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EDITORIAL

Polygenic risk scores and the prediction of common disease

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There is growing interest in the potential translational applications of omics data. This applies to, e.g., metabolomics, an area in which the *Journal* published a themed issue in 2016 with an accompanying editorial titled ‘Metabolic profiling—multitude of technologies with great research potential, but (when) will translation emerge?’.¹ Despite two decades of extensive investigations with optimistic statements of potential translational applications, there is no metabolomics-derived biomarker (of either an individual metabolite in isolation or multiple metabolites in combination) that has yet to mature into clinical utility. On appraising the recent activity in polygenic risk scores (PRSs) and disease prediction, we notice parallel themes to the decades-old search for conventional (non-genetic) predictive biomarkers. An overwhelming sense of hype and a rush to translate dominates the field of genetic research of disease prediction using GRSs.

A PRS is a combination of single nucleotide polymorphisms (SNPs) that associate with the outcome of interest.² There are multiple approaches to constructing PRSs, ranging from inclusion of SNPs surpassing stringent genome-wide significance thresholds (typically called a genetic risk score, or GRS) to use of millions of SNPs including those that individually only very weakly associate with the phenotype of interest (a PRS). From a statistical standpoint, a GRS or PRS can be considered as a single biomarker similar to an individual (e.g. metabolic) biomarker (or a biomarker score). Thus, we can evaluate the predictive performance of a PRS with the same metrics that have been developed and applied over recent decades. A plethora of literature on the statistical basis of predictive modelling subverts the recent optimism placed in PRSs to predict common complex diseases,³ the key concepts being that moderate relative risks (achievable by individual SNPs or biomarkers, or their combination into a polygenic or metabolic risk score) struggle to translate into clinically relevant prediction models.⁴ These epidemiological principles of disease prediction are robust to ‘genetic exceptionalism’.

Several recent high-profile papers have presented interpretations that PRSs convey potential for remarkable opportunities of improved (clinically relevant) predictions of complex diseases, for example coronary heart disease.⁵⁻⁷ Parallel themes are well-recognised in biomarker-focused omics research where (as with genome-wide data) technological advances have facilitated the discovery of multiple biomarkers independently associated

with disease.⁸ However, while such discoveries may provide important aetiological insights into disease, such associations may not necessarily reflect utility in disease prediction.^{1,3,4,9}

This is particularly the case for common (polygenic complex) diseases, in other words, for quantitative traits or as put even more succinctly by Plomin and co-workers: ‘what we call common disorders are, in fact, the quantitative extremes of continuous distributions of genetic risk’.¹⁰ This continuity of polygenic traits for common complex diseases is superimposed on non-static environmental contributions¹¹ and stochastic (patho)physiological processes.¹² The oversight in considering these issues, together with unrealistic expectations for ‘precision medicine’, are likely drivers for the predictive misconceptions.^{4,9,13} The ability to reliably categorise individuals into ‘healthy’ and ‘diseased’ using biomarkers that are normally distributed under typical physiological settings in the general population – which includes variation in common genetic polymorphisms combined into a PRS, and phenotypic traits, such as low-density lipoprotein (LDL) cholesterol and systolic blood pressure – is likely to remain an unattainable goal.¹⁴ For example, with a 5% false-positive rate, the recently published GRSs by Khera et al.⁶ and Inouye et al.⁷ would give a disease detection rate of 15% and 13%. In both these cases, the vast majority (≥85%) of individuals that eventually develop disease would be missed when using such PRSs for disease prediction.⁴

Complex diseases can be considered as the end product of the dynamic interplay between multiple genetic and environmental risk factors. Notably, some of the PRS associations with a disease (or trait) are very likely to be picking up environmental contributions – which may have implications on the temporal performance of a PRS. Unlike genetic variants, environmental risk factors change over the lifespan of individuals and between generations. For example, population characteristics have changed dramatically since the early days of cholesterol and atherosclerosis research. In modern society, individuals have spurious and energy-dense eating patterns, with most individuals living in a non-fasting state. In addition to many general clinical conditions as obesity, hypertension, insulin resistance and type 2 diabetes, the average population lipid profiles have changed substantially. The metabolic consequences of this relate to the ‘contemporary’ risk factors of CHD and up to a certain extent also to the definition and estimation of PRSs.

An individual's genome is inherited randomly and not generally modifiable, and these characteristics form the basis for the role of human genetics in elucidating causality through Mendelian randomization. The fact that SNPs are not able to dynamically reflect the extent of disease (or indeed subclinical disease) through reverse causality represents a further hindrance for the use of PRS in disease prediction. If a hypothetical biomarker is generated in response to a disease (i.e. through the process of reverse causality), this may be where such a biomarker might have a role for prediction. Such a biomarker would be different to those that are routinely measured because, unlike LDL cholesterol, the hypothetical biomarker would not be present (or measurable) under normal physiological conditions in disease-free individuals (providing near-perfect discrimination). For example, if the tunica intima of the arterial wall produced a substance in response to subclinical atherosclerosis that 'leaked' into the circulation in such a concentration that it would be detectable before the manifestation of symptomatic disease, but where the same biomarker was not detectable in individuals without disease, this biomarker might be able to discriminate between those that go on to develop disease from those that do not. While a GRS may be used to identify a biomarker arising from reverse causality, the GRS itself in isolation cannot reflect reverse causality.¹⁵

In contrast to reverse causality, where such a feature may be an advantage of a biomarker for prediction, the causal role of a biomarker is *not* a requirement for predictive modelling.¹⁵ This is evident from LDL cholesterol, one of the most well-recognised causal biomarkers with well understood molecular pathways and specific drug treatments available; notably, LDL cholesterol is a poor predictor of coronary heart disease. However, causality of a biomarker makes all the difference in terms of use in developing population-level interventions for disease prevention.^{12,16}

An interesting exception from the predictