


EDITORIAL

Genetic testing and actuarial science

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In 1995, Robert Pokorski, MD, wrote a far-seeing article in *Nature* (Pokorski, 1995) on how the new world of clinical genetics might affect life insurance. Writing before any actuarial modeling of costs had been attempted, and indeed some years before the human genome was sequenced, he surveyed the range of clinical investigations that might be captured by broader definitions of “genetic,” the variability of outcomes given most genetic test results, and the resulting problems of interpretation, especially for predictive purposes. In fact, he pointed out, once the hype surrounding all things genetic was stripped away, genetic information was not so different from other medical information, and he looked forward to the day when it would be treated as such by underwriters and others.

The canonical model of a genetic condition was, and tends still to be, Huntington’s disease (HD). A variation in a single gene (the huntingtin gene) leads inexorably to premature death, but not so premature that persons carrying the variation fail to pass it on to children; Mendel’s laws of genetics ensure that each child inherits the variation with probability 1/2. It is unfortunate that HD keeps appearing as the canonical model, because it is, in fact, so untypical. Even among rare single-gene disorders, few have 100% *penetrance*,¹ 100% lethality, and no known treatment. More common disorders, for example schizophrenia, are *polygenic* – associated with variations of small effect at numerous genetic loci, variable penetrance, great variation of outcomes, environmental interactions, and a range of possible treatments, sometimes prophylactic. Some disorders, such as breast cancer, while associated with single genes (BRCA1/2 in this case), also have a large polygenic component and a large non-heritable residue of cases.

Genetics is a sensitive issue because individuals have no control over their genetic makeup. Sex and race are examples of genetic variation that are already “protected characteristics” in anti-discrimination law in many countries. Many would argue that all genetic variation should be similarly protected in law and that this should extend to its use in insurance underwriting.

Insurers’ fears are driven by the possibility of adverse selection, but what kind of adverse selection might they face? Haçarız et al. (2020) distinguished between *precautionary* adverse selection, where individuals take out insurance to cover necessities, and *speculative* adverse selection, where individuals invest heavily in life insurance at favorable premium rates as a financial gamble, even borrowing money to cover the premiums (see also Thomas, 2017). The more lurid claims for large insurance losses depend on the latter; for example, Howard (2014) assumed that “adverse selectors” took out 10 times the average sum insured. US insurers did indeed suffer an epidemic of

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¹ Penetrance: the proportion of those carrying a gene variant who will go on to develop the associated disorder.

STOLI (stranger-originated life insurance²) in the years before 2009 – nothing to do with genetics, just a consequence of the belief that all kinds of risk could be commodified and traded (Aspinwall *et al.*, 2009; Sheridan, 2019) – but whether investors could gamble successfully on genetic test results seems doubtful, at best (see Haçarız *et al.*, 2020).

Actuaries and underwriters depend on medical studies, particularly in genetic epidemiology, to calibrate underwriting decisions and models of costs. Studies of the major single-gene disorders, in some cases, provide useable estimates of gene variant frequencies, age-related penetrance, and mortality hazard rates. There are pitfalls; see for example the “mystery of the non-fatal deaths” in the Hypertrophic Cardiomyopathy (HCM) literature³ (Haçarız *et al.*, 2021). Nevertheless, models can be constructed (Macdonald, 2003; Macdonald & Yu, 2011; Howard, 2014). Their impact, in the face of the much larger social science literature generated by the ELSI program,⁴ is debatable. The focus of epidemiology has since broadened from single genes to Genome-Wide Association Studies (GWAS), which seek out statistical associations between loci on the human genome and particular disorders (Uffelmann *et al.*, 2021). These lead to models in which the effects of DNA variants at many loci (tens or hundreds), each quite small, and environmental effects, combine to produce an overall effect on an onset rate or mortality hazard. There is rarely any *a priori* known causal link between variant and disease (hence the “A” in “GWAS”) indeed the loci need not even lie in functional genes. The manner of combination is essentially unknown, but it is almost always assumed that individual effects act multiplicatively and independently on the underlying hazard. Then, the small size of each individual effect, plus the central limit theorem, results in log-normally-distributed overall hazard rates of mortality.⁵ Although these are largely mathematical artifacts, the range of the combined risk is usually comparable with other medical risks familiar to underwriters (Macdonald & McIvor, 2009; Adams *et al.*, 2015; Maxwell *et al.*, 2021; Zhao *et al.*, 2023). Therefore, predictive genetics, single-gene disorders apart, may be finding its place in “normal” medicine, and there is no reason to suppose that insurers will be unable to cope with it (Joly *et al.*, 2013; Golinghorst *et al.*, 2022).

