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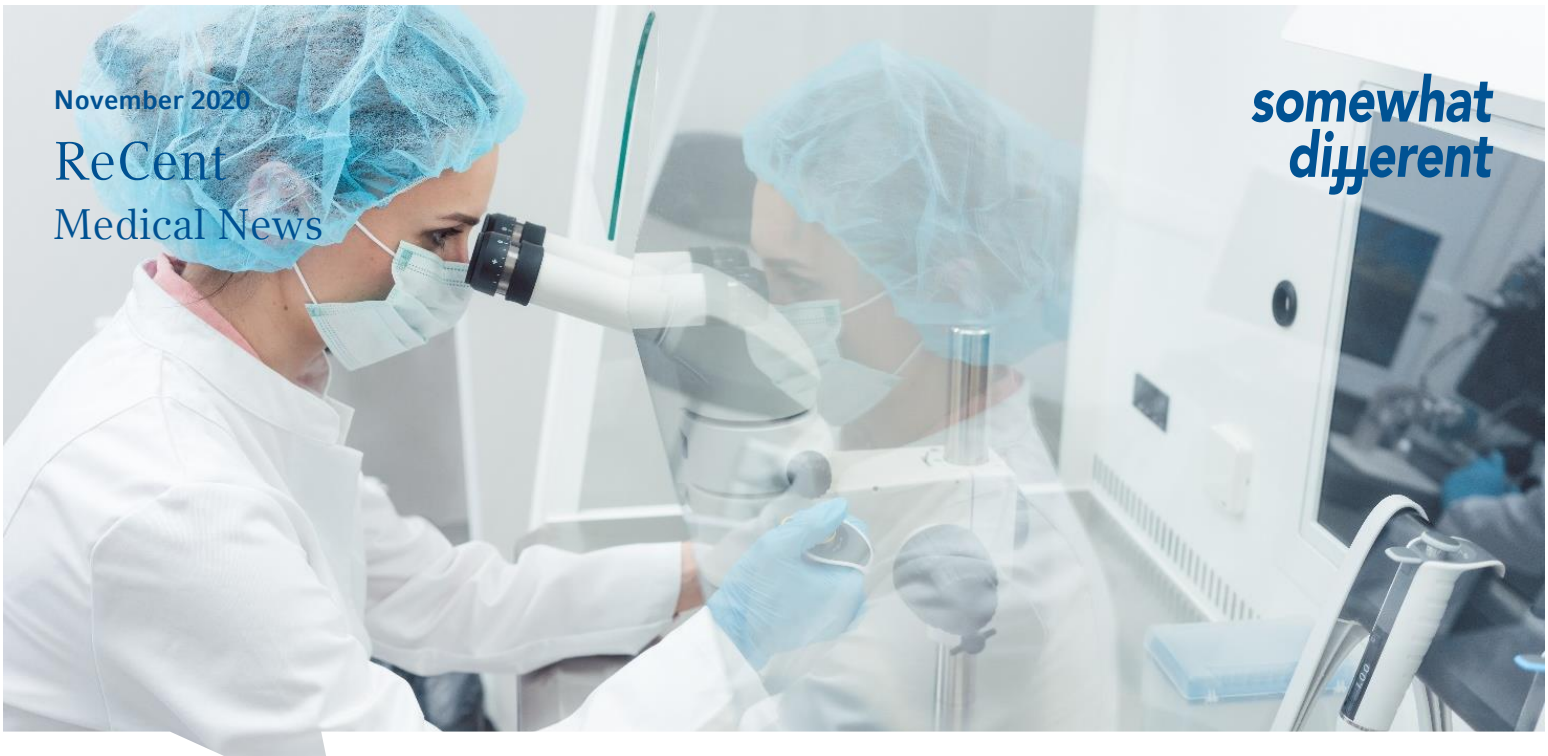
somewhat different



Polygenic risk scores are being vigorously researched across different fields of medicine.

Clinical utility of polygenic risk scores

Introduction

The practice of preventive medicine requires estimating the risks of developing chronic diseases so as to enable risk-mitigating measures such as diet, lifestyle and medical interventions to be implemented.

Similarly, in insurance underwriting we assess applicants' risks of developing life-shortening common chronic diseases in order to correctly assort each person to the appropriate risk classification for pricing purposes.

