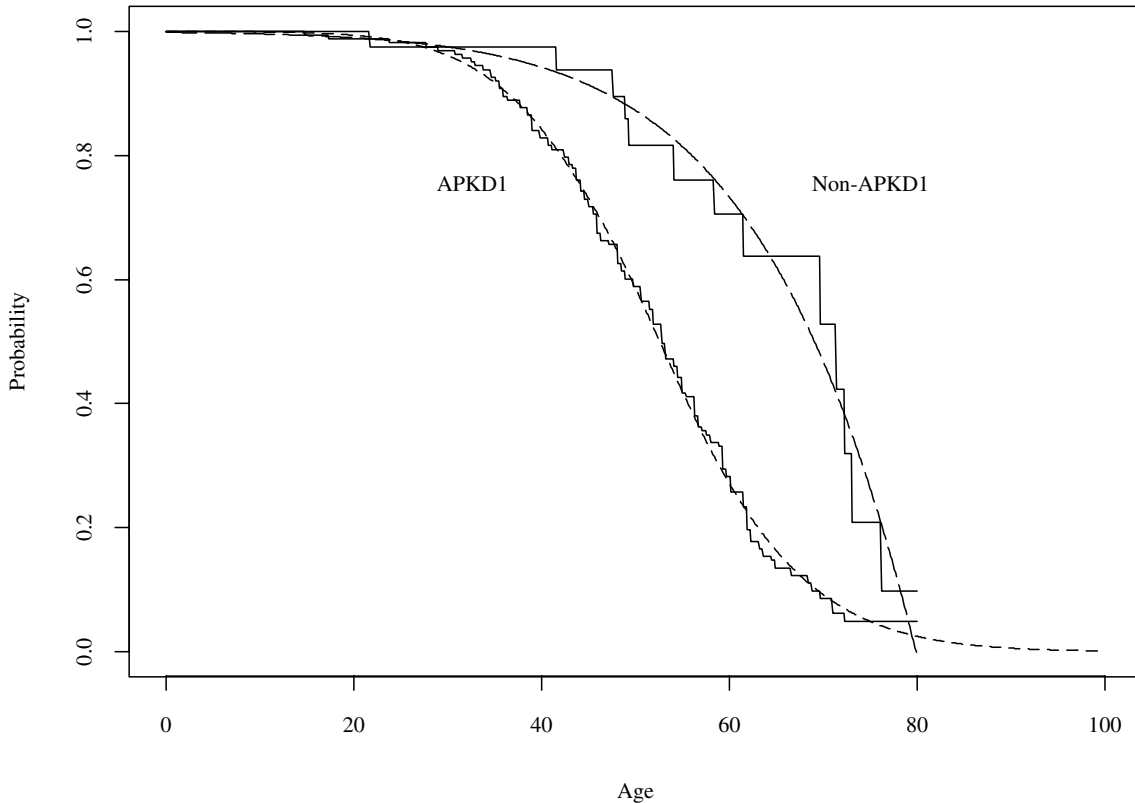
- The aggregate experiences lie more or less between those for APKD1 and APKD2 as we expect, at least up to age 70.
- Churchill et al. (1984) treated death (except by uremia) as censoring. Adjusting the survival function to include other deaths as an event would move it closer to the survival functions for APKD1.
- The USRDS experience has been adjusted here 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 eq. [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 and Gabow (1997); the results are shown in Figure 6.

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



3. SURVIVAL AFTER ONSET OF ESRD

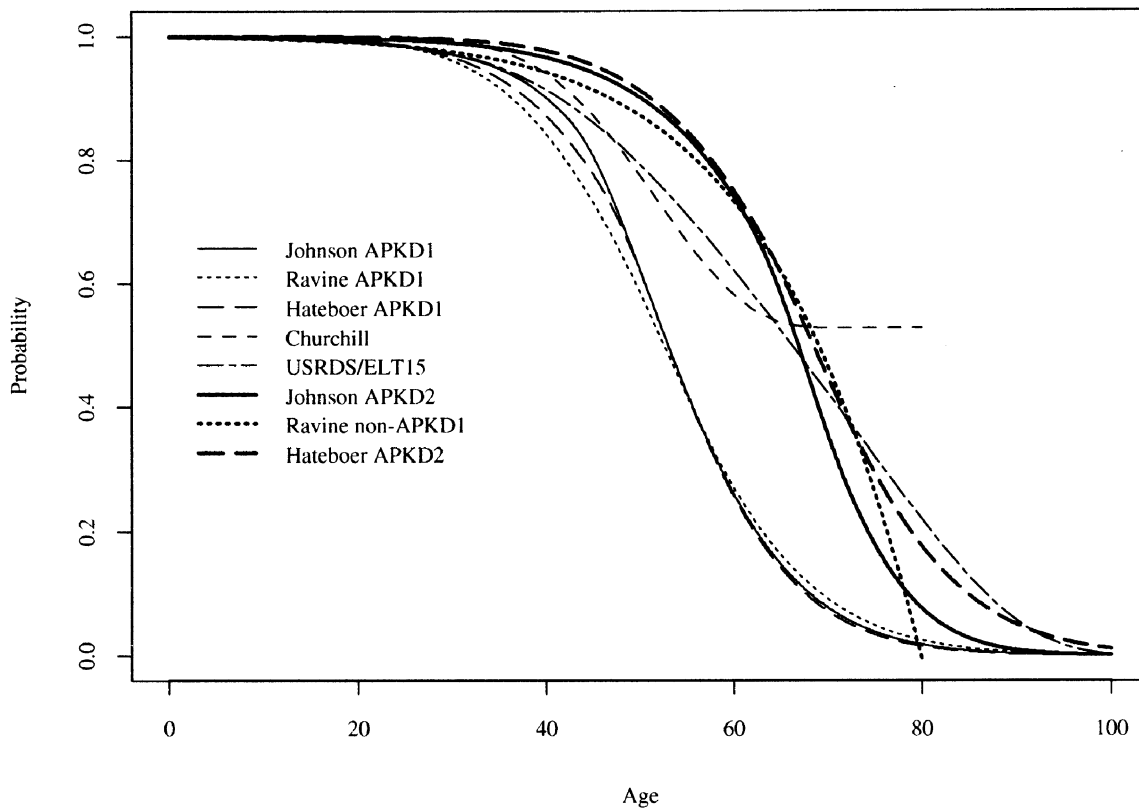
3.1 General Features

APKD subjects who develop ESRD (called ESRD-APKD patients) require RRT, meaning dialysis (hemodialysis 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 over 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-center experiences (Gabel and Brynner 1980; Fitzpatrick et al. 1990; Florijn et al. 1994; Hadimeri et al. 1997), on data from national registries (Abbot and Agodoa 2002a,b; McDonald and Russ 2002; Meier-Kriesche et al. 2001; Perrone, Ruthazer, and Terrin 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 and 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

