# Complex Genetic Risk:

# The Implications for Insurance

**Angus Macdonald**

Heriot-Watt University, Edinburgh

The Maxwell Institute for Mathematical Sciences

“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.

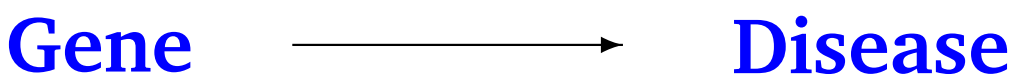
Family history of common diseases — unclear genetics.

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



# 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?

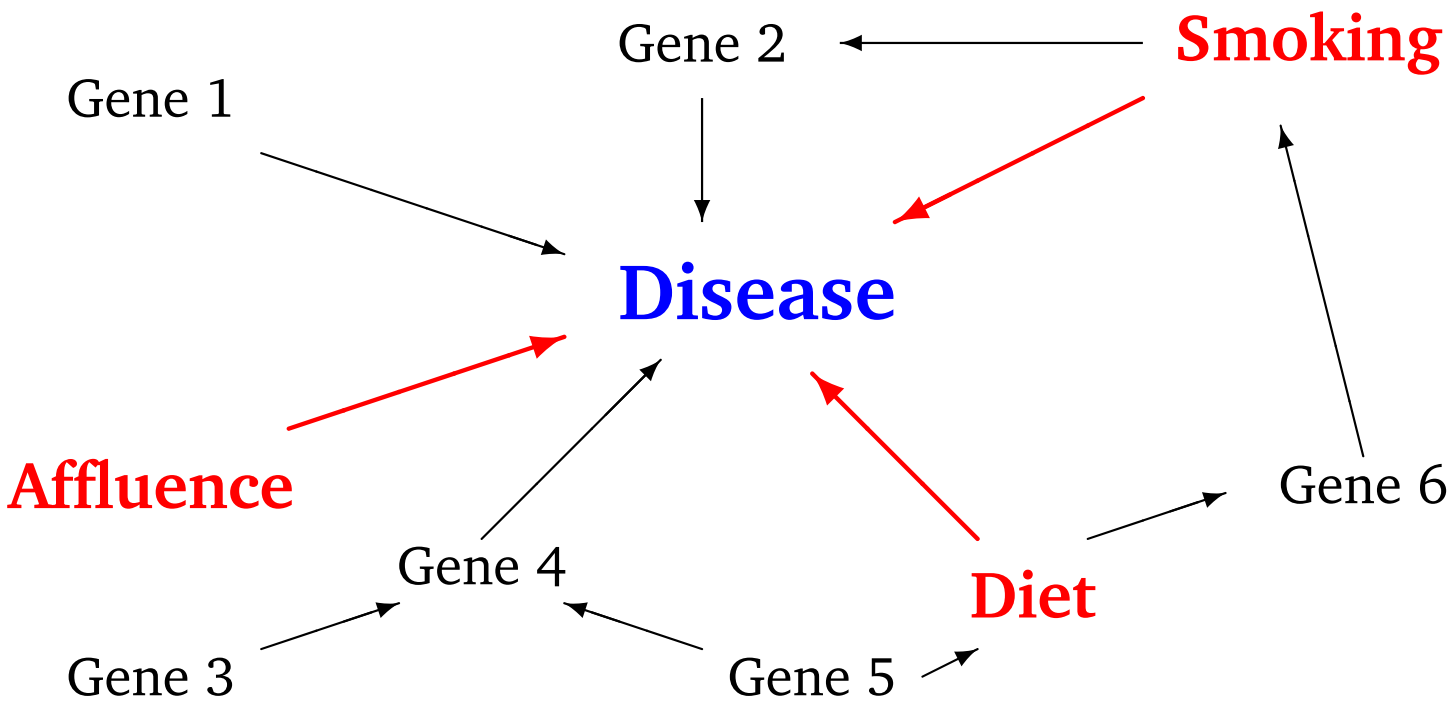
So far, one application only, but more planned for Huntington's and breast cancer.

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

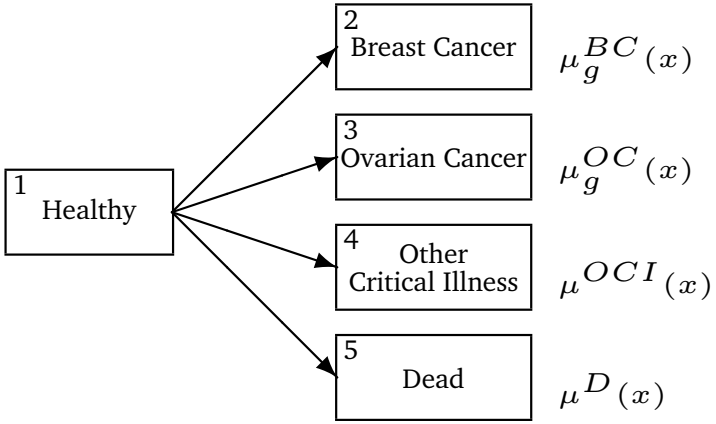



Figure 1: A model of the life history of a critical illness insurance policyholder, beginning in the Healthy state. Transition to the non-Healthy state $d$ at age $x$ is governed by an intensity $\mu^d(x)$ depending on age $x$ or, in the case of BC and OC, $\mu_g^d(x)$ depending on genotype $g$ as well.

