

Complex Genetic Risk: The Implications for Insurance

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“Indeed, the sociology of risk . . . is an academic subject akin to the black actuarial arts which set our insurance premiums. Even now insurance companies are plotting to use genetic medicine to limit their own risks.”
(Arnold Kemp, the *Observer*, 29 October 2000.)

“I am not opposed to people knowing their predisposition to an illness. . . . I do oppose insurance companies and others taking this into account when they are assessing premiums, the prospects of getting a mortgage and employment.” (Dr Ian Gibson MP, reported in the *Daily Mail*, 12 October 2000.)

Outline

- Genetics and Insurance
- The UK Moratorium and GAIC
- Single gene disorders (the past) and complex disorders (the future)
- Critical Illness Insurance (1) BRCA1 and BRCA2
- Critical Illness Insurance (2) Family History
- Critical Illness Insurance (3) A Polygenic Model
- What Next?

Genetics (and Insurance) of Yesterday

Family history of Mendelian disorders — clear genetics.

Family history of common diseases — unclear genetics.

DNA-based genetic tests — mid 1990s to now.

The “genetics and insurance” debate:

- unfair discrimination *versus* adverse selection
- genetics = precise prediction?
- argument from a few models, *e.g. Huntington’s disease*
- strong media focus.

The Single-Gene Paradigm

Gene → **Disease**

Genetics and Insurance in the UK

- 1996: ABI Moratorium
 - Not ask applicants to take a genetic test
 - Not use genetic tests to charge lower premiums
 - Ignore genetic tests, mortgage life insurance > £100,000
- 1999: Genetics and Insurance Committee (GAIC)
- 2000: GAIC approved Huntington's test for life insurance
- 2001: New moratorium, ceilings raised:
 - life insurance > £500,000
 - other forms of insurance > £300,000
- 2005: Moratorium renewed until 2011

The GAIC Process

Insurers may apply to GAIC to be allowed to use [specific](#) test results, above the limit in the moratorium.

GAIC will assess:

- the technical relevance of the test
- the clinical relevance of the test — does it predict outcomes?
- the actuarial relevance of the test — is it material?

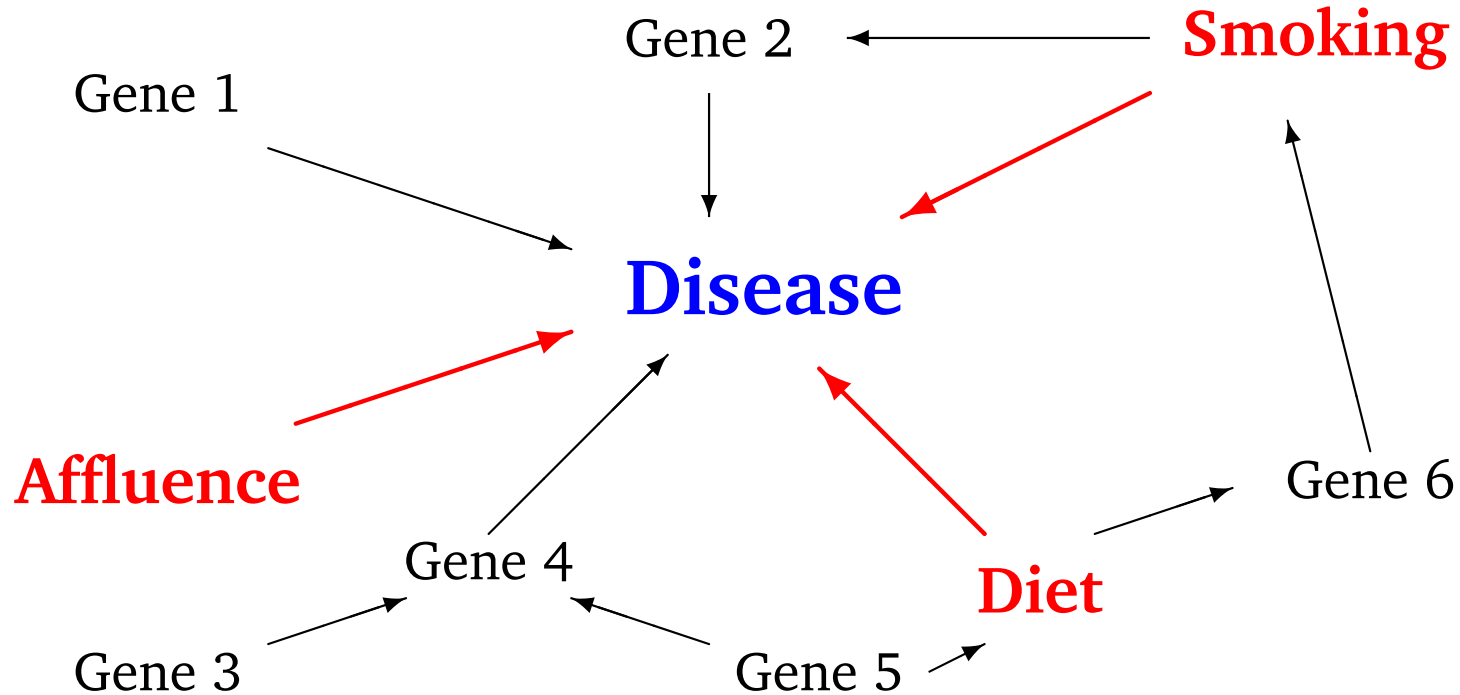
So far, one application only, but more planned for Huntington's and breast cancer.