Figure 4
**Survival Probabilities to ESRD Compared with Estimates Based on Churchill et al. (1984) and the
 USRDS (1999)**



Note: See Gutiérrez and Macdonald (2001).

of APKD patients at ESRD. The same reasons make ESRD-APKD patients more likely to be placed on a waiting list for transplantation.

Studies comparing survival after a transplant with survival while on dialysis or on a waiting list (McDonald and 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 3.4.

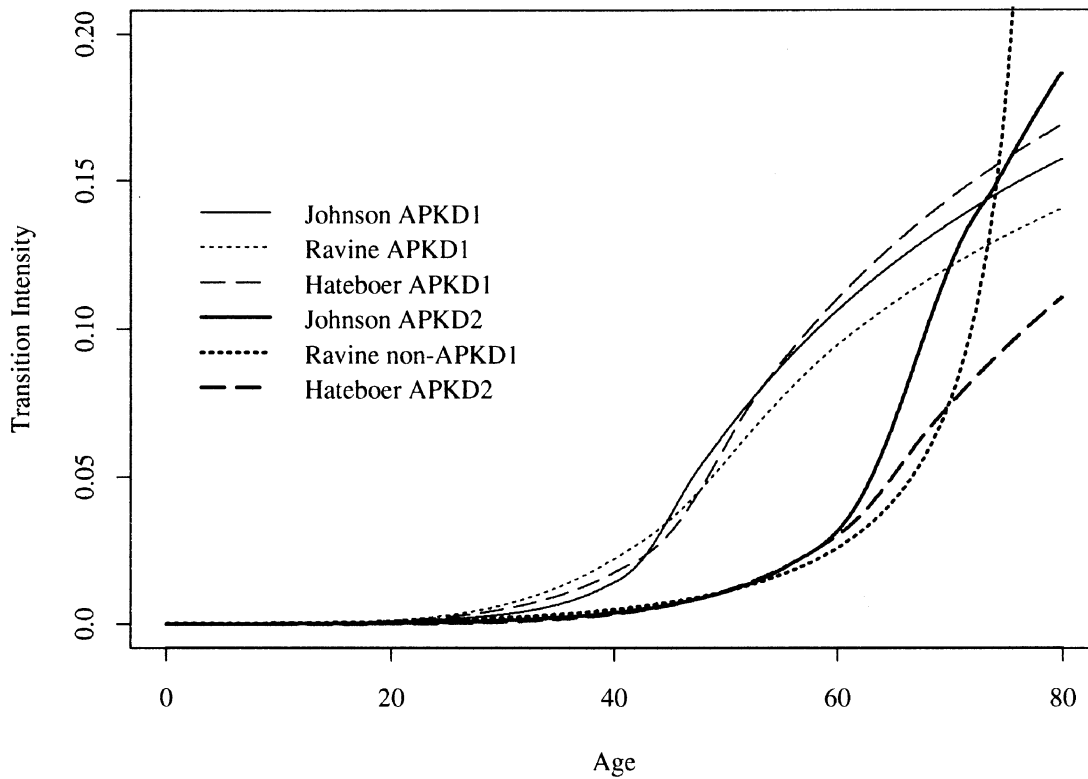
3.2 Short-Term Survival after Onset of ESRD

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 6792 ESRD-APKD patients, 1.4% died within 90 days. We will use this figure to adjust the post-onset mortality rates presented in Section 3.4.

3.3 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

Figure 5
Fitted Rates (Equivalently Forces or Intensities) of Onset (to the First of ESRD or Death)



of CORR using the LIFTEST (life table) procedure in SAS. The resulting Kaplan-Meier estimates (and standard errors) are shown in Tables 1 and 2.

Table 1 shows the survival probabilities for all 2688 patients who started dialysis (of all kinds) and who survived at least 90 days. Transplantation is treated as a censoring event. Table 2 shows the survival probabilities for 1128 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 fitted Gamma functions by least squares (shown in Figs. 7 and 8) to the probability $1 - S(d)$ of dying by duration d years:

$$1 - S(d) = \frac{\alpha^b}{\Gamma(b)} \int_0^d t^{b-1} e^{-\alpha t} dt \tag{3.1}$$