Regulatory responses to genetic information have varied; Prince (2019) surveys the responses in Australia, Canada, the UK, and the USA. One of the earliest, and probably most influential, was the Concordat and Moratorium agreed between the UK life insurance sector and the government in the UK, whose roots go back to 1996 at least. The headline clause barred insurers from using genetic test results for underwriting, except for very large policies. Among other things, this preserved insurers’ use of family medical history. However, one less-reported detail, which may prove significant in the long run, was that the agreement covered only predictive genetic tests – those revealing future risks to currently healthy individuals. It explicitly did not cover diagnostic or prognostic tests – those assisting in the diagnosis and treatment of affected individuals. If the latter should become more prominent in clinical practice, perhaps even replacing some non-genetic procedures,⁶ the results should not be withheld from insurers in the UK. The more recent example of the Canadian Genetic Non-Discrimination Act (GNDA) of 2017 makes no such distinction, it bans Canadian insurers from using predictive, diagnostic, and prognostic tests equally. Comparing the long process of consultation that preceded the GNDA with the UK experience of

²Stranger-originated life insurance is life insurance for an individual with a health impairment or risk, initiated and funded by a third party to whom the policy will be assigned as a speculative investment.

³The headline “mortality rates” in survival studies of Hypertrophic Cardiomyopathy (HCM) consistently are based on a definition of “sudden cardiac death” that includes resuscitated cases. Excluding these reduces the mortality hazard by nearly one-half. Oddly, this endpoint is not used in studies of another major inherited heart disorder, Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC, see Haçarız *et al.*, 2022).

⁴The Ethical, Legal, and Social Implications (ELSI) Research Program was set up in 1990 as part of the publicly-funded Human Genome Project, with substantial funding.

⁵The combined mortality hazard rate is $\mu(x) \exp(\beta_1 z_1 + \beta_2 z_2 + \dots + \beta_n z_n)$ where there are variants at n genetic loci, $\mu(x)$ is a baseline mortality hazard rate, each z_i has value 0 or 1 indicating absence or presence, respectively, of the risky variant at the i th locus, and the β_i are regression coefficients.

⁶For example, the risk associated with raised cholesterol should be mediated by a genetic characteristic.

20 years before, we may well conclude that the same lessons have to be learned over again, whenever the subject grabs the attention of legislators.

So has Pokorski's vision of genetic testing taking its place in "normal" medicine come to pass almost 30 years on? The answer must be "not yet." The accumulation of knowledge has been vast, but mostly pre-clinical so far. There have been rather few magic bullets in the form of gene therapies and interventions. We may compare the workings of the genome to thousands of deposits of precious minerals buried beneath a vast and confusing landscape. We know they must be precious, because if only we could find them, we could surely invent wondrous things. Family medical history provided some promising formations and a few actual outcrops in the form of pedigrees, where single-gene disorders were exposed. Now genetic testing has turned outcrops into quarries, producing useful output, but GWASs have mostly planted hundreds of flags on the surface, with the promise of minerals beneath, perhaps.

Is there a distinctive role for actuaries in this continuing process? Pokorski (1995) sketched the future of life insurance in gloomy terms:

"Suggesting that genetic information should not be used to classify risks is tantamount to advocating a fundamental restructuring of the life insurance industry . . . Large-scale cross-subsidies would be required . . . Premiums would become intolerably high for most people . . . mandatory participation by all consumers would be required and the government would need to subsidize life insurance purchases of those unable to afford higher premiums."

In other words, life insurance would face an adverse selection doom spiral unless insurers could use genetic information. Bear in mind that in 1995, DNA-based genetic tests did not yet exist and genetic epidemiology was limited to HD and a few other single-gene disorders. If all of genetics would look like that, once we could read the genome, then maybe "doom spiral" would be right. But we know now that it will not. Maybe it would still be right if circumstances were so extreme that the single-gene disorders could swamp the rest of life insurance – STOLI based on genetic tests, for example. Actuaries are quite right to model such extremes as part of the bigger picture of many possible futures. There is still plenty for actuaries to do, in mapping that bigger picture, to help inform decision-makers in government and in commerce.

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