

Inherited Heart Disorders

and Implications for Life Insurance and Health Insurance

Oytun Haçarız, Torsten Kleinow and Angus Macdonald, Heriot-Watt University and the Maxwell Institute for Mathematical Sciences

About the speaker



- **Angus Macdonald**
- Professor of Actuarial Mathematics
- FFA 1984, PhD 1995



- **Heriot-Watt University, Edinburgh**
- Dept of Actuarial Mathematics & Statistics
- IFoA accredited programmes
- SoA-accredited Center of Actuarial Excellence

Agenda



1. Genetics background
2. Conclusions from the 'bottom-up' programme
3. Developments in Canada
 - Bill S-201
 - The CIA model
4. Cardiomyopathies
5. Modelling Hypertrophic Cardiomyopathy (HCM)
6. Conclusions and questions

Genetics Background

- From mid-1990s **genetic tests** developed, identifying disease-causing mutations in single genes.
- Mutations were heritable so occurred in families with a Mendelian pattern of inheritance.
- These **single-gene disorders** were severe but rare.
- Examples:
 - Huntington disease (HD), Early-onset Alzheimer's disease
 - Inherited breast cancer (BC), colon cancer (HNPCC)
 - Adult polycystic kidney disease (APKD)
 - Myotonic dystrophy (MD)

Single-Gene Disorders

Typical outcome for a family member:

- Asymptomatic up to age 30–50 (or later)
- May develop symptoms at ages 30–50 (or later) **if they carry the mutation** — 50% chance they do
- Survival often beyond age 60 for some disorders

Taking a genetic test will ‘resolve their risk’ — no mutation means no *inherited* disease is possible.

1. Only a member of a family ‘at risk’ would have reason to be tested.
2. Not everyone at risk will choose to be tested.

Life and Critical Illness Insurance



- Life insurance pays out on death
- Critical illness (CI) insurance pays out on onset or diagnosis

Medical underwriting: Insurers ask applicants about health, weight, smoking, medical conditions, **family history**

- Most information can be used to set premiums **including family history**.
- Some information cannot be used to set premiums — race and (since 2012 in the EU) gender.

What about genetic test results?

Should Insurers Use Genetic Test Results?

Arguments for:

- It is just information, no different from *e.g.* blood tests.
- It just refined what insurers already know from family history.
- Without it, people who have been tested and know they carry the mutation will **adversely select**:
 - Be more likely to buy insurance.
 - Take out larger amounts of insurance.

Should Insurers Use Genetic Test Results?



Arguments against:

- It is a form of discrimination.
- It affects people who are unfortunate and blameless.
- Insurers will predict who will die and deny them cover.
- Genetic information is exceptional — it defines the person.
- Insurers are evil.

A 'Bottom-Up' Modelling Programme



Aim: To estimate the magnitude of the cost of adverse selection to life and CI insurers if insurers could not use genetic test results.

Method: to model life histories of members of families at risk of specific single-gene disorders in life and CI markets allowing for the timing of key events:

Markov and semi-Markov models were ideal for modelling such life histories.

Key Events in the Model

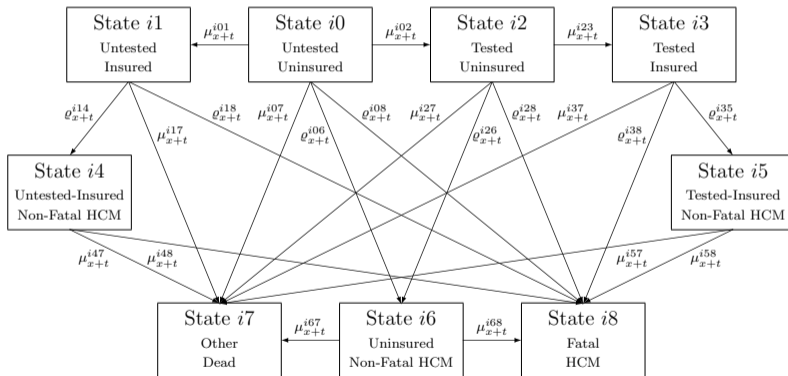
Events:

- Becoming aware of a family history.
- Deciding to be tested, or not.
- Buying life or CI insurance.
- Onset of disease.
- Death.

People decide to buy insurance based on information available to them.

Insurers price insurance based on information available to them.

