

Inherited Heart Disorders: and Implications for Life Insurance and Health Insurance

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Plan of Talk

1. Genetics background and adverse selection
2. Conclusions from the 'bottom-up' programme
3. Developments in Canada — 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:
 - ▶ Huntingdon 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 member of a family carrying a single-gene mutation:

- ▶ 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.

GIRC — 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**.

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)

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

Source: Macdonald & Yu (2011).

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.

The CIA Model

The Canadian Institute of Actuaries (CIA) commissioned Bob Howard to model the impact of Bill S-201. Headline results:

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 comprise a family of diseases in which the heart muscle develops defects.

Responsible for sudden, unexpected heart attacks in young, apparently healthy individuals.

An example is hypertrophic cardiomyopathy. Epidemiology is fairly crude because first indication is often death.

- ▶ Thought to affect about 1% 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.

Life insurance premium increases from our model just from information above, (large market, severe adverse selection) are about 1%.

Cardiomyopathies in the CIA Model

Cardiomyopathies account for a large proportion of costs in the CIA model.

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

- ▶ Hypertrophic cardiomyopathy 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.
- ▶ Breast cancer cost \$ 5 million.

Our purpose: to model **Hypertrophic Cardiomyopathy (HCM)** in insurance markets.

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.

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HCM Mortality Rates

Earliest studies of HCM based on severely symptomatic persons.

- ▶ Always pre-existing conditions (in underwriting terms).
- ▶ Annual mortality rates 3% or more.

Later, larger, better controlled studies \Rightarrow annual mortality rates about 1%. Very high indeed at all ages.

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

The HCM literature uses **sudden cardiac death (SCD)** as an endpoint. Typical 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 antecedent history of worsening symptoms, **and successfully resuscitated 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

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

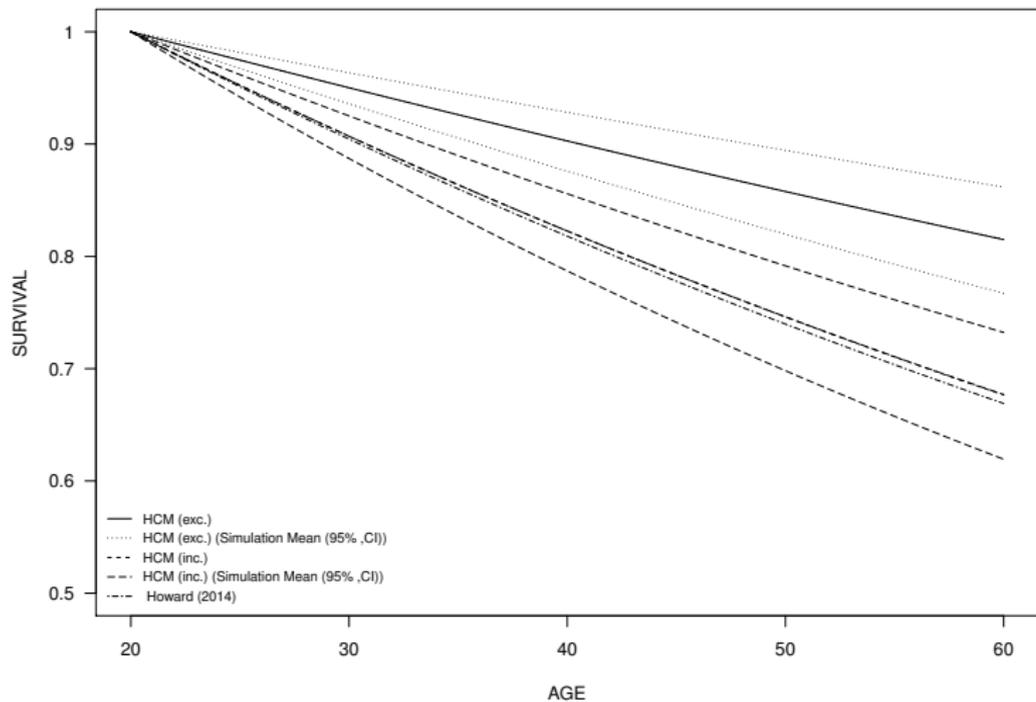
Ages	Annual 'Mortality' Rate		
	Fatal	Non-Fatal	Total
7-29	0.00535	0.00951	0.01486
30-59	0.00556	0.00347	0.00903
60-91	0.00483	0.00162	0.00645

A 'non-fatal' event:

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

means **diagnosis** \Rightarrow **pre-existing condition**.