Evidence of impact precedes use in underwriting — a precedent for insurance or a one-off?

The Genetics of Tomorrow

- Genetics of common diseases
- Gene-gene, gene-environment interactions
- Whole-genome scans
- Genetic arrays
- Large-scale population studies
- Novel mechanisms (epigenetics, RNA interference)
- Genetic therapy?

The Multifactorial Paradigm



Breast/Ovarian Cancer

- BC is the main cancer affecting women — about 9% will be affected.
- About 5% of BC appears to be familial.
- Mutations in two **major genes** identified:
 - BRCA1 in 1994
 - BRCA2 in 1995

each of which alone increases BC/OC risk.

- But BRCA1/2 mutations only account for about 25% of familial clustering of BC.

The Critical Illness Model

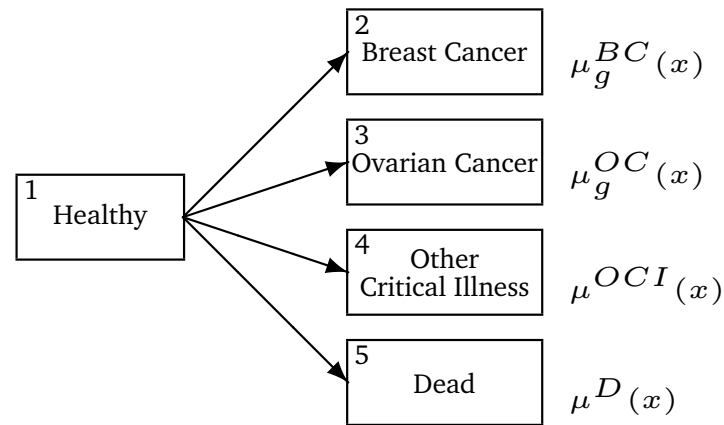


Figure 1: A model of the life history of a critical illness insurance policyholder, beginning in the Healthy state. Transition to the non-Healthy state d at age x is governed by an intensity $\mu^d(x)$ depending on age x or, in the case of BC and OC, $\mu_g^d(x)$ depending on genotype g as well.