Model of a Life History



Disorders Modelled

Choice of disorders to model strongly influenced by:

1. Prof A J Raeburn's list of disorders significant for insurance.
2. Availability of epidemiology, in particular **age-dependent rates of onset and death after onset**.
3. Existence of **presymptomatic** genetic testing at young adult ages.

Disorders Modelled

Disorders modelled (over *circa* fifteen years):

- Huntington disease (neurological)
- Early-onset Alzheimer's (neurological)
- Myotonic dystrophy (muscular)
- APKD (renal function)
- Inherited breast/ovarian cancer (cancer)
- HNPCC (cancer)

Models of Insurance Markets

The relative cost of adverse selection depends on market size:

- if no-one else buys insurance, the cost will be large;
- if everyone else buys insurance, the cost will be smaller.

Adverse selection cost = uniform increase in premiums to pay for it

We modelled market size as the annual rate of insurance purchase by uninsured persons between ages 20 and 60:

- large market: rate of insurance purchase 5% per year;
- small market: rate of insurance purchase 1% per year

Adverse Selection Costs

Adverse selectors buy insurance:

- at rate 25% per year (severe) or;
- at rate 10% per year (moderate).

Insurers may or may not be barred from using family history as well as test results.

We assume a higher **rate** of insurance purchase but not higher **amounts** of insurance. Results for higher amounts are approximately proportionate.

Adverse Selection Costs



The costs of adverse selection will be highest for:

- CI rather than life insurance — the ‘event’ is more likely;
- the small market rather than the large market;
- severe rather than moderate adverse selection;
- ‘at risk’ family members not buying insurance; and
- banning use of family history as well as test results.

Examples — Life Insurance

Worst-case adverse selection costs (% premium increases) arising in the life insurance market operating between ages 20 and 60.

Size of Market	Adverse Selection	Family History	Females	Males
			(%)	(%)
Large	Moderate	Allowed	0.15	0.11
		Banned	0.94	0.58
	Severe	Allowed	0.20	0.14
		Banned	1.03	0.64
Small	Moderate	Allowed	0.17	0.12
		Banned	0.94	0.58
	Severe	Allowed	0.60	0.44
		Banned	2.00	1.23

Examples — CI Insurance

Worst-case adverse selection costs (% premium increases) arising in the CI insurance market operating between ages 20 and 60.

Size of Market	Adverse Selection	Family History	Females	Males
			(%)	(%)
Large	Moderate	Allowed	0.32	0.31
		Banned	0.94	0.90
	Severe	Allowed	0.40	0.38
		Banned	1.06	1.03
Small	Moderate	Allowed	0.35	0.37
		Banned	1.14	1.07
	Severe	Allowed	1.23	1.16
		Banned	2.85	2.67

Comments

1. This research covers a representative sample of single-gene disorders. It indicates order of magnitude.
2. If more disorders emerge, with testing and epidemiology, scale up the answers to allow for this.
3. We have covered the important disorders, which tended to be investigated first by epidemiologists.

Developments in Canada



The Canadian Senate has been debating [Bill S-201](#) to outlaw all forms of genetic discrimination.

Insurance companies may not use any genetic test results for insurance pricing unless the sum assured is \$ 1,000,000 or more, or regular payment is \$ 75,000 per year or more,

Bill S-201 was passed in 2017 and has received Royal Assent.

Provincial legislatures may also decide to make their own provisions.

The CIA Model



The CIA commissioned Bob Howard to model Bill S-201's impact.

- Models Canadian market volumes.
- Models term assurance convertible to whole-life.
- Covers 13 disorders (including all of ours).
- Mortality based on expert medical opinion.
- 75% of lives testing positive buy \$ 1,000,000 of insurance.
- High conversion rate among 'at-risk' lives.
- Lower lapse rate among 'at-risk' lives.
- Takes no account of family history.

Results of the CIA Model

Two different approaches used.

1. *Cost Sub-Model*: Estimates additional adverse selection costs emerging each year if adverse selection is added to current volumes of business in Canada. Result: Claim costs each year from persons tested positive are **12% of total**.
2. *Experience model*: is based on the CIA's mortality investigation (equivalent to CMI in the UK). Essentially it models a stationary population and adds adverse selection costs. Results: overall mortality experience at ages 20–60 increases by **36% for males and 58% for females**.