Both clinical and insurance underwriting approaches used to derive such disease risk estimates are well known and includes consideration of the following:

- Demographic characteristics such as age and gender
- Lifestyle criteria, for example BMI, smoking status, alcohol consumption and physical exercise habits
- Clinical risk factors such as blood pressure, blood chemistries and biomarkers

Conspicuously absent from these lists is routine genetic testing. The emergence of polygenic risk scores for common adult-onset diseases aims to change this and ultimately enhance available risk estimation tools.

Genetic concepts

Our genes serve as blueprints to make molecules called proteins, the building blocks for everything in our body. In single-gene (monogenic) disease, a mutation in just one of our estimated 20,000 genes is responsible for disease, although one should note that the presence of a mutation does not guarantee disease penetrance.

Despite the relative success in identifying genes responsible for many monogenic diseases, the majority of diseases do not trace back to a single genetic cause. The common-disease, common-variant hypothesis posits that 'if a disease that is heritable is common in the population, then the genetic contributors to the disease must also be common in the population.[1]

Each cell nucleus contains around 3 billion nucleobase pairs with any two people differing by on average 3 million positions in their DNA. The majority of these differences – or 'single nucleotide polymorphisms' (SNPs) – do not appear to have any effect, but a small number are considered functional polymorphisms. Scientists determine the significance of the SNP by comparing genetic sequences of individuals with a trait or disease (phenotype) to those without it. SNPs present in those with the phenotype and absent in the control are considered to be 'associated' with the phenotype and the degree of association is termed the 'effect size'. These 'genome-wide association studies' (GWAS) have identified hundreds of thousands of SNPs associated with various phenotypes and while GWAS have been undertaken for over 15 years, availability of data and enhanced processing capabilities has accelerated research in this space in more recent times.

Further accelerating the usability of GWAS is the advent of polygenic risk scoring (PRS); a weighted sum of the

[1] See El-Fishawy P. (2013) Common Disease-Common Variant Hypothesis. In: Volkmar F.R. (eds) Encyclopedia of Autism Spectrum Disorders. Springer, NY

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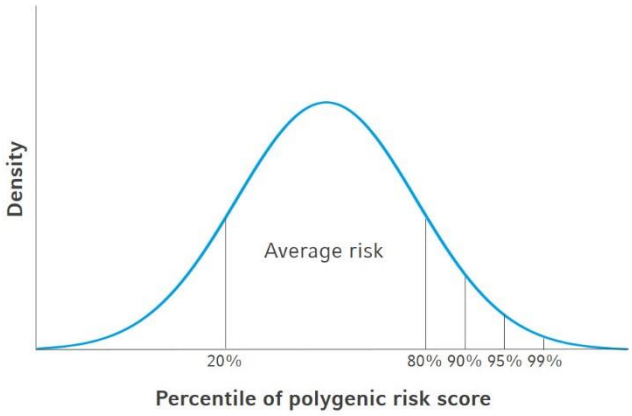
number of risk variants for a particular disease, distilled into a very transparent score fitting a normal distribution. Essentially, you can think of PRS as a debit/credit model for genetic profiles, with the highest PRS correlating with the highest relative risk of developing the particular disease or trait over your lifetime. Arguably, PRS represents one of the most digestible means of reflecting genetic risk, one which we can readily transpose over the traditional insurance paradigm approach to risk classification where the majority of lives are average risk (standard rates) and lives either side of the normal curve represent the lowest and highest (preferred or substandard) risks respectively. While the ability to predict lifetime likelihood of disease increases as more phenotype-associated SNPs are identified and the PRS moves towards and into the 90th percentile, development of the disease often still relies upon other stimuli. Indeed, common, complex diseases appear to occur as a result of many genomic variants with small effect sizes, interacting with often modifiable environmental influences such as diet, sleep, stress and smoking; i.e. the genetics are not deterministic.

Polygenic risk scores and coronary artery disease

Familial hypercholesterolaemia (FH) – an autosomal dominant disease – is most commonly caused by a mutation of the low-density lipoprotein receptor (LDLR) gene.[2] While other monogenic mutations have been found, approximately 15% of FH cases appear to be caused by monogenic mutations of undetermined prevalence or multiple genes interacting additively to influence the trait (polygenic disease). Roughly one in 250 members of the global population develop FH[3] and they are predicted to have up to 3.9 times more cardiovascular events over their lifetime than non-familial hypercholesterolemia patients with an otherwise similar risk profile.[4] While much of this risk can be attenuated by early and aggressive cardiovascular risk factor modification, the challenge is often one of timely identification – bearing in mind that exposure to elevated low-density lipoproteins begins in utero for those with FH.[5]