Used with Thiele's Equations to calculate level net premiums.

$$\frac{d}{dx} V_x^H = \delta V_x^H + p_x^H - \sum_{i \neq H} \left(b_x^d + V_x^i - V_x^H \right) \mu^i(x).$$

Penetrance Estimates

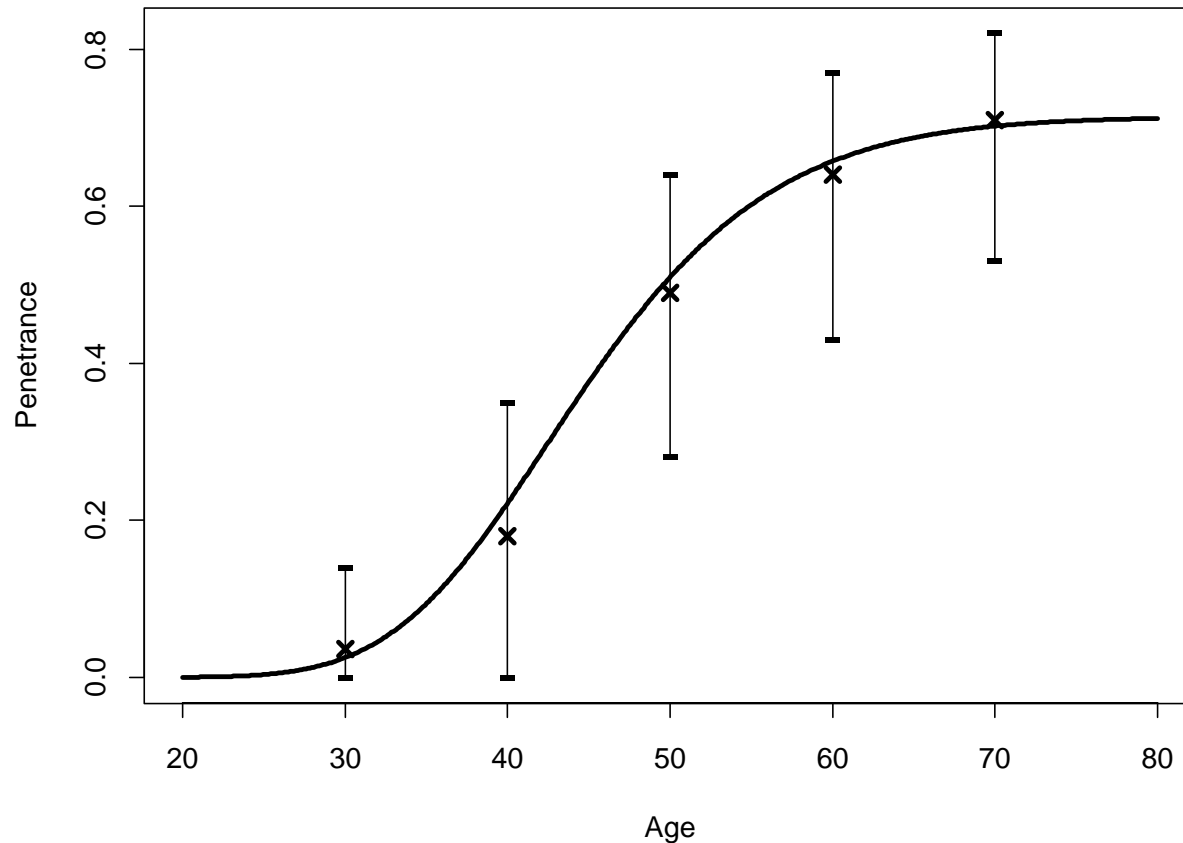


Figure 2: *Observed values (x) and 95% confidence intervals of breast cancer penetrance associated with BRCA1 mutations, based on Ford et al. (1998). Also shown is the fitted function from Macdonald, Waters & Wekwete (2003a).*

Premiums for Mutation Carriers

Table 1: *Examples of premium ratings for CI insurance for female mutation carriers, as percentages of standard rates.*

Disorder	Gene	Age 30	Age 40	Age 50
		Term 30 Yrs %	Term 20 Yrs %	Term 10 Yrs %
APKD	APKD1/2	335–435	332–468	297–422
BC/OC	BRCA1	381–1,110	355–1,112	259–740
BC/OC	BRCA2	252–578	296–768	352–1,056
EOAD	PSEN1	866–2,040	1,032–3,022	1,076 – 3,714
HD	IT15 (40 CAG)	165–268	169–298	133–247
HD	IT15 (45 CAG)	635–1,181	455–1,018	224–630
HD	IT15 (50 CAG)	1,002–2,007	591–1,372	276–840

Family History

Although the use of genetic test results has probably been reduced to negligible levels, insurers may still use a **family history** of a genetic disorder.

In some other countries, moratoria on the use of genetic information cover family histories as well as genetic tests.

Unlike a clinical pedigree, insurers usually only ask about affected first-degree relatives. A typical example would be for breast cancer: **two or more first-degree relatives affected with breast or ovarian cancer before age 50.**

Premiums Given a Family History

Table 2: *Examples of premium ratings for CI insurance for female applicants with a family history, as percentages of standard rates.*

Disorder	Gene	Age 30	Age 40	Age 50
		Term 30 Yrs	Term 20 Yrs	Term 10 Yrs
		%	%	%
BC/OC	BRCA1/2	103–184	-	102–158
EOAD	PSEN1	432–769	363–605	153–198
HD	IT15	203–296	142–202	107-128

The Search for More BRCA Genes

Antoniou *et al.*, 2002 fitted a large number of different genetic models to BC family histories, finding:

- no evidence for a BRCA3 major gene
- best fit for a model with major genes BRCA1, BRCA2 and a **polygene** affecting BC but not OC risk.

Polygene: A collection of genes, variations in each of which exert a small influence on risk, that together can add up to a large influence on risk.

A polygenic model must account for:

- variation in risk
- pattern of inheritance from parents to children.

The Polygenic Model

(Antoniou *et al.*, 2002). There are n genetic loci, which implies $2n$ individual genes. Each gene j for individual i has a risk-adding or risk-subtracting allele:

$$X_{ij} = \begin{cases} -1/2 & \text{w.p. } 1/2 \\ 1/2 & \text{w.p. } 1/2 \end{cases}$$

So the ‘Polygenotype’ for individual i is the summation of all alleles:

$$P_i = \sum_{j=1}^{2n} X_{ij} \sim \text{Bin}(2n, 1/2) - n \quad \text{where } 2n \text{ is small.}$$

So founder members of a population have polygenotype values p_f with probability distributed $\text{Bin}(2n, 1/2) - n$

The Polygenic Model

$$P_i \sim \mathcal{N}(0, n/2) \quad \text{for } 2n \rightarrow \infty \quad (\text{Normal approx. to Binomial})$$

However, P_i is only an index of the risk transferred by polygenes.

We want to transform this to R_i which will be the actual risk conferred by the polygenotype, subject to the estimated value of σ^2 .

So for small $2n$:

$$R_i \approx \frac{P_i}{\sqrt{n/2} \sigma}.$$

And now this is applied to the baseline BC morbidity to calculate the morbidity given polygenotype p_i :

$$\mu_i^{BC}(x, R_i) = \mu_i^{BC}(x) e^{R_i}.$$

The Polygenic BC Model

Polygenes are transmitted from parents to children by independently sampling, without replacement, n polygenes from the mother and n from the father. Conditional probabilities for the offspring's polygenotypes are then:

$$P[P_c = p_c | P_m = p_m, P_f = p_f] = \sum_{r=\max[0, p_c - p_f]}^{\min[p_m + n, p_c + n]} \frac{\binom{p_m + n}{r} \binom{n - p_m}{n - r} \binom{p_f + n}{p_c + n - r} \binom{n - p_f}{r - p_c}}{\binom{2n}{n}}.$$

This is the convolution of two independent hypergeometric distributions representing the sum of the father's and the mother's contribution to their child's polygenotype.

Table 3: Level net premium for women with BRCA0/1/2 genotype, depending on polygenotype, as a percentage of the level net premium for a woman free of BRCA1/2 mutations and with the mean polygene $P = 0$.