Reasons for Differences (?)

- **Methodology**: Many differences make comparison difficult.
- **Different contracts**: Simple term *versus* convertible term.
- **Selective lapsing**: Ignored by us.
- **Sums assured**: Our scalable model *versus* very high insurance purchase rates in the CIA model.
- **Rates of insurance purchase**: Our levels of adverse selection are not so different.
- **Diseases covered**: Our six *versus* CIA model's thirteen. The thirteen include three forms of **cardiomyopathy**.

Cardiomyopathies

Cardiomyopathies are inherited defects of the the heart muscle.
Responsible for unexpected heart attacks in young, healthy individuals.
An example is **hypertrophic cardiomyopathy**.

- Thought to affect about 0.2% of the UK population.
- Mortality rate among those affected of around 1% per year.
- Recently associated with DNA variants at a number of genetic loci, hence testing now feasible.
- Premium increases in our LI model $\sim 1\%$ per year.

Cardiomyopathies in the CIA Model

Cardiomyopathies account for most of the costs in the CIA model.

Of \$ 405 million in the 'costs sub-model':

- Hypertrophic cardiomyopathy (HCM) cost \$ 89 million.
- Dilated cardiomyopathy cost \$ 56 million.
- Arrhythmogenic right ventricular cardiomyopathy cost \$ 111 million.
- Brugada syndrome cost \$ 49 million.

For comparison, Huntington disease cost \$ 3 million and breast cancer cost \$ 5 million.

Cardiomyopathies in the CIA Model

Cardiomyopathies account for most of the costs in the CIA model.

Of \$ 405 million in the 'costs sub-model':

- **Hypertrophic cardiomyopathy (HCM)** cost \$ 89 million.
- Dilated cardiomyopathy cost \$ 56 million.
- Arrhythmogenic right ventricular cardiomyopathy cost \$ 111 million.
- Brugada syndrome cost \$ 49 million.

For comparison, Huntington disease cost \$ 3 million and breast cancer cost \$ 5 million.

Features of HCM

1. HCM is an inherited single-gene disorder associated with mutations in multiple genes. A person inheriting a mutation is **genotype-positive**.
2. The physical manifestation of HCM is **thickening of the left ventricular wall** of the heart muscle.
 - Left ventricular wall thickness (LVWT) > 15 mm is considered diagnostic.
 - A person meeting this criterion is **phenotype-positive**.
3. Major symptoms include **sudden cardiac death (SCD)** and progressive heart failure, less commonly stroke.

Key Questions About HCM

- **Prevalence** of mutations in population.
- Age-related **penetrance** (onset of phenotype).
- Age-related onset of **symptoms** and **diagnosis**.
- HCM as a pre-existing condition?
- Age-related **mortality rates**.
- Family history.
- Genetic testing.

Key Questions About HCM

- Prevalence of mutations in population.
- Age-related penetrance (onset of phenotype).
- Age-related onset of symptoms and diagnosis.
- HCM as a pre-existing condition?
- **Age-related mortality rates.**
- Family history.
- Genetic testing.

HCM Mortality Rates

Earliest studies of HCM based on severely symptomatic persons \Rightarrow annual mortality rates $\geq 3\%$.

Later, larger, better controlled studies \Rightarrow annual mortality rates about 1%.

Latest studies (Maron et al. 2013, 2015, 2016):

Ages	Annual Mortality Rate
7-29	0.01486
30-59	0.00903
60-91	0.00645

The Mystery of the Non-Fatal Deaths

HCM studies use **sudden cardiac death (SCD)** as an endpoint. Example:

*“The following endpoints were used in the survival analysis: (1) sudden cardiac death — witnessed sudden death with or without documented ventricular fibrillation, death within one hour of new symptoms, nocturnal death with no antecedant history of worsening symptoms, **and successfully re-suscitated cardiac arrest**; (2) ...”* (source: Elliott et al. (2006))

Terminology is seriously misleading! Annual mortality rates of about 1% include non-fatal SCD. We prefer **‘sudden cardiac arrest’ (SCA)**.

Similarly, **heart failure** ‘deaths’ include non-fatal **heart transplants**.

Excluding 'Non-Fatal' Deaths

Ages	Annual 'Mortality' Rate		
	Fatal	Non-Fatal	Total
7-29	0.00535	0.00951	0.01486
30-59	0.00556	0.00347	0.00903
60-91	0.00483	0.00162	0.00645

Main 'non-fatal' events:

- resuscitated sudden cardiac arrest (sudden)
- heart failure (progressive).