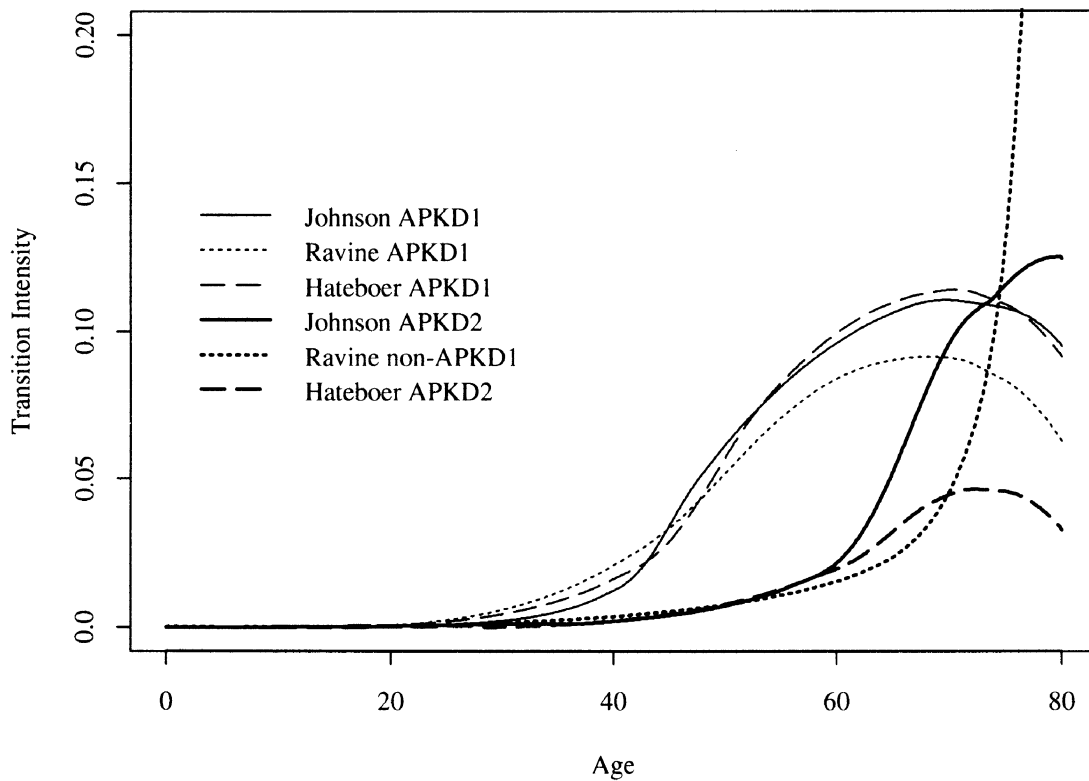
with the parameters shown in Table 3.

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 7. This is unnecessary for ages 45–59 at onset.

3.4 Forces of Mortality While in Renal Replacement Therapy

We obtain forces of mortality based on the graduated survival functions in Section 3.3. However, the CORR-CIHI data excluded the first 90 days of RRT (almost all dialysis). Based on Tsakiris et al. (1999) (see Section 3.2) 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 3 are used thereafter.

Figure 6
Fitted Rates (Equivalently Forces or Intensities) of Onset of ESRD



Note: Based on Fig. 5 adjusted using the mortality of English Life Tables No. 15 (Hateboer et al. 1999; Ravine et al. 1992) or the 1989–91 Colorado life tables (Johnson and Gabow 1997).

Table 1
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

Duration (yrs)	Ages 20–44 (n = 518)		Ages 45–59 (n = 1252)		Ages 60–74 (n = 752)		Ages 75+ (n = 166)		All Ages (n = 2688)	
	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

Source: CORR-CIHI.
 Note: Sample sizes are denoted n.

Table 2
Kaplan-Meier Survival Probabilities (and Standard Errors) since Transplantation, of the 1981 Cohort of ESRD-APKD Patients in Canada

Duration (yrs)	Ages 20–44 (n = 211)		Ages 45–59 (n = 669)		Ages 60–74 (n = 244)		Ages 75+ (n = 4)		All Ages (n = 1128)	
	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

Source: CORR-CIHI.

Note: Sample sizes are denoted *n*.

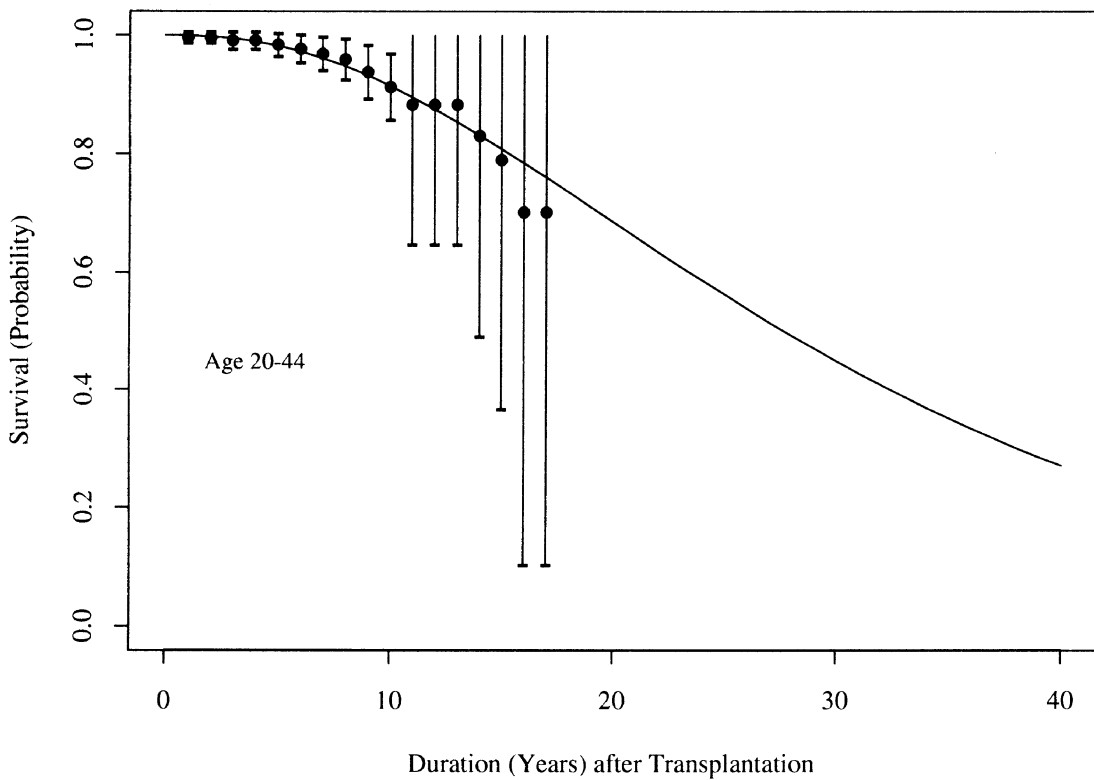
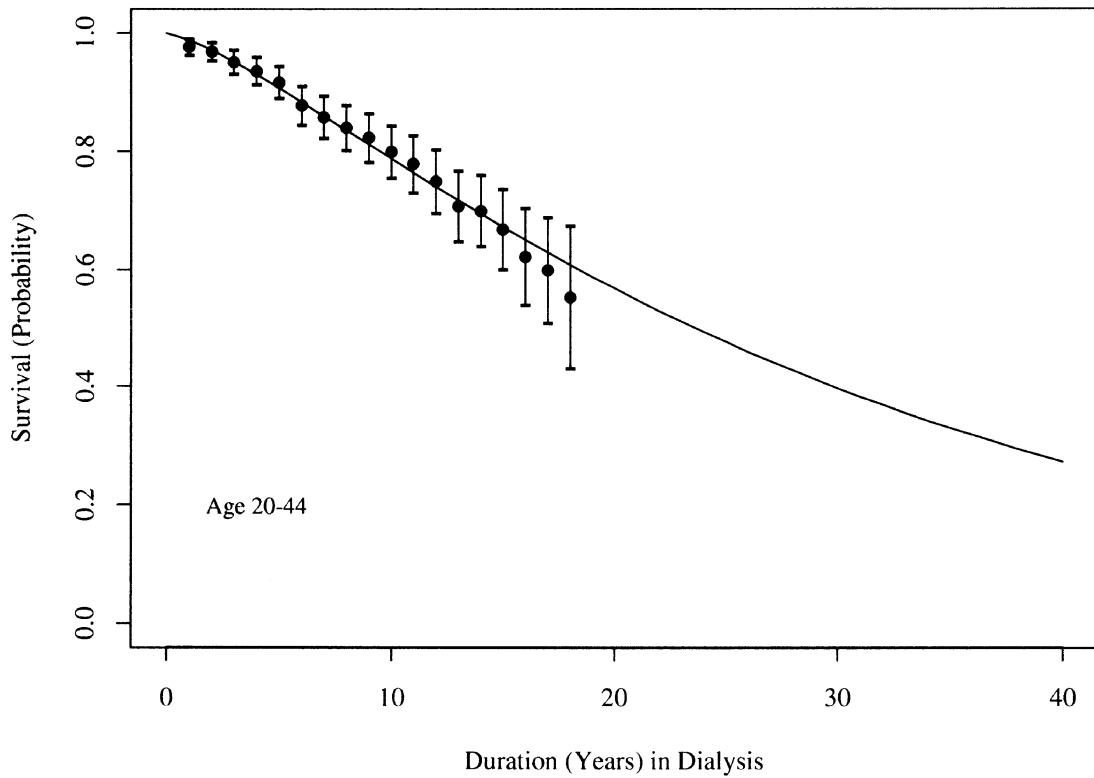
For the life insurance model in later sections, we represent ESRD and RRT by passage into “Dialysis” and “Transplant” states. The forces of mortality out of these states are taken to be the greater of the duration-dependent forces described above, and that of English Life Tables No. 15. Thus mortality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

