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Underwriting Insights

Predicting common disease with polygenic risk scores Could it disrupt life insurance?

While the use of polygenic risk scores are new, they are quickly gaining speed in literature and the media. Therefore we as insurers should continue to watch the development and implementation of these scores to fully understand the impact on our industry.

History of predictive genetic testing – from monogenic to polygenic disease

Polygenic risk scores (PRS) are a new technology covered well in scientific literature and by the media. Some well-known genetic testing companies already sell PRS reports for specific impairments (i.e. type 2 diabetes).

Traditional nature versus nurture debates had assumed that common diseases are caused primarily by either genetic factors or environmental differences. Today we know that most common diseases are influenced by both genetic and environmental influences. PRSs can help quantify the risk from genetic influences in polygenic disease by condensing millions of single nucleotide polymorphisms (SNPs), which are mutations within the genome, to create a score indicating an individual's risk of disease in the future.

Polygenic risk score vs Genome-wide polygenic score

Polygenic risk scores (PRSs) summarise genome-wide genotype data into a single variable that measures genetic risk for a disorder or a trait. PRS is calculated from genome-wide association study (GWAS) summary statistics as the sum of the number of risk alleles carried by an individual, weighted by the effect size from the discovery GWAS. Use of PRS has appeal in its simplicity, summarising millions of genotyped common genetic variants. The genome-wide polygenic score (GPS) is used for quantitative traits, such as intelligence and is a genetic tool to triangulate health options over the life course. The 'genome-wide' addition to PRS distinguishes GPSs from polygenic scores that aggregate candidate genes only or just the top hits from genome-wide association studies (GWAS). A GPS uses a very large number of variants, and makes assumptions, which allows showing greater stratification of risk at the tail ends of the distribution.

Significance of PRS in Clinical medicine

Improved risk assessment tools are welcome in the era of precision medicine. The overall power or PRS to predict a specific disease is modest, because most people will have an 'average risk,' and quantifying the exact degree of genetic risk by PRS will not be particularly useful. However, the real value of the PRS stratification is to pick individuals who have particularly high or a very low genetic risk.

PRSs can predict a person's risk for conditions like coronary artery disease, breast cancer, and type 2 diabetes which can be especially useful for people who lack common warning signs. The goal of PRSs is to stratify patients into risk categories based on their genetic mutations. Diseases are mediated by a collection of common and low frequency genetic variants. Although each variant has a small effect, taken together, they could indicate a person's overall risk. PRSs are poised to improve biomedical outcomes via precision medicine.

PRSs benefits and challenges for clinical implementation:

Clinical implementation benefits

- Easy to calculate and store
- Tested once, and remain constant throughout life
- Prediction before the usual age of onset of a disease

Clinical implementation challenges

- Paradigm shift from rare-disorder genetics (i.e. yes/no for the presence or absence of a high-risk variant) to the model of a genetic effect along a continuous score
- Complexity of the topic for clinicians and the public

Published Examples of PGR

Genetic risk profiling has focused on common adult-onset polygenic conditions, which are typical causes of death in the developed world: Alzheimer disease, cancer (breast and prostate), coronary artery disease and type 2 diabetes mellitus. For these conditions, studies have linked polygenic risk prediction to actionable outcomes, including the prioritisation of preventive interventions or non-genetic screening, prediction of age at disease onset, benefit from lifestyle modifications and changes in clinical decision-making.

The study, "Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations" by the group of Sekar Kathiresan, director of the Center for Genomic Medicine at Massachusetts General Hospital, was celebrated in 2018 in the media as groundbreaking science[1]. Analysing data from the UK Biobank population with bio statistical techniques for polygenic risk prediction, Kathiresan calculated polygenic risk scores of individuals for five common diseases: coronary artery disease, atrial fibrillation, type 2 diabetes (T2D), inflammatory bowel disease (IBD), and breast cancer. Interestingly, the risk for individuals at the extreme tails of the distribution were in the range seen in monogenic mutations.

As a very recent example a University of Michigan-led team looked at several polygenic risk scores for skin cancer, using a phenome-wide association approach to look for potential PRS for the three skin cancer melanoma, basal cell carcinoma, and squamous cell carcinoma[2]. The Epidemiology group from Bristo University has published an atlas covering 162 PRS derived from GWAS and 551 heritable traits from the UK Biobank study (N = 334,398). Findings can be viewed using a web application (http://mrcieu.mrsoftware.org/PRS_atlas/)[3].

PGR as a diagnostic test

Some PRSs do not have predictive, but diagnostic utility. For example, a coronary artery disease PRS is not only able to stratify individuals by risk for disease, but also by clinical benefit of statin therapy. Many psychiatric disorders are highly heritable, but also polygenic, with genetic risk conferred by interactions between many variants of small effect that can be summarised in a polygenic risk score. However, pathologic polygenic risk scores associated with psychiatric disease could be easily misinterpreted in stigmatising or discriminatory ways.

Ethnic bias of PGR leading

The Human Genome Project was based on the genetic sequencing of a handful of volunteers, most of whom were from European descent. GWAS continue to gather data primarily from the exact same population. 78 percent of data used in GWAS comes from people of European descent, but that particular group makes up only 16 percent of the global population. Our genome is constantly evolving in response to environmental and biological cues, causing genetic variation from person to person and population to population. Some genetic variants are completely insignificant; others can have a profound effect on a person's health. Commercial DNA tests will tell an individual's risk for a disease, but those risk scores are based on the results from people of European descent, so the predictions are much more accurate for Europeans. Only genome-wide studies with diverse populations can expand the reach of precision medicine to non-Caucasian individuals who otherwise would not be included.

Overview of the insurance risks with PGRs

Underwriting

- Insurers could start to see PGRs at the underwriting stage as the tests are refined and offered direct to consumers – even before the tests are fully validated.
- Direct-to-consumer PGR tests could lead to information asymmetry at the underwriting stage and opportunities for anti-selection.
- Applicants with positive PGRs should be fully investigated. If market regulations allow, it's good to assess medical history and identify other red flags that could suggest a possible pre-disposition or diagnosis.
- Underwriters should be aware of local regulations that prevent the use of genetic testing and/or PGRs as part of genetic information bans.

Claims

- Mortality – If these tests are successfully used to manage established therapy or as part of early detection and diagnosis, we could expect an improvement in mortality in the long run.
- PGRs could increase incidence rates of certain impairments (i.e. cancer) and therefore increase related claims for critical illness (CI) or standalone cover products possibly impacting the overall experience of the portfolio.

Polygenic Scores are available as direct to consumer tests

Some genetic testing companies already think polygenic risk scores are ready for direct to consumer tests. The personal genomics company 23andMe has declared their plan to change health care by introducing PGR risk reports, specifically to help customers learn about their genetic predisposition to certain impairments (i.e. Type 2 diabetes, colorectal cancer, breast cancer, Parkinson's and Alzheimer's). The company's reports have already been approved by the Food and Drug Administration (FDA). The goal is that the customer would learn early enough to seek proactive medical care and make lifestyle changes that help prevent or delay onset of the disease, such as losing weight by eating healthy.

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