Symptoms/Deaths Before Age 20

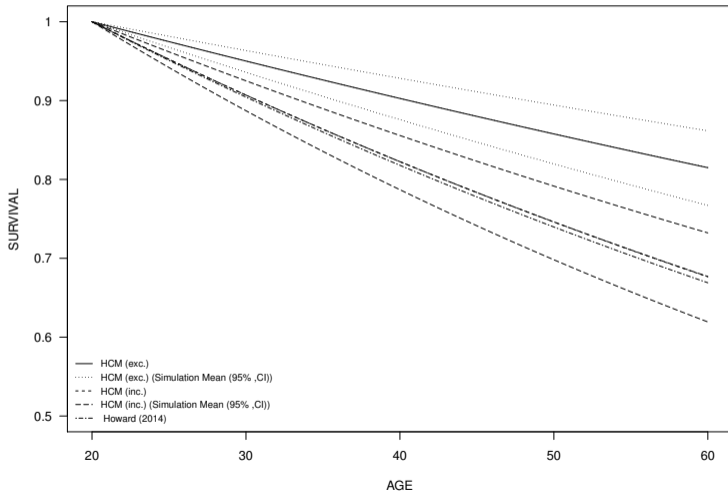
Purchase of life insurance is mainly at ages of economic activity.

Proxy for modelling purposes, insurance cover in place at ages 20–60.

Highest rates of fatal and non-fatal events at ages < 20 (plus other diagnoses from lesser symptoms) will remove a significant proportion of the population from the insurance 'at-risk' pool.

A non-fatal event means **diagnosis** \Rightarrow **pre-existing condition AND family history**.

HCM Mortality



Key Questions About HCM

- **Prevalence of mutations in population.**
- Age-related penetrance (onset of phenotype).
- Age-related onset of symptoms and diagnosis.
- HCM as a pre-existing condition?
- Age-related mortality rates.
- Family history.
- Genetic testing.

Prevalence of Mutations

- HCM is associated with mutations in **many different genes**.
- 40–60% of clinically affected persons carry **known** mutations. Others presumed to carry **unidentified** mutations.
- Major genes: MYBPC3 (15–30%, late-onset), MYH7 (10–20%, early-onset), TNNT2 (3–5%), TNNT3 (< 5%), TPM1 (< 5%).
- Estimated prevalence of **clinical HCM** in general population ~ 0.2% (7/4111) (Maron et al. (1995)).
- Estimated prevalence of **known HCM mutations** in general population ~ 0.6% ($n \approx 3600$) (Bick et al. (2012)).

Prevalence of Mutations

Population prevalence of **known** mutations greatly exceeds population prevalence of clinical HCM.

Allowing for as-yet unidentified mutations, population prevalence of HCM mutations \sim 5 times population prevalence of clinical HCM.

If **genetic test** \rightarrow **identified mutation** \rightarrow **insurance purchase** adverse selection is diluted by limited penetrance of HCM mutations.

OR genetic tests of clinical significance are a (small?) subset of all HCM mutations. Evidence from local NHS genetics clinic that number of HCM mutations tested for has been scaled back.

Key Questions About HCM

- Prevalence of mutations in population.
- Age-related penetrance (onset of phenotype).
- Age-related onset of symptoms and diagnosis.
- HCM as a pre-existing condition?
- Age-related mortality rates.
- Family history.
- Genetic testing.

Early-Onset and Late-Onset HCM

Estimated 70–85% of HCM mutations may be early-onset.

- Changes to heart muscle during childhood and adolescence.
- High rates of SCA (sudden) before ages 20–29.
- High rates of heart failure (progressive) before ages 20–29.
- Pre-existing condition, if clinically diagnosed.
- **Modelling assumption**: phenotype-positive by age 20.

Estimated 15–30% of HCM mutations may be late-onset.