3.5 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 and 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 localized in space and time, but we use four possible scenarios as follows:

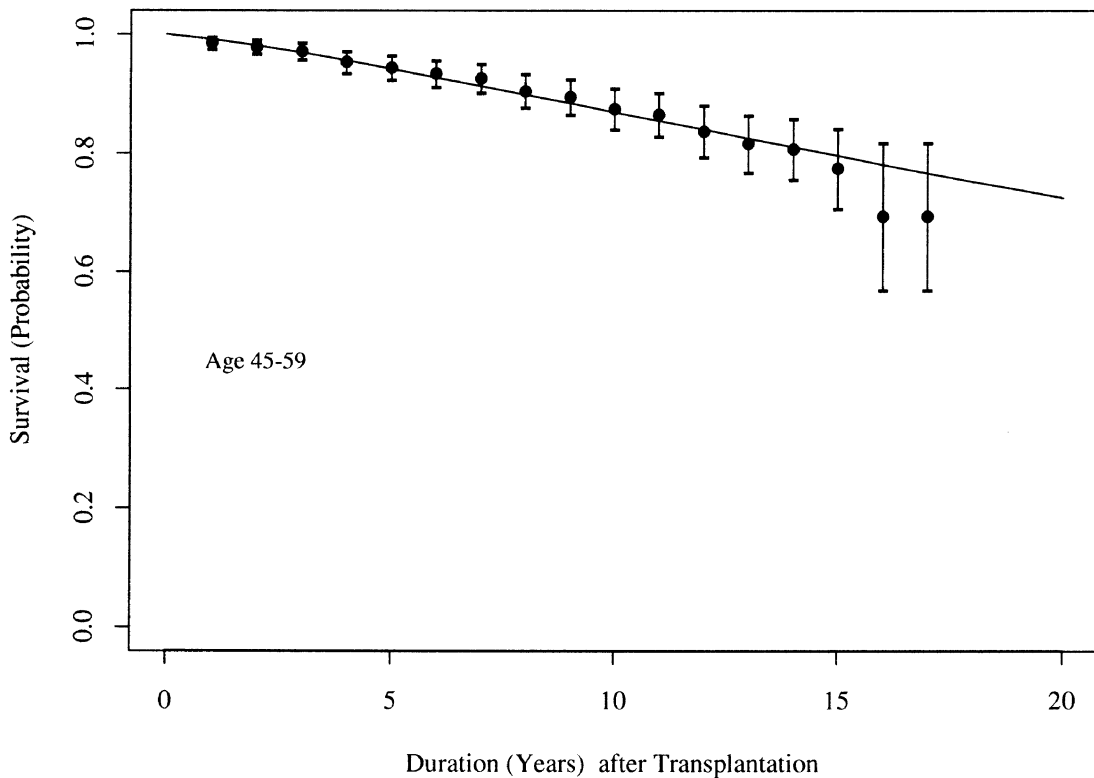
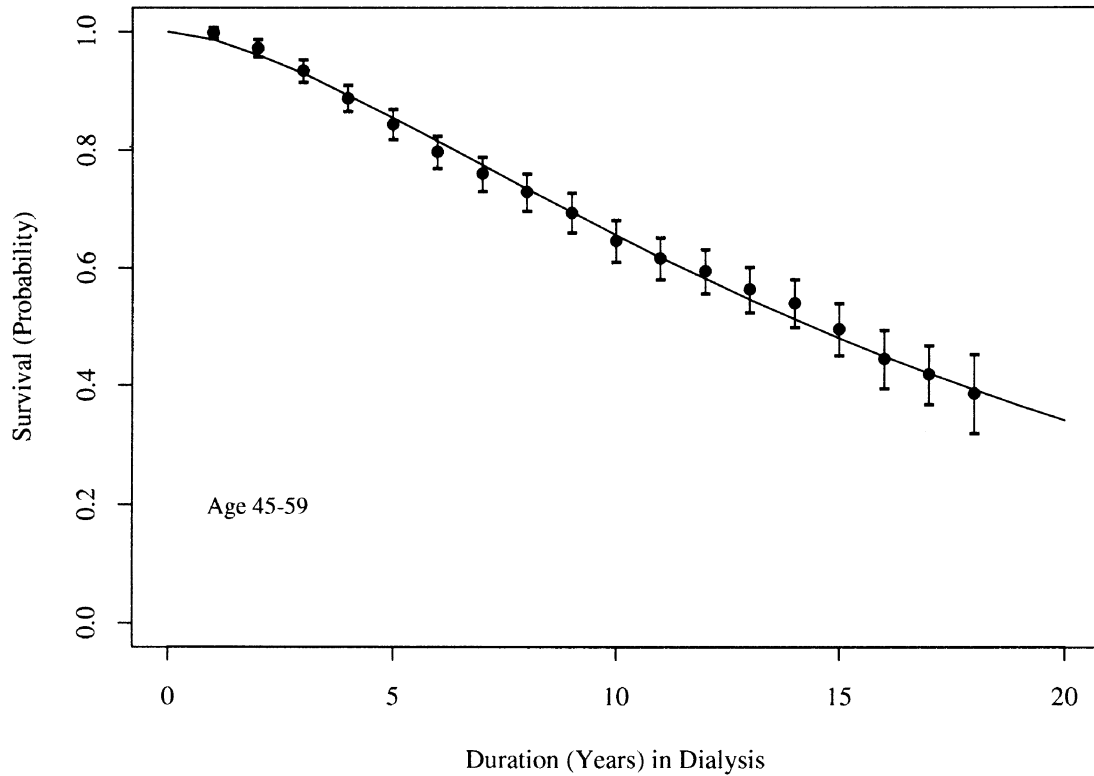
- Only dialysis is available, and the intensity to transplantation is zero. This sets one boundary for the sensitivity analysis.
- There is a low intensity to transplantation, and about 22% of ESRD-APKD patients on dialysis will receive a transplant within five years (an intensity of 0.05 per year). This is consistent with the U.K. Transplant 2002 report for the whole cadaveric kidney program, 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.
- 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.