HCM Mortality



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- ▶ 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 $\sim 0.2\%$ (7/4111) (Maron et al. (1995)).
- ▶ Estimated prevalence of **known HCM mutations** in general population $\sim 0.6\%$ ($n \approx 3600$) (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** then any adverse selection is diluted by preponderance of HCM mutations of limited penetrance.

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.

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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

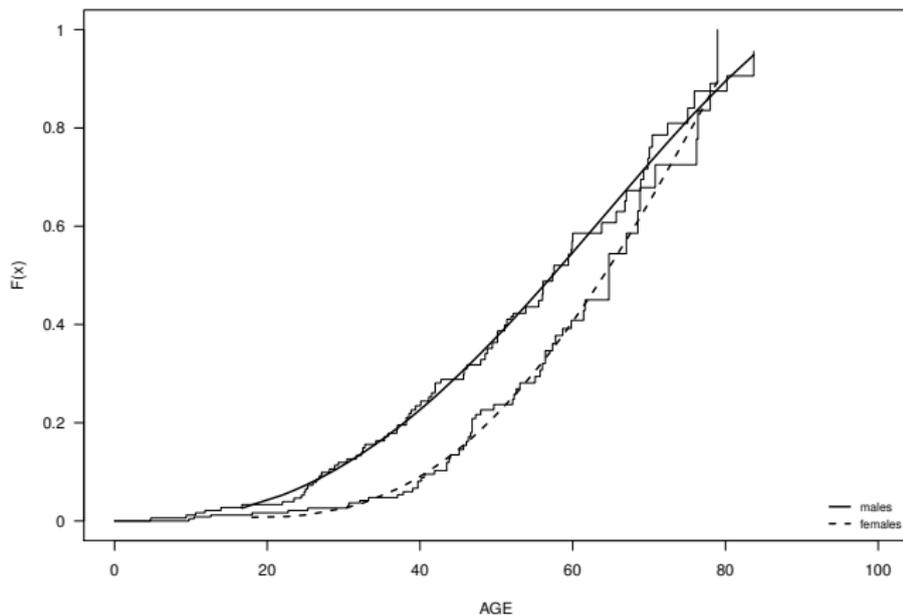


Figure: Late-Onset Penetrance Rate of HCM from Christians et al. (2011).

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- ▶ **Family history.**
- ▶ **Genetic testing.**

Cascade Genetic Testing

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

Screening (whole population) testing:

- ▶ Expensive (though this will change).
- ▶ Also 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.

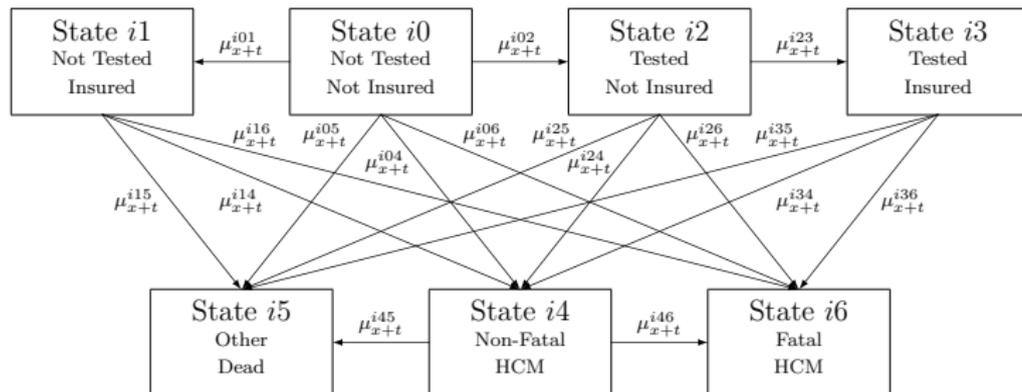
Consequences of Cascade Testing

- ▶ 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.

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 $\sim \text{Poisson}(\lambda)$ (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.
 - ▶ Cascade genetic clinical testing is offered for unknown mutations.
 - ▶ Insurance purchasing may change.

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

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.

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