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

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

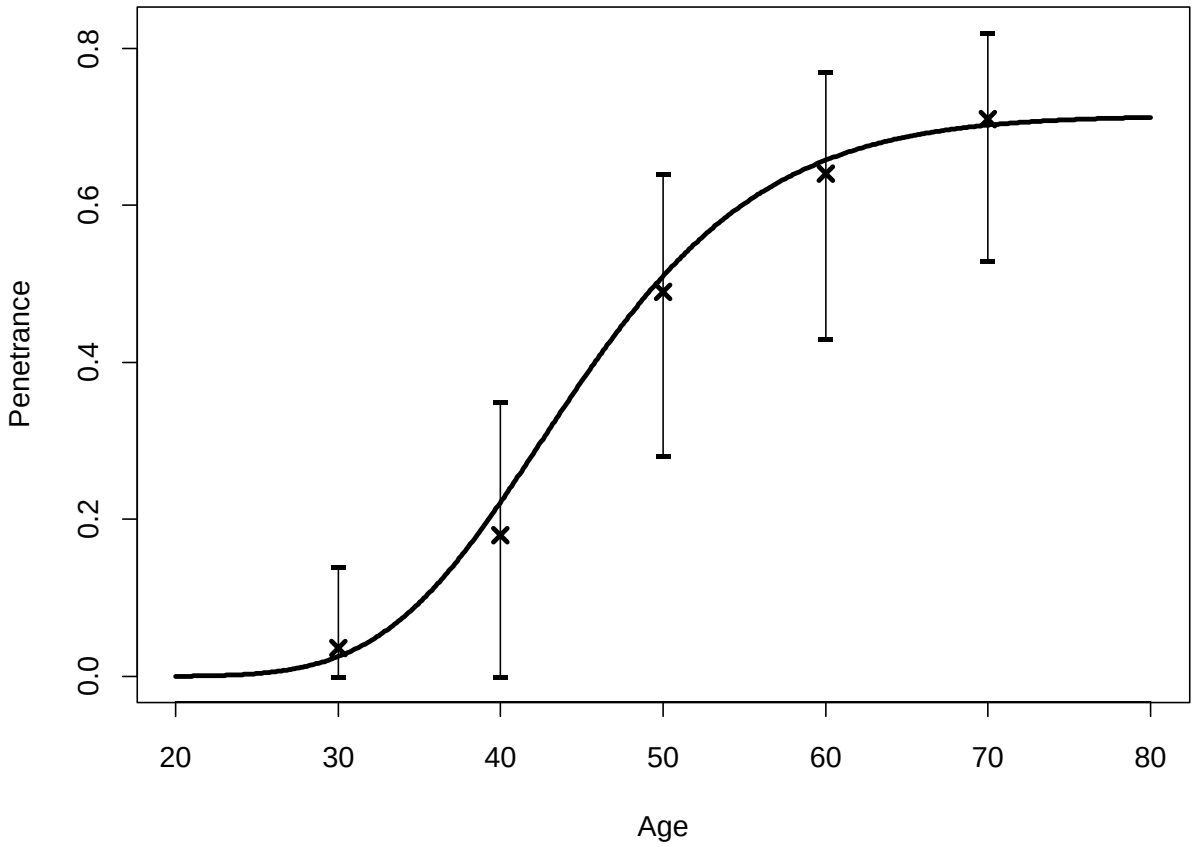



Figure 2: *Observed values ($\times$) and $95\%$ confidence intervals of breast cancer penetrance associated with BRCA1 mutations, based on Ford* et al. *(1998). Also shown is the fitted function from Macdonald, Waters & Wekwete (2003a).*

# Premiums for Mutation Carriers

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

| | | Age 30 | Age 40 | Age 50 |
|---|---|---|---|---|
| Disorder | Gene | 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 Term 30 Yrs % | Age 40 Term 20 Yrs % | Age 50 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:

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

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

# The Polygenic Model

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

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 $\sigma^2$.

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:

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

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 | | Age 20 | | | Age 30 | | | Age 40 | | Age 50 |
|---|---|---|---|---|---|---|---|---|---|---|
| Genotype | Polygenotype | 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 $P = 0$.

| | Age 30 | | |
|---|---|---|---|
| Polygenotype | 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 $P = 0$.

| | Age 30 | | |
|---|---|---|---|
| Polygenotype | 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 $P = 0$.

| | Age 30 | | |
|---|---|---|---|
| Polygenotype | 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:

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

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 | Genetic | | Age 30 | | | Age 40 | | Age 50 |
|---|---|---|---|---|---|---|---|---|
| Family History | Model | 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 *et al.* (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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