Major Genotype	Polygenotype	Age 20			Age 30		Age 40		Age 50	
		20 years %	30 years %	40 years %	10 years %	20 years %	30 years %	10 years %	20 years %	10 years %
BRCA0	-3	87.1	83.7	85.2	83.0	81.4	83.9	80.3	83.8	86.5
	-2	88.8	85.9	87.2	85.4	84.0	86.1	83.0	86.0	88.3
	-1	92.5	90.5	91.5	90.2	89.2	90.7	88.5	90.6	92.2
	0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
	+1	115.4	119.2	117.3	120.2	122.0	119.0	123.4	119.2	116.1
	+2	147.0	158.0	151.9	161.6	166.7	157.3	171.4	158.5	149.1
	+3	211.1	235.3	219.2	246.4	256.8	233.2	269.5	238.2	216.7
BRCA1	-3	124.5	202.1	181.4	140.4	225.5	194.8	283.7	217.5	160.5
	-2	160.9	234.4	203.8	196.2	265.7	221.4	317.0	238.1	169.6
	-1	234.9	299.1	248.6	310.2	347.3	275.8	385.0	280.4	188.3
	0	383.3	425.6	336.1	542.5	511.7	386.2	523.8	367.8	226.7
	+1	673.8	660.9	497.9	1012.5	837.3	607.4	805.1	549.0	305.2
	+2	1215.7	1057.5	767.3	1949.6	1460.1	1037.6	1368.7	927.1	465.6
	+3	2130.8	1615.8	1138.8	3765.0	2585.9	1827.3	2474.5	1714.2	792.1
BRCA2	-3	115.7	111.9	122.2	126.9	115.6	125.9	108.9	126.2	142.8
	-2	142.6	139.3	146.2	167.8	148.9	153.5	138.2	151.2	165.3
	-1	197.3	194.5	193.7	251.6	216.6	209.0	198.2	202.0	211.5
	0	307.7	303.1	284.3	422.7	353.1	318.7	320.6	304.3	306.0
	+1	526.6	508.0	445.1	770.1	623.3	527.9	569.1	507.1	498.8
	+2	945.5	862.7	696.3	1467.8	1139.4	903.3	1068.3	896.7	890.5
	+3	1690.3	1385.9	1023.5	2839.6	2066.6	1532.3	2051.4	1616.0	1680.6

Table 4: Level net premium for women with BRCA0 genotype, depending on polygenotype, as a percentage of the level net premium for a woman free of BRCA1/2 mutations and with the mean polygene $P = 0$.

Polygenotype	Age 30		
	10 years	20 years	30 years
	%	%	%
-3	83.0	81.4	83.9
-2	85.4	84.0	86.1
-1	90.2	89.2	90.7
0	100.0	100.0	100.0
+1	120.2	122.0	119.0
+2	161.6	166.7	157.3
+3	246.4	256.8	233.2

Table 5: Level net premium for women with BRCA1 genotype, depending on polygenotype, as a percentage of the level net premium for a woman free of BRCA1/2 mutations and with the mean polygene $P = 0$.

Polygenotype	Age 30		
	10 years	20 years	30 years
	%	%	%
-3	140.4	225.5	194.8
-2	196.2	265.7	221.4
-1	310.2	347.3	275.8
0	542.5	511.7	386.2
+1	1012.5	837.3	607.4
+2	1949.6	1460.1	1037.6
+3	3765.0	2585.9	1827.3

Table 6: Level net premium for women with BRCA2 genotype, depending on polygenotype, as a percentage of the level net premium for a woman free of BRCA1/2 mutations and with the mean polygene $P = 0$.

Polygenotype	Age 30		
	10 years	20 years	30 years
	%	%	%
-3	126.9	115.6	125.9
-2	167.8	148.9	153.5
-1	251.6	216.6	209.0
0	422.7	353.1	318.7
+1	770.1	623.3	527.9
+2	1467.8	1139.4	903.3
+3	2839.6	2066.6	1532.3

A Family History

If members of a family have BC or OC before age 50, all healthy family members are considered to have a family history.

1. Estimate the distribution of completed family size, females only.
2. Simulate a family, mother and daughters.
3. For each member, simulate the age at which each event in the CI model occurs, if at all.
4. If BC or OC is first to occur, before age 50, that person is removed from the healthy population and may contribute to a family history.
5. Repeat 9,999,999 times.

A Family History

Family history EPVs can be calculated from the EPVs of all possible genotypes:

$$EPV_f(x) = \sum_g P[\text{Genotype is } g \mid \text{Family history exists at age } x] EPV_g(x)$$

Table 7: Level net premium for females with a family history of BC or OC, as a percentage of the standard premium. The polygenic model is compared with the major-gene-only model of Gui *et al.* (2006). The latter assumed that onset rates of BC and OC among BRCA1/2 mutation carriers were either 100% or 50% of those estimated, as a rough allowance for ascertainment bias.

Definition of Family History	Genetic Model	Age 30			Age 40		Age 50
		10 years %	20 years %	30 years %	10 years %	20 years %	10 years %
2 Affected FDRs	P + MG	134	136	131	175	154	131
	MG	100	100	100	122	115	105
Gui <i>et al.</i> (2006)	100%	330	251	204	208	174	142
	50%	217	179	156	154	139	120

Conclusions from the Model

- Possibility of a counteracting polygene configuration being used to void a known BRCA1/2 mutation.
- BRCA1/2 carriers remain at such high BC/OC risk that our results concur with past studies that have deemed them an uninsurable risk.
- Because the polygene inheritance mechanism is less 'clear-cut' when compared to the inheritance of major genes, the genetic risk of an individual with a family history is not as strong.
- Testing for polygenes is on the distant horizon.

Biobanks

Many large-scale genetic studies of common diseases are being set up, e.g.

UK Biobank:

- recruit 500,000 subjects age 40–69
- obtain blood samples, medical exam and lifestyle questionnaire
- follow up for 10 years with linkage to health records and registries.

Macdonald, Pritchard & Tapadar (2006) simulated actuarial use of UK Biobank results, concluding:

- studies could lead to **point estimates** of premium ratings of +50% or more,
- but unless very large numbers of cases were used the **distributions** of such estimates might fail GAIC-type scrutiny.

Insurance in the Multifactorial World

High-throughput genetic arrays **will** reveal much about complex genetic influences on biological processes — but this is not the same as disease.

Understanding biological processes better **will** help to understand disease — but this is not the same as epidemiology.

Epidemiology **will** emerge:

- but it will not be highly predictive, as for single-gene disorders
- and if subject to GAIC-like criteria it might fail “reliability”.

What Will the Press Think?

The chain from genetic discovery to reliable underwriting is very long and getting longer:

- Association of genes with disease
- Understanding complex mechanisms
- Gene-environment and other interactions
- Epidemiological studies (especially prospective studies)
- Moratoria and GAIC-type processes.

But the press will not understand this.

THIS is the actuarial research message.

References

GUI, E.H., LU, B., MACDONALD, A.S., WATERS, H.R. & WEKWETE, C.T. (2006). The genetics of breast and ovarian cancer III: A new model of family history with applications. *Scandinavian Actuarial Journal*, **2006**, 338–367.

MACDONALD, A.S. & McIVOR, K. (2006). Application of a polygenic model of breast and ovarian cancer to critical illness insurance. *To appear in Annals of Actuarial Science*.

MACDONALD, A.S., WATERS, H.R. & WEKWETE, C.T. (2003a). The genetics of breast and ovarian cancer I: A model of family history. *Scandinavian Actuarial Journal*, **2003**, 1–27.

MACDONALD, A.S., WATERS, H.R. & WEKWETE, C.T. (2003b). The genetics of breast and ovarian cancer II: A model of critical illness insurance. *Scandinavian Actuarial Journal*, **2003**, 28–50.