Fueled by signi cant technological advances in genome sequencing, arti cial intelligence and machine learning capabilities, the scienti c community continues to explore this relatively new eld, anticipating outcomes such as enhanced clinical applications, tailored treatments and overall improvements in mortality and healthy longevity. Initially our understanding of certain diseases, and more recently tailoring personalised treatments, was focused on single high-penetrance genetic mutations. But many more commonly encountered diseases have a polygenic architecture meaning that multiple genetic variants in combination a ect disease risk. Genome-wide association studies (GWASs) have certainly helped to highlight this, and

Genetic testing already plays a key role in clinical medicine and there are many di erent types of genetic tests that are currently available. This is certainly the current paradigm in oncology, but also in pre-natal and newborn screening as well as in the rare disease elucidation. There is no doubt that genomics will drive a number of additional clinical applications in the near future and, as a result, we are likely to expect both mortality and healthy longevity improvements.

A key concern for our industry is to understand the economic impact that advances in genetics and genomics will have. If regulations continue to limit the use of genetic information then the impact is clearly dependent on how useful genetic information is to risk selection. Thus, a critical question to ask is: how accurately can genomics help predict the risk of developing common diseases?

From SNP's to GWAS to PRS to clinical application

One of the most considerable advances in the genomics space at the current time is the demonstration of polygenic risk pro ling to identify disease risk. This is signi cant because most common diseases are not caused by a single mutation or variation in a gene (which is more straightforward to explain and predict), but result from multiple genetic variants and their interaction with lifestyle as well as environmental factors.

What is polygenic risk pro ling?

The basic building blocks of the deoxyribonucleic acid (DNA) in all our cells consist of four nucleotides or base pairs. Altogether there are three billion of them that make up the complete blue print of our genetic code, and it is the order of these nucleotides that program the production of proteins and overall cell function.

Genetic variation describes the natural genetic di erences that occur between individuals. Single nucleotide polymorphisms (SNPs) are individual variations in a nucleotide, where a nucleotide in a particular position in the genome is di erent from a reference nucleotide. A SNP is the most common type of genetic variation that exists, and we each carry millions of them, some of which we know make a di erence and some which do not appear to have an impact.

A SNP is the most common type of genetic variation that exists, and we each carry millions of them

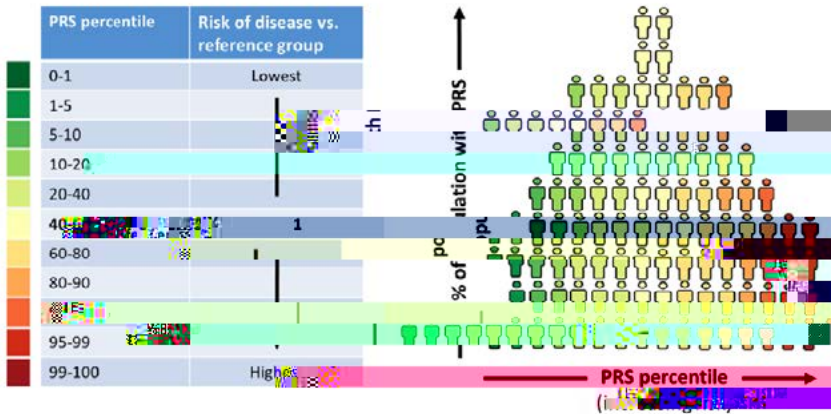
Geneticists have long noticed that certain SNPs occur more commonly in people with a particular disease or trait than those without. A genome-wide association study (GWAS) is a study technique that compares those with a disease to those without a certain disease using a DNA chip or microarray. The microarray can di er in number of genetic variants studied, and usually statistical geneticists use a very low probability value to suggest a SNP is statistically signi cant, indicating that a particular SNP or variation is likely to be associated with the disease or trait in question.

Genome-wide association studies have been highly successful at identifying genetic variants associated with disease. The rst GWAS, conducted in 20051, compared 96 patients with age-related macular degeneration with 50 healthy controls. It identi ed two SNPs with signi cantly di erent allele frequency between the two study groups. An allele is one of two or more alternative forms of a gene at the same position in a chromosome.

Since this rst GWAS, sample sizes have expanded, which allows SNPs with smaller odds ratios for a particular disease outcome, often at a lower frequency, to be identi ed. The importance of this, as mentioned, is because many common diseases are associated with multiple genetic variants that cumulatively a ect disease risk.

