Protective genetic variants – a balanced view of genetic testing results
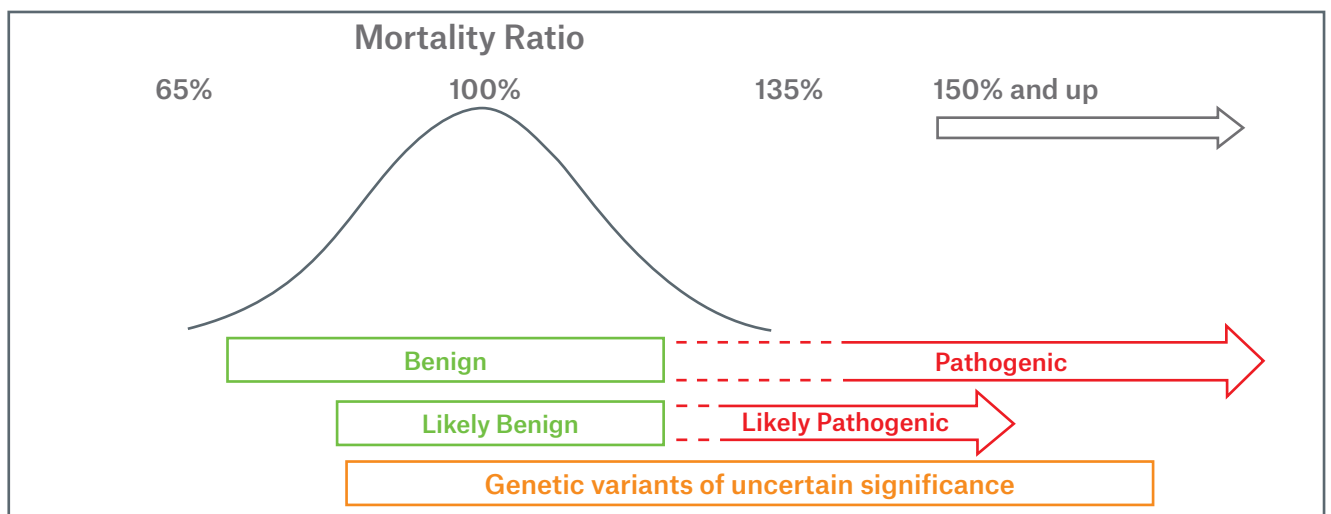
Until recently, most genetic testing has been directed towards detecting a pathologic genetic variant in targeted high risk populations where family history suggests an increased likelihood for a specific inheritable disease. DNA sequencing techniques used in clinical medicine have, up until now, focused on detecting pathologic genetic variants in such specific settings where likelihood is relatively greater because of expense, and because of knowledge limitations in interpretation of findings. These diseases are usually "monogenic" such as inherited breast cancer and ovarian cancer syndromes or inherited hypertrophic cardiomyopathy. Such limited use of clinical testing has led to the impression that finding a genetic variant represents a negative

indicator regarding health and longevity. However, this is not necessarily so.

The American College of Medical Genetics and Genomics established guidelines for the classification of genetic variants in 2015. DNA sequence variants were classified into five groups: pathogenic, likely pathogenic (associated with increased risk for disease), uncertain significance, likely benign (not associated with increased risk for disease) and benign. The associated mortality risk represented by these genetic variant groups may be graphically depicted in relation to the Gaussian distribution of mortality ratios as traditionally conceptualized in the insurance industry (see illustration below).

Concerns that individuals in whom pathogenic or likely pathogenic variants are detected would be adversely affected if this information was accessible by various parties, including those selling insurance products, has led to the passage of legislation by many governments that prohibits the availability and use of genetic information. Such legislation includes the Genetic Information Nondiscrimination Act (GINA), which was signed into law in the United States in 2008, and Bill S-201, which was passed earlier this year in Canada.

The concept of the relationship of genetic variants to mortality risk is not a complete representation, as it doesn't address the significance of "protective genetic variants." A

Mortality Ratio

65%   100%   135%   150% and up

Benign

Likely Benign

Pathogenic

Likely Pathogenic

Genetic variants of uncertain significance

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protective genetic variant is a genetic variant associated with decreased risk of disease. In a review of the current state of the study of protective genetic variants in *Nature Reviews/Genetics* the authors conclude, "In the context of a generalized preoccupation with disease susceptibility, the concepts of protection against diseases and maintenance of health have been largely neglected within genomics."[1] For example, in 2005 it was discovered that loss of function in the gene PCSK9 resulted in markedly lower levels of LDL cholesterol. This protective genetic variant has since been shown to be associated with significantly lower levels of coronary atherosclerotic heart disease.[2,3] In another example, a small deletion variant of the caspase[7] (CASP7) gene has been found to significantly diminish the incidence of late onset Alzheimer disease in individuals who are carriers of the high risk APOE ε4 allele.[4]

Protective genetic variant effects are not necessarily isolated to single genes, especially in disease processes that are multifactorial, such as coronary atherosclerotic heart disease (CAD). Since 2007, genome-wide analysis has identified more than 50 independent genetic loci that are associated with risk for CAD. One study assessed risk in over 55,000 participants without CAD, using a polygenic risk score derived from analyzing 50 single-nucleotide variants that were associated with risk (more or less) for developing CAD. After a follow up of 20 years, it was found that the highest risk score quintile (riskiest 20% of entrants) had a hazard ratio of nearly twice that of the lowest risk quintile for developing overt CAD.[5] The multiple genetic loci in this study were concerned with typical risk factors used in assessing life insurance applicants for possible placement in a "preferred" underwriting class (e.g., lipid values, blood pressure, build, etc.). Some favorable combination(s) of the 50 single-nucleotide variants in the lowest risk quintile likely code for protective phenotypic expression of these classic cardiovascular risk factors.