Late-Onset HCM Mutations: Penetrance

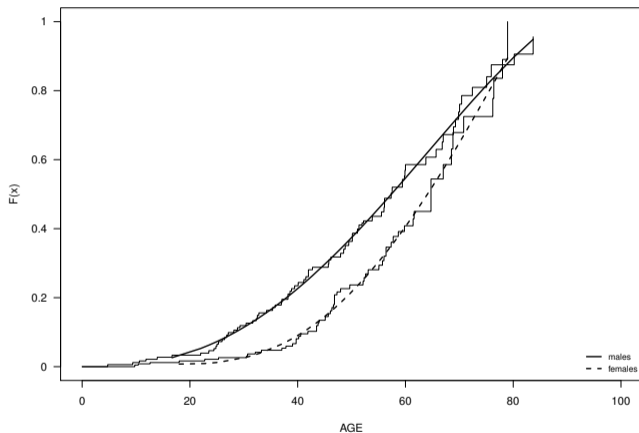


Figure: Late-Onset Penetrance Rate of HCM from Christiaans et al. (2011).

Key Questions About HCM

- Prevalence of mutations in population.
- Age-related penetrance (onset of phenotype).
- Age-related onset of symptoms and diagnosis.
- **HCM as a pre-existing condition?**
- Age-related mortality rates.
- Family history.
- Genetic testing.

HCM as a Pre-Existing Condition?

Compare with [breast cancer](#) and the [BRCA1/2 genes](#):

- BRCA1/2 mutations very heterogeneous.
- Conditional on family history, predictive of very high risk.
- Young person testing +ve is probably entirely free of cancerous tissue.
- Rarely a pre-existing condition, [detectable by genetic test only](#).

HCM mutations:

- Mutations affect many genes, very heterogeneous.
- Young person testing +ve quite likely to have clinical HCM.
- Clinical HCM may have symptoms [detectable by non-genetic tests](#).

HCM as a Pre-Existing Condition?

Conditions for adverse selection to be a risk:

- Applicant has had an adverse genetic test.
- Applicant has no disclosable medical symptoms.
- Applicant has had no non-genetic medical investigations.
- Applicant has no disclosable family history.

In extreme case, a genetic test result is the **only** information the applicant has that links to HCM.

How often will this happen?

Key Questions About HCM

- Prevalence of mutations in population.
- Age-related penetrance (onset of phenotype).
- Age-related onset of symptoms and diagnosis.
- HCM as a pre-existing condition?
- Age-related mortality rates.
- **Family history.**
- **Genetic testing.**

Family History and Genetic Testing



Heterogeneous inherited disorders (**multiple genes, multiple mutations per gene**) are hard to interpret predictively.

Recall HCM population prevalences: 0.2% clinical, 0.6% known mutations.

Even known mutations operate in a complex biological/environmental setting.

Family history is important in interpreting genetic tests in such disorders.

A mutation in an affected family may be more significant than the same mutation in an unaffected family.

Cascade Genetic Testing

Genetic testing for HCM (also inherited breast cancer, colon cancer) is almost always **cascade genetic testing**.

Screening (whole population) testing is expensive (for now) and ineffective for heterogeneous disorders, too many **mutations of unknown significance**.

Cascade testing:

- **When** a person is diagnosed with HCM in a previously unaffected family;
- **then** offer genetic testing to their first-degree relatives (FDRs);
- and then also to the FDRs of anyone who tests +ve;
- and so on.

Consequences of Cascade Testing

- There must be a first affected family member (**index patient, proband**). That person has discloseable medical evidence.
- In a family with n members, no more than $n - 1$ can be adverse selectors, and $(n - 1)/2$ on average.
- Average number of children in a family $\sim 1.8 \Rightarrow n$ is small unless cascade testing spreads beyond nuclear family.
- Each person may decline the offer of testing.

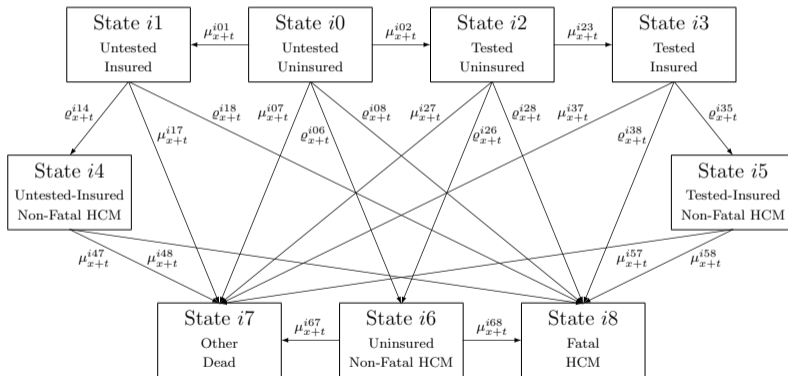
Consequences of Cascade Testing



Evidence from BRCA and HCM cascade testing is that:

- Testing is often declined; take-up rate $\sim 50\%$, higher in large 'pedigrees'.
- Testing usually does not go beyond nuclear family.