Statistical geneticists have developed the 'polygenic risk score' (PRS), identifying hundreds, thousands and even millions of SNPs (variants) that can be included in a single score that measures the individual's genetic predisposition to speci c diseases or traits. It is essentially an index derived by adding up the number of variants multiplied by their e ect size to give an overall risk of developing a disease. PRSs are often expressed as a risk percentile. In individuals with a PRS close to the population mean, the person's predicted genetic risk will be similar to the population's risk, but a person with a PRS in either the 91st to 100th or 10th percentile of a population, would be considered to have the highest and lowest genetic risk, respectively. (Figure 1)

Figure 1: PRS Distribution



S ce: RGA

Researchers continue to develop PRSs for many di erent conditions[2,3,4] (and Table 1). Many show that there is powerful disease risk di erentiation when comparing those with the highest and lowest quintiles of genetic risk.

Table 1

Disorder	No. of Genetic Variants	Relative risk, comparing top 20% to bottom 20% PRS	Reference
Coronary artery disease	50	2.0	Khera AV. et al. (2016), N Engl J Med.
Coronary artery disease	49,310	1.8 to 4.5	Abraham G. et al. (2016), Eur Heart J.
Type 2 diabetes	1000	3.5	Läll K. et al. (2017), Genet Med.
Ischemic stroke	10	1.2 to 2.0	Hachiya T. et al. (2017), Stroke
Breast cancer	77	3.0	Mavaddat N. et al. (2015), J Natl Cancer Inst.
Breast cancer (East Asian ancestry)	44	2.9	Wen W. et al. (2016), Breast Cancer Res.
Prostate cancer	25	3.7 (25%)	Amin Al Olama A. et al. (2015), Cancer Epidemior . Tc T1 (.3 (id)-1.5 (emi)1.5 (o)-2.M)-14.9 ()(se)]

Study, with a combined number of 16,802 participants and 1,344 incident CAD events. After controlling for clinical risk factors including family history, the PRS still proved to be a very powerful di erentiator of CAD risk. Those in the highest quintile of genetic risk compared to those in the lowest quintile of genetic risk in the Framingham cohort showed a 12 year age di erential in 10% of each group going on to su er an MI. The di erence in the FINRISK cohort was even greater at 18 years.

Another potential clinical application for PRSs is in identifying those with higher cancer risk, which could lead to personalised screening programs. In a study by Mavadatt and colleagues[11] looking at genetic risk and breast cancer, women whose PRSs were in the top 20% were shown to have a higher lifetime incidence of breast cancer compared with women in the lowest quintile (17.2% vs. 5.3%). Accordingly earlier screening intervention could be recommended in those women with higher genetic predisposition; these high risk women could develop breast cancer well before the usual age for population screening.

Research Collaboration

In collaboration with King's College London[13], RGA has recently looked to establish how accurately mortality and certain morbidity risk can be predicted based on detailed phenotypic information and whether such estimations could be improved by including genetic data in the form of polygenic risk scores.

This research collaboration has explored the UK Biobank data, which is a population-based cohort prospective linkage study of 500,000 participants across the UK. This incredible cohort study o ers researchers an opportunity to research mortality and morbidity outcomes using genetic and environmental risk factors. In addition to typical biometric data on the participants, 20 million genetic variants have been collected.

-39 (t)7 (s)-17.5 ()-1.5 ()2.9 (o t)-414.8 (e)-11 1ra oi58 [(l)0.6 (i)-11 1ran15.4 (h)-6 ( )]TJ 0nec ri(es)7 (uves)7.9 ()-6.4 (i)-5.5 (o)-8.5

In Conclusion

Overall, polygenic risk scores should be considered an emerging risk issue for the protection insurance industry. Medical science will continue to push the boundaries of genetic discovery which could translate into greater predictive ability, but there is still signi cant work to be done. One drawback of many of the current published scienti c research is that its application is limited to Caucasian populations and so more evidence from non-Caucasian cohorts needs to emerge for wider adoption and applicability. Education for clinicians and the public is crucial as we all begin to navigate this new world. Industry supervisory bodies will continue to monitor and regulate this space. This is a time for both risk and opportunity in the industry. Undoubtedly, polygenic risk scores will be a speci c area of focus as we continue to explore this fascinating eld of scienti c discovery, particularly as we seek to better understand common disease risk and outcomes through our genome.

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References

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