Figure 7
Probability of Survival as Function of Duration since Onset of Dialysis or since Renal Transplantation



Notes: Conditional on surviving 90 days since dialysis (top) 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 8
Probability of Survival as Function of Duration since Onset of Dialysis or since Renal Transplantation



Notes: Conditional on surviving 90 days since dialysis (top) at ages 45–59, based on CORR-CIHI data. We show Kaplan-Meier estimates, with approximate 95% confidence intervals and our fitted curves.

Table 3
Parameterization of Gamma Functions (Eq. [2]) 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

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.

4. APKD1, APKD2, AND CRITICAL ILLNESS INSURANCE

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

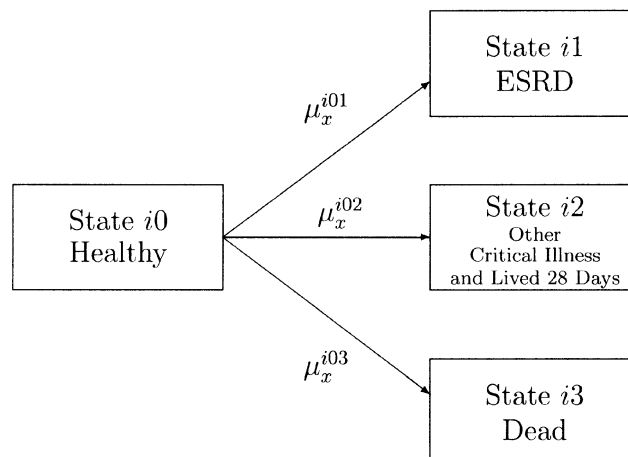
4.1 Model Specification

We propose the model in Figure 9 for APKD and critical illness (CI) insurance. This assumes that effective dialysis is available, so that death by uremia is not an endpoint, which seems appropriate for modeling future insurance risk. The model is parameterized by age-dependent intensities μ_x^{ijk} , where i labels the genotype and j, k are states. We need to estimate the following:

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

Figure 9

Model for APKD and Critical Illness Insurance, in Respect of the i th of Several Genotypes



4.2 CI Premiums If the APKD1 or APKD2 Genotype Is Known

Table 4 shows the level net premium for level CI coverage for persons with a known APKD mutation, expressed as a percentage of the premium for standard risks (taken to be nonmutation 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 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 that APKD1 mutations indicate much higher premiums than APKD2 mutations; carriers of the former would probably be uninsurable for almost all of these ages and terms, while carriers of the latter would all be insurable based on Hateboer et al. (1999). These premiums bear the expected relationship to those in Gutiérrez and Macdonald (2003, Table 5), based on aggregate data, namely, that the latter lie between the premiums for APKD1 and APKD2 carriers.

At older ages the premiums for carriers of either mutation based on the three studies are reasonably similar. At younger ages, however, those based on Johnson and 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.