Schwartz, Williams and Murray note in an April 2017 article in the *Journal of the American Medical Association* (emphasis added by this author):

"If genetic tests could reliably be used to help stratify individuals at all levels of disease risk into more accurate risk categories – **including moving individuals to a lower risk category based on the presence of protective variant(s)** – this would allow a broader range of individualized preventive care recommendations that include both more and less intensive screening protocols based on risk."[6]

Genetic testing may well provide a different technique for assessing the same risk represented by various factors currently commonly employed in risk assessment which are measured by traditional means (e.g., blood tests), such as risk factors for CAD. Favorable expression of these traditional cardiovascular risk factors routinely supports "preferred" classification of insurance applicants. Why should genetic test results not be available to assess such traditional and commonly evaluated risk factors? Schwartz, et al, suggest adding two additional categories to the American College of Medical Genetics and Genomics classification system—"Protective variants" and "Likely protective variants." These additional categories would fit into the "standard" insurance Gaussian curve in the region that would be considered as "preferred," as roughly depicted in the illustration below by the blue rectangles representing the two protective variant categories.

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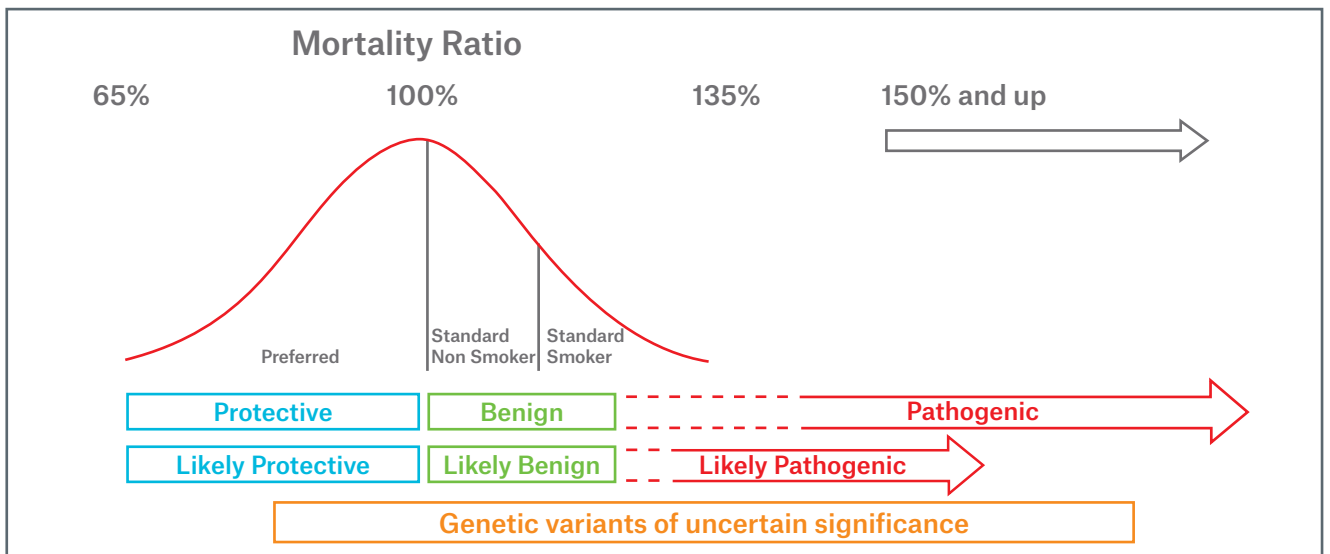
Technological advances in the field of genetics now make possible DNA sequenced-based screening of larger, healthy populations. This increases the potential for identification of more protective variants. Extensive research will be needed to characterize the amount of risk reduction associated with different protective variants. When a body of knowledge has been developed that accurately and comprehensively records protective genetic variants, as well as adverse genetic variants, it is very possible that the current genetic laws in both the United States and Canada directed at shielding individuals from adverse effects, if their personal genetic information is revealed, will need to be reconsidered. The view that "genetic variant" refers only to genetic information that is detrimental to risk assessment will need to be revised. The reality may well be that, in the case of life insurance applicants, many more will not be able to be classified as "preferred" as supported by their genetic code because this information will not be able to be used in underwriting. This would violate a basic principal of insurance: cost of insurance should be commensurate with risk of the insured—both worse risk and better risk.

What Underwriters Should Know

- Genetic testing up until now has focused mainly on detecting genetic variants associated with increased likelihood for developing specific inheritable diseases.

- DNA sequencing techniques are improving and becoming less expensive, making possible DNA sequenced-based screening of larger healthy populations.

- It is now becoming recognized that genetic variants may also be associated with protection against the development of certain diseases.

Key Points

- Polygenic risk scores now can predict future risk for developing CAD by assessing genetic expressions associated with traditional CAD risk factors.

- In the future, genetic testing results may indicate "preferred" mortality risks as well as standard and substandard mortality risks.

- Ironically, current genetic testing laws may well need to be revised in order that the public not be adversely affected because their genetic code results are prohibited from being used in routine underwriting assessments.

References

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NOT IF, BUT HOW