Fig. 1: The clinical impact of a high polygenic risk score for coronary artery disease[6]



PRS - CAD	Reference Group	Odds Ratio	95% CI
Top 20%	Remaining 80%	2.55	2.43-2.67
Top 10%	Remaining 90%	2.89	2.74-3.05
Top 5%	Remaining 95%	3.34	3.12-3.58
Top 1%	Remaining 99%	4.83	4.25-5.46
Top 0.5%	Remaining 99.5%	5.17	4.34-6.12

Coronary artery disease polygenic risk scores in the top 5% have odds ratios for CAD at a similar level to monogenic disease. PRS appears to identify a different subset of lives at risk for CAD than those identified through monogenic sequencing and it has very low correlation with traditional cardiovascular risk factors.[7] Considering that around 15% of first heart attacks are in the context of no traditional major cardiovascular risk factors[8], could it be that PRS can help identify a significant sub-set of these lives early enough that intervention could mitigate the risk of a heart attack? Given that roughly 2% of early heart attack patients are identified as having a monogenic mutation, versus 17% of patients having a PRS in the top 5%, the scope to intervene appears significant. Hazard ratios for CAD in the top 20% of PRS are around 4 times

[2] See Chial, H. (2008) Rare Genetic Disorders: Learning About Genetic Disease Through Gene Mapping, SNPs, and Microarray Data. Nature Education
[3] See Henderson, Raymond et al. "The genetics and screening of familial hypercholesterolaemia." Journal of biomedical science vol. 23 39. 16 Apr. 2016
[4] See Guillermo Villa, et al., Prediction of cardiovascular risk in patients with familial hypercholesterolaemia, European Heart Journal - Quality of Care and Clinical Outcomes, Volume 3, Issue 4, (2017)
[5] See Gidding S.S., et al. (2015) The agenda for familial hypercholesterolemia: a scientific statement from the American Heart Association.
[6] See Khera, Amit V et al. "Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations." Nature genetics vol. 50,9 (2018)
[7] See Biobank UK; Genome-wide polygenic scores to stratify risk for common diseases. (2018)
[8] See Canto, John G et al. "Number of coronary heart disease risk factors and mortality in patients with first myocardial infarction." JAMA vol. 306,19 (2011)

greater than for the bottom 20% and this pattern is observed across numerous diseases, showing significant potential for screening and treatment protocol change.[9]

However, other results are mixed. The authors of a 2020 study[10] published in JAMA journal found that the same polygenic risk score used in the study by Khera et al.[11] did not improve on the risk stratification of incident coronary heart disease in middle-aged Caucasian populations when compared to traditional clinical risk scores, suggesting that the clinical utility of PRS wears off as people age.

Polygenic risk scores and psychiatry

Given the polygenic architectures of psychiatric disorders, polygenic risk scoring seems primed to fundamentally inform and change our understanding and indeed classification of psychiatric disorders.[12] The advent of polygenic risk scores has generated significant interest in the field of psychiatry, largely due to the lack of reliable biomarkers in the field. Apart from family history, there are currently no clinical or laboratory predictors of the probabilistic risk of psychiatric disorders in healthy populations.

However, recent psychiatric research has begun to explore the use of PRS and this has highlighted two areas of development:

1. Estimating the latent risk of various psychiatric disorders in healthy individuals – there is data to show that in a general population of college students, a high PRS score for schizophrenia and neuroticism can identify individuals at an increased risk of developing anxiety and depression.[13]
2. Predicting mental health outcomes in those with an existing psychiatric diagnosis: both bipolar polygenic risk scores and schizophrenia polygenic risk scores have been shown to predict likely outcomes in substance addiction disorders.[14]

Polygenic risk scores and breast cancer

Different studies[15, 16] have shown that women with polygenic risk scores for breast cancer in the highest 1% have a lifetime risk of developing breast cancer almost equivalent to the lifetime risk seen in women with high-risk monogenic mutations such as BRCA1 and BRCA2. These polygenic high-risk women should therefore be offered the same intensive risk-reducing strategies as if they were carrying a high-risk BRCA mutation.