4.3 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 $\frac{1}{2}$. 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 subpopulations labeled $i = 1, \dots, 5$, 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

Table 4

Level Net Premium for Level CI Coverage for Persons with Known APKD Mutation, as Percentage of Premium for Standard Risks

Sex of Applicant	Age at Entry (yrs)	Policy Term (yrs)	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	909	829	879	232	207	200		
	50	20	801	800	821	221	221	217		
		10	840	954	954	218	239	237		
		Male	20	10	896	724	362	366	199	328
				20	1031	818	513	330	183	246
30	875			760	665	268	194	217		
40	653			614	561	225	194	205		
30	10		1128	882	592	315	176	208		
	20		927	803	739	256	194	201		
	30		698	659	621	219	195	199		
	40		905	825	875	231	205	200		
50	20		711	709	728	205	202	201		
	10		690	780	781	194	206	209		

Table 5
Level Net Premium for Level CI Coverage for Persons with Family History of APKD (50% Risk at Birth), as Percentage of Premium for Standard Risks

Age at Entry (yrs)	Policy Term (yrs)	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

$i = 4$ 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 subpopulations 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 subpopulations 2 and 3, and 7.5% (= 15/2) in each of subpopulations 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^{ik} be the probability that a person in subpopulation 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 subpopulations 2–5 who are in subpopulation i , conditional on being healthy at age x , is

$$\frac{p_i p_x^{i00}}{p_2 p_x^{200} + p_3 p_x^{300} + p_4 p_x^{400} + p_5 p_x^{500}} \tag{4.1}$$

The probabilities p_x^{ik} all may 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 EPVs of benefits and premiums in each subpopulation, 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 5.

As indicated in Section 1.1, these lie between the premiums for known APKD1 and APKD2 mutation carriers in Table 4. 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 coverage 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 United Kingdom, the ABI in 1997 listed eight (later seven) disorders of significance for insurance. APKD was the disease dropped from 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 toward those with “clear” test results. Therefore, the question we have raised here is very relevant.)

4.4 Adverse Selection Associated with APKD1 and APKD2 Mutation Testing

To measure the potential costs of adverse selection, we must introduce insurance purchasing behavior to the model. This is illustrated by Figure 10, based on the five subpopulations defined in Section 4.3. It represents the life history of a person who may (or may not) choose to buy insurance in an insurance market, rather than one who has just bought insurance. A person in the i th subpopulation starts in State i_0 , uninsured and not having had a genetic test. From there they may buy insurance (State i_1) or have a genetic test (State i_2) and perhaps then buy insurance (State i_3). 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 subpopulations represent the market size, the level of genetic testing among at-risk groups or in the population, and adverse selection. The proportions in each subpopulation 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 (2003b) or Gutiérrez and Macdonald (2003).

Table 6 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 and Macdonald (2003) for full details:

- a. Entry ages and policy terms are absent from the table because insurance purchase (between ages 20 and 60) is one of the events modeled. If insurance is purchased it remains in force until age 60.

Figure 10

Markov Model of a Critical Illness Insurance Market, Allowing for Family History of APKD and Insurance Purchasing Behavior

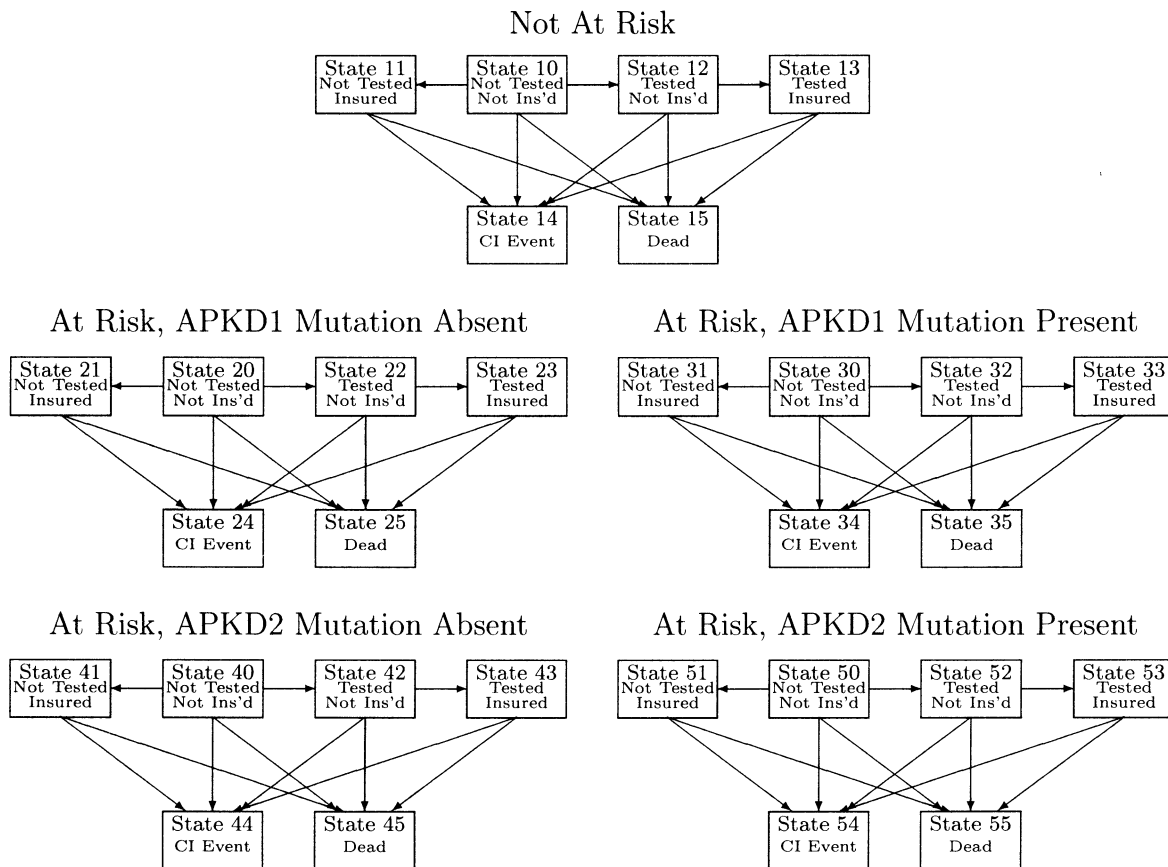


Table 6
Percentage Increases in Premium Rates Arising from Severe Adverse Selection

Market Size	Insurance Purchasing of At-Risk Persons	Source of Data	Moratorium on Using			
			All Test Results		Adverse Test Results	
			Females	Males	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

Notes: Moratorium on the use of genetic test results, but family history underwriting still allowed. CI insurance market operating between ages 20 and 60. Rate of genetic testing 0.035 per annum.

