RISK

Polygenic risk scores: Quantifying the inheritability of common diseases

Significant and rapid progress in genetics research and data analytics is currently enabling an unprecedented expansion in science's understanding of the genetic underpinnings of rare and common diseases. Large-scale cohort studies such as the UK Biobank are helping scientists build powerful prognostic models for a number of diseases, including breast cancer and coronary artery disease, and hastening the development of a new tool for quantifying the inheritability of common diseases: Polygenic risk scores. **RGA**'s **Richard Russell** explains.

Genetic testing has commonly been used to search for high-penetrance single gene mutations known to cause the rarer Mendelian or monogenic diseases. However, most cases of major diseases such as coronary artery disease, diabetes and cancers are multifactorial in nature. This means the risk of actually developing one of these diseases is due to a combination of genetic and environmental factors, and the genetic mechanism is difficult to measure.

Since 2005, genome-wide association studies (GWAS) have enabled the discovery of differences in the DNA sequences of individuals with a disease compared to individuals without the disease. These genetic differences, known as single nucleotide polymorphisms (SNPs), are positions in the genome at which some individuals in the population have one particular nucleotide that differs from the one normally found in that place. In recent years, geneticists have combined the genetic risk information from the millions of SNPs discovered in GWAS in order to predict an individual's predisposition to specific diseases or complex traits. The resultant genetic risk metric is called a polygenic risk score (PRS).

This article reviews recent developments in polygenic risk profiling and the predictive utility of PRSs in relation to a person's susceptibility to two diseases: Breast cancer and coronary artery disease. We discuss the possibility of adverse selection where genetic information on disease risk is available for insurance purchasers but not underwriters. Additional research is imperative to understand how PRSs, and other advances in genomic medicine, could cause adverse selection if consumers use this information to alter their insurance purchasing behaviour.

Genetic susceptibility

How informative are genetic test results for predicting major morbidities and mortality? Many researchers are now using large-scale cohorts such as UK to explore genetic information alongside traditional health risk factors. UK Biobank offers tremendous opportunities to research mortality and morbidity outcomes using both genetic and environmental risk factors.

Recent studies utilising UK Biobank data have begun to demonstrate the considerable potential for

PRSs to identify individuals at higher (and lower) risk of disease. Indeed, researchers have now developed PRSs for many common diseases and have shown their vast potential in risk prediction. For example, recent research about coronary artery disease risk and PRSs demonstrated that people with a PRS in the highest 5% in the UK Biobank data have a threefold increased risk of experiencing the condition compared to the remaining 95% UK Biobank of individuals with lower PRSs. Furthermore, PRSs have been shown to be effective predictors of risk even after adjusting for conventional risk factors.

In collaboration with a team of academics from King's College London, researchers from RGA have been studying UK Biobank genetic, environmental and clinical data to determine if it can enable reliable prediction of onset of breast cancer and coronary artery disease. Breast cancer and coronary artery disease are long recognised to have a heritable component, and PRSs have helped to unravel the genetic underpinnings of these diseases. Our focus in this research is on assessing the utility of PRSs to predict incidence of these diseases after controlling for typical risk factors used in underwriting.

Breast cancer is the most common invasive cancer in women worldwide, with approximately 39% cases diagnosed in Asia, according to the WHO's International Agency for Research on Cancer. Overall, researchers are finding that although the incidence of breast cancer in Asia is still lower than in western countries, rates are increasing rapidly.

Coronary artery disease is the leading cause of mortality in the world, and researchers in Asia estimate that half of the cases of the disease worldwide occur in the region.

Early disease detection as well as disease prevention are critical for reducing mortality associated with breast cancer and coronary artery disease. Since PRSs capture important information about an individual's risk of developing these common diseases, and because a person's genetic risk can be measured from birth, PRSs could theoretically be used to aid disease prediction long before the typical age of onset.

In the RGA-King's College London study, the UK Biobank cohort was divided into two based on disclosed medical histories. Risk prediction models were built to study each subpopulation, adjusting for relevant biometric, lifestyle and socioeconomic factors including BMI, blood pressure, smoking and family history.

The results demonstrated an approximately twofold increased risk for those in the top 5% of genetic risk compared to those in the middle for both disease outcomes and in both the standard group and the whole population. These results establish how important PRSs are for risk differentiation, alongside, and largely independent of, traditional underwriting risk factors.

Implications

For insurers, rapid developments in genomics will bring many opportunities and will have a positive impact on the insurance industry. As genetics research continues to advance our understanding of morbidity risk, developments in genomic medicine will almost certainly lead to improvements in mortality and longevity. Nonetheless the falling costs of DNA sequencing technology coupled with the growth in direct-to-consumer genetic testing poses immediate concerns around information asymmetry, which insurers hope to avoid as much as possible. In particular, widespread access to personal genetic data and disease risk information, in the form of PRSs, has the potential to increase anti-selection behaviours.

Right now, anti-selection due to knowledge of genetic risk information is believed to be low, but growing access to information on one's genetic susceptibility to common diseases, through PRSs, might affect insurance-purchasing decisions in the near future. These decisions could significantly alter the mortality and morbidity experience of an insured book if the balance shifts towards those with high-risk of disease.

Around the world, regulations limit the use of genetic information in individually underwritten life, critical illness, long-term care, and income protection policies, so it seems unlikely that PRSs could become a common part of underwriting. As a consequence the possibility of anti-selection may rise as the predictive power of PRSs increases, due to the ever-growing pool of GWAS and as additional genetic variants that contribute to disease risk for more and more conditions are identified.

The rapid growth of genetic information could also fuel the development of personalised treatments to reduce morbidity and mortality risk. Women with PRSs indicating higher breast cancer risk, for example, could be offered more regular breast cancer screening, or screenings at younger ages. Interventions such as prophylactic surgery and chemoprevention could also be adopted for those at the highest risk levels.

The use of genetic information in insurance will continue to be a sensitive subject for life and protection insurers. A key concern is the adverse financial impact advances in genetics may have if restrictions continue to limit the use of genetic information in underwriting.

Genomic medicine

The era of genomic medicine is approaching fast: The leap in the scientific understanding of polygenic risk to common diseases and the explosion in public interest in genetics have brought us to a point where PRSs may have a place in clinical risk prediction in the near future.

Access to PRSs remains an emerging risk issue for insurers. The topic raises ethical and privacy concerns so scrutiny from regulators, already high, is likely to remain high or increase. New regulations and policies may emerge to control the use of genetic information. Insurers, meanwhile, must continue to keep up with advances in genetic research and how they might impact consumer behavior. The industry should also consider that genomic medicine will almost certainly lead to improvements in mortality and longevity, which will be positive for life and health insurers and for society as a whole.

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