Model of a Life History



Key Features of the Model

- Nine sub-populations, indexed by i :
 - Not at risk
 - Known early-onset mutation (carriers & non-carriers)
 - Known late-onset mutation (carriers & non-carriers)
 - unknown early-onset mutation (carriers & non-carriers)
 - unknown late-onset mutation (carriers & non-carriers)
- State i_0 contains a mix of clinically affected and unaffected depending on age-related penetrance.
- Transition $i_0 \rightarrow i_4$ includes non-fatal HCM events and any other form of diagnosis except a genetic test.
- Transition into i_4 or i_5 is deemed diagnostic of HCM.

Simulation

- A family has one parent carrying an HCM mutation.
- Simulate type of HCM mutation (known early-onset, known late-onset, unknown early-onset, unknown late-onset).
- Simulate number of children \sim Poisson(λ) (baseline $\lambda = 1.8$).
- Simulate sex of each child.
- Simulate genotype of each child (Mendel's laws).
- Simulate life history of each person.
- When a proband first appears, behaviour changes:
 - Cascade genetic testing is offered for known mutations.
 - Insurance purchasing may change.

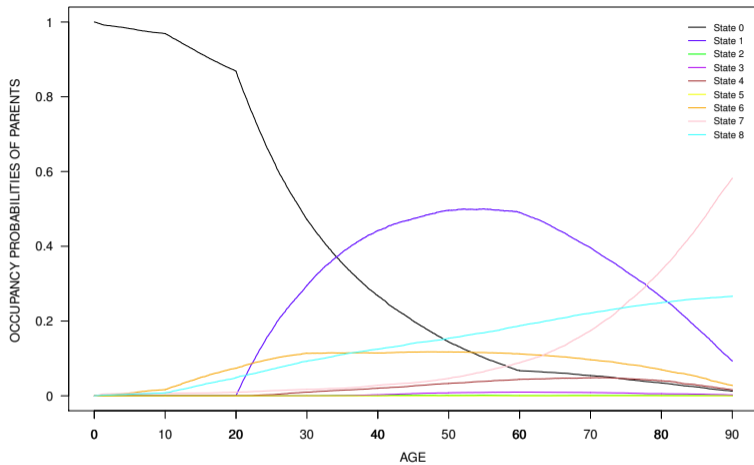


Figure: Model for Given HCM Genotype.

Factors Affecting Adverse Selection

Medical factors:

- Absence of discloseable symptoms.
- Absence of medical investigations.
- Absence of family history.
- Cascade testing, family size and the need for a proband.
- Mutations of unknown significance.
- Treatments

Factors Affecting Adverse Selection



Behavioural factors:

- Decision to take genetic test.
- Decision to buy life insurance before or after genetic testing.
- Decision to overinsure as investment.
- Affordability of life insurance.

Work in Progress and in Future



Future developments all flow from the rapidly falling costs of sequencing DNA, up to and including the whole genome.

- Whole-genome scans instead of targeted tests not too far away.
- Problem of **incidental findings** (IFs): what action to take if a mutation is discovered while looking for something else?
- Epidemiology of large ensembles of gene mutations (polygenic disease, environment).
- Genetic tests **replacing** existing physical tests because cheaper, quicker, more accurate, less invasive.

Thank you very much for your attention!

Contact details:

Angus Macdonald

address: Heriot-Watt University
Edinburgh EH14 4AS, UK
phone: +44 (0)131 451 3209
mail: A.S.Macdonald@hw.ac.uk
web: www.macs.hw.ac.uk/~angus

References

- Howard, R.C.W. (2014). *Report to CIA research committee: Genetic testing model: If the underwriters had no access to known results.* Canadian Institute of Actuaries.
- Macdonald, A.S. & Yu, F. (2011). *The impact of genetic information on the insurance industry: Conclusions from the 'bottom-up' modelling programme.* ASTIN Bulletin, **41**, 343–376.