- b. 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.
- c. 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.
- d. 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).
- e. 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 their also buying above-average amounts of insurance, but note that this is proportionate to the figures in the table.
- f. Another form of adverse selection, which we do not model, could occur when an insured person obtains a clear test result and decides to reduce their insurance cover. See Subramanian et al. (2000) for an example. Thus genetic information could have an impact after insurance purchase, not just at the time of purchase.
- g. 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 4.2.
- h. 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.
- i. 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.
- j. 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). Or, if the ages at ESRD among affected relatives were known, the probabilities of APKD1 or APKD2 mutations being responsible might be found using a Bayesian approach. Both seem quite remote possibilities, but we did

rerun the figures in Table 6 assuming that mutations were identifiable 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 and 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 7 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 and Macdonald (2003, Table 9) but consistent with Figure 4.

5. THE LIFE INSURANCE MODEL

Figure 11 shows a semi-Markov model of a life insurance market. The intensities $\mu_{s+t,s}^{i48}$, $\mu_{x+t,s}^{i58}$, $\mu_{x+t,s}^{i68}$, $\mu_{x+t,s}^{i78}$ represent mortality after ESRD and depend on both age $x + t$ and duration s . The intensities μ_s^{i46} and μ_s^{i57} represent the rate of transplantation and depend on duration since ESRD alone. (In the fourth scenario in Section 3.5, 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 and Macdonald (2004), of splitting the calculations into two parts:

Table 7

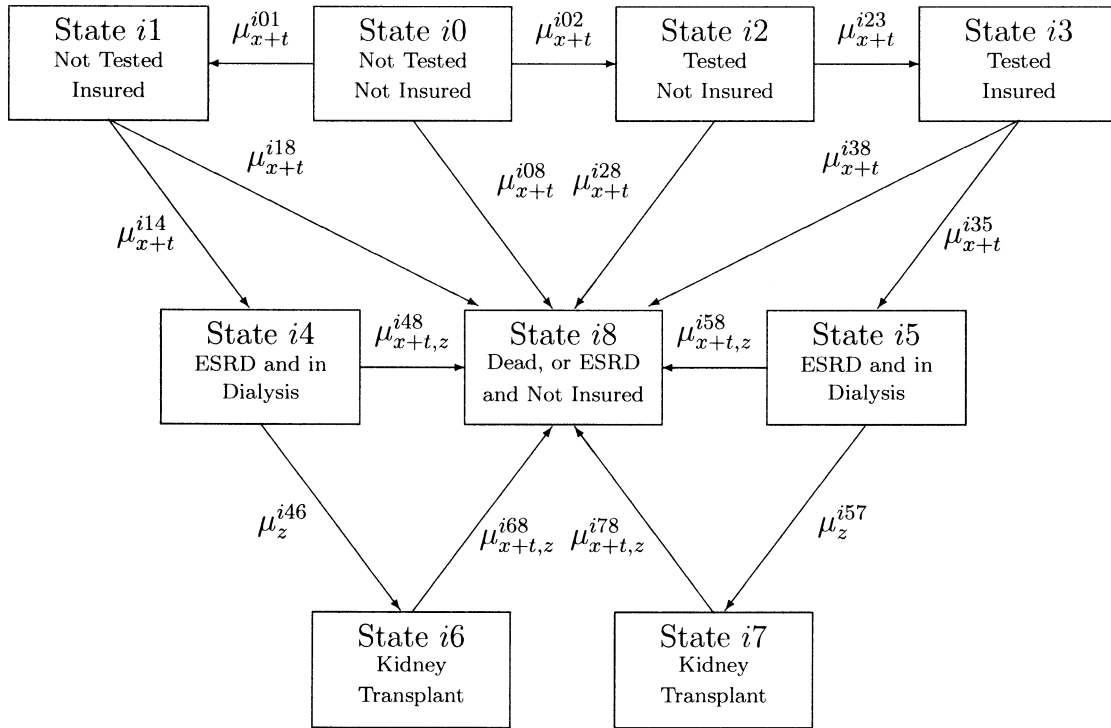
Percentage Increases in Standard CI Premium Rates Arising from New Underwriting Classes and Severe Adverse Selection Following a Moratorium on Use of Adverse Genetic Test Results and Family History

Market Size	Source of Data	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

Notes: CI insurance market operating between ages 20 and 60. Rate of genetic testing 0.035.

Figure 11

Semi-Markov Model of Genetic Testing, Life Insurance Purchase, and Clinical History of APKD, for a Person in i th Subpopulation



Note: The duration since entering the current state is denoted z .

- 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 8–11 show the level premium for level life insurance cover, as a percentage of the standard (noncarrier’s) premium, under each of the four transplantation scenarios outlined in Section 3.5.

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 4.2 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%.

Table 8

Level Net Premium for Level Life Insurance Coverage for Persons with Known APKD Mutation, as Percentage of Premium for Standard Risks

Sex of Applicant	Age at Entry (yrs)	Policy Term (yrs)	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	250	230	233	127	120	119	
	40	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	193	180	182	116	112	112	
40		20	232	230	236	125	123	122	
		50	10	175	184	185	113	114	114

Notes: Dialysis only, no transplants available.

Table 9

Level Net Premium for Level Life Insurance Coverage for Persons with Known APKD Mutation, as Percentage of Premium for Standard Risks

Sex of Applicant	Age at Entry (yrs)	Policy Term (yrs)	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	239	220	224	124	118	117	
	40	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	186	174	176	115	111	111	
40		20	217	215	221	121	120	119	
		50	10	169	177	178	111	113	112

Notes: Low level of transplantation.

Table 10

Level Net Premium for Level Life Insurance Coverage for Persons with Known APKD Mutation, as Percentage of Premium for Standard Risks

Sex of Applicant	Age at Entry (yrs)	Policy Term (yrs)	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	221	205	209	121	116	115	
	40	20	277	272	280	131	129	127	
		20	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	175	165	168	113	110	109	
40		20	200	197	202	117	116	115	
		20	160	168	169	110	111	111	

Notes: Moderate level of transplantation.