Low polygenic risk scores for breast cancer may also be useful to determine the subset of asymptomatic middle-aged women for whom mammographic screening – and its associated risks of false positive diagnoses and unnecessary treatments – may not be required.[17]

Polygenic risk scores as predictors of all-cause mortality

A few studies have emerged that have looked for genetic variants associated with lifespan.[18, 19] Wright et al. reported on eleven loci (the positions of a gene or mutation on a chromosome) significantly associated with paternal lifespan and four loci significantly associated with maternal lifespan.[20] Not surprisingly, a number of these lifespan-associated loci are also significantly associated with life-shortening diseases. In their estimation, only 10% of variation in observed human lifespan is due to genetic variants, which does not bode well for the development of robust polygenic risk scores for all-cause mortality.

Is there a polygenic risk score to predict a person's lifespan?

Rather than pursue a study of polygenic risk scores for all-cause mortality using putative lifespan genetic variants, the authors of an intriguing study published in September

[9] See Inouye, Michael et al. Genomic risk prediction of coronary artery disease in nearly 500,000 adults: implications for early screening and primary prevention. bioRxiv 250712
[10] See Mosley JD et al. Predictive Accuracy of a Polygenic Risk Score Compared With a Clinical Risk Score for Incident Coronary Heart Disease. JAMA (2020)
[11] See Khera AV et al. Whole-Genome Sequencing to Characterize Monogenic and Polygenic Contributions in Patients Hospitalized with Early-Onset Myocardial Infarction. Vol 139 (2019)
[12] See Anderson JS et al. Polygenic risk scoring and prediction of mental health outcomes. Current Opinion in Psychology (2019)
[13] See Docherty AR et al. Polygenic prediction of the phenome across ancestry, in emerging adulthood. Psychological Medicine 8/2018
[14] See Reginsson GW et al. Polygenic Risk Scores for Schizophrenia and Bipolar Disorder associate with Addiction. Addiction Biology Vol 23
[15] See footnote 2
[16] See Mavaddat N et al. Polygenic Risk Scores for Prediction for Breast Cancer and Breast Cancer Subtypes. The American Journal of Human Genetics (2019)
[17] See footnote 2
[18] See Wright KM et al. A Prospective Analysis of Genetic Variants Associated with Human Lifespan. G3 : Genes, Genomes, Genetics (2019)
[19] See Timmers PRHJ et al. Genomics of 1 million parent lifespans implicates novel pathways and common diseases and distinguishes survival chances. eLife 2019;
[20] See footnote 18

2020 in *The American Journal of Human Genetics* developed a composite all-cause mortality polygenic risk score incorporating polygenic risk scores for 13 common diseases and 12 established risk factors.[21] These diseases and risk factors are known to have some genetic component and have been shown to be significantly associated with mortality. They conducted their analyses on a large dataset from the UK Biobank. Mortality data was obtained from death and cancer registries linked to the UK Biobank.

Overall, their sex-specific polygenic risk score for all-cause mortality showed modest predictive ability. At the extremes of score distribution, the PRS may be more useful as it is able to identify those with both significantly reduced and elevated risks of all-cause mortality. Differences in life expectancy between the top and bottom 5% of the composite PRS were estimated to be 4.79 years and 6.75 years for women and men, respectively. Comparatively, Timmers et al. found polygenic risk score differences of 5 years of life between the top and bottom deciles for both males and females.[22] Clearly, such results would be of interest to life insurance actuaries and underwriters particularly in markets offering preferred life insurance classes.

Conclusion

Polygenic risk scores are still in their infancy, yet they are being vigorously researched across different fields of medicine. Overall, these scores' current predictive ability for incident phenotypic traits appears to be modest with increased clinical utility for individuals scoring at the higher and lower ends of the score distributions. Recent studies suggest that PRS in the presence of monogenic mutation significantly modifies the penetrance of the disease risk variants, circling us back to a continuum of common low-risk to rare high-risk genetic variants acting cumulatively to drive overall risk in any individual.[23] Polygenic risk scores for all-cause mortality have yielded results that would be of interest to actuaries and underwriters although access to incorporate these new genomic tools is likely to be significantly restricted due to the legislative and regulatory restrictions that exist in several countries and regions.

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[21] See Meisner A et al. Combined Utility of 25 Disease and Risk Factor Polygenic Risk Scores for Stratifying Risk of All-Cause Mortality. The American Journal of Human Genetics (2020)

[22] See Timmers PRHJ et al. Genomics of 1 million parent lifespans implicates novel pathways and common diseases and distinguishes survival chances. eLife 2019;8:e39856 pp. 1-40

[23] See Fahed, A.C., et al. Polygenic background modifies penetrance of monogenic variants for tier 1 genomic conditions. Nat Commun 11, 3635 (2020).

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