Table 11

Level Net Premium for Level Life Insurance Coverage for Persons with Known APKD Mutation, as Percentage of Premium for Standard Risks

Sex of Applicant	Age at Entry (yrs)	Policy Term (yrs)	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	136	131	133	106	105	105		
	40	20	176	172	175	114	113	112		
		20	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	119	117	117	103	103	102			
40	20	134	132	133	106	105	105			
	20	111	112	112	102	102	102			

Notes: Immediate transplantation, no time spent on dialysis.

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 coverage, as a percentage of the standard (noncarrier'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 coverage 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 6 and 7 that there was very little difference in the CI adverse selection costs based on the three different studies. Therefore, here we show only adverse selection costs based on one treatment 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 modeled 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 or 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

Table 12
Level Net Premium for Level Life Insurance Coverage Based on Family History of APKD, as Percentage of Premium for Standard Risks

Age at Entry (yrs)	Policy Term (yrs)	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

Notes: Dialysis only, transplants unavailable.

Table 13
Level Net Premium for Level Life Insurance Coverage Based on Family History of APKD, as Percentage of Premium for Standard Risks

Age at Entry (yrs)	Policy Term (yrs)	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

Notes: Immediate transplantation, no time spent on dialysis.

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

Market Size	Insurance Purchasing of At-Risk Persons	Moratorium on Using			
		All Test Results		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
	None	0.025	0.013	0.022	0.011
Small	None	0.076	0.039	0.066	0.033

Notes: Life insurance market operating between ages 20 and 60; rate of genetic testing 0.035 per annum; rates of onset based on Hateboer et al. (1999); moderate rate of transplantation.

Table 15

Percentage Increases in Standard Premium Rates Arising from New Underwriting Classes and Severe Adverse Selection Following a Moratorium on Use of Adverse Genetic Test Results and Family History

Market Size	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

Notes: 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.

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 realize that this problem falls away if the moratorium extends to family history, but this would seem to us to be an overreaction 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 periodically 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 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 affects only 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 shows 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 normalize 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 practicality of using genetic tests in underwriting, even if it is allowed, depends on accurate tests being cheaply available. This is not yet the case for APKD1 and APKD2 mutations, but it is a possibility in the reasonably near future. They could be used predictively, before cysts appear, but this is likely to be confined to people with an affected relative, who choose to be tested. A more likely use is perhaps diagnostically, as an aid to prognosis.
- h. 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 modeling 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.

APPENDIX A

FITTED SURVIVAL FUNCTIONS BASED ON TIME TO ESRD OR DEATH

A.1 JOHNSON AND GABOW (1997)

For APKD1:

$$S(x) = 1 - \exp(-6.12251 + 0.058346x + 0.000921743x^2) \quad (x < 39), \quad (\text{A.1})$$

$$S(x) = 25.6616 \left(\frac{0.310552^{13.2644} \exp(-0.310552x)x^{12.2644}}{\Gamma(13.2644)} \right) \quad (x > 49) \quad (\text{A.2})$$

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

$$S(x) = 1 - \exp(-8.51304 + 0.14592x - 0.000441722x^2) \quad (x < 56), \quad (\text{A.3})$$

$$S(x) = 17.7985 \left(\frac{0.673076^{39.8749} \exp(-0.673076x)x^{38.8749}}{\Gamma(39.8749)} \right) \quad (x > 74) \quad (\text{A.4})$$

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

A.2 HATEBOER ET AL. (1999)

For APKD1:

$$S(x) = 1 - \exp(-9.08371 + 0.231087x - 0.00138536x^2) \quad (x < 40), \quad (\text{A.5})$$

$$S(x) = 23.0056 \left(\frac{0.345615^{15.1344} \exp(-0.345615x)x^{14.1344}}{\Gamma(15.1344)} \right) \quad (x > 55) \quad (\text{A.6})$$

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

$$S(x) = 1 - \exp(-11.8117 + 0.25559x - 0.00136435x^2) \quad (x < 58), \quad (\text{A.7})$$

$$S(x) = 24.7781 \left(\frac{0.364067^{21.278} \exp(-0.364067x)x^{20.278}}{\Gamma(21.278)} \right) \quad (x > 70) \quad (\text{A.8})$$

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

A.3 RAVINE ET AL. (1992)

For APKD1:

$$S(x) = 1 - \exp(-10.0993 + 0.294084x - 0.00219349x^2) \quad (x < 40), \quad (\text{A.9})$$

$$S(x) = 24.4878 \left(\frac{0.277887^{12.0004} \exp(-0.277887x)x^{11.0004}}{\Gamma(12.0004)} \right) \quad (x > 60) \quad (\text{A.10})$$

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

$$S(x) = 1 - \exp(-6.53247 + 0.102286x - 0.000256903x^2) \quad (x < 80). \quad (\text{A.11})$$

APPENDIX B

THE CRITICAL ILLNESS INSURANCE MODEL

Gutiérrez and 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 the following:

1. *Cancer (excluding nonmalignant skin cancers)*. For males:

$$\mu_x^c = \exp(-11.25 + 0.105x) \quad (x < 51),$$

$$\mu_x^c = \exp(0.2591585 - 0.01247354x + 0.0001916916x^2 - 8.952933 \times 10^{-7}x^3) \quad (x \geq 60)$$

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

$$\mu_x^c = \exp(-10.78 + 0.123x - 0.00033x^2) \quad (x < 53),$$

$$\mu_x^c = -0.01545632 + 0.0003805097x \quad (x \geq 53)$$

2. *Heart Attack*. For males:

$$\mu_x^h = \exp(-13.2238 + 0.152568x) \quad (x < 44),$$

$$\mu_x^h = (-0.01245109 + 0.000315605x) \quad (x > 49)$$

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. Twenty-eight-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

Table A.1
**28-Day Mortality Rates ($q_x^h = 1 - p_x^h$) Following
 Heart Attack**

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

Note: Based on Dinani et al. (2000).

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 are given in Table A.1. From the same source, $p_x^s = (0.9 - 0.002x)/0.9$ for both males and females.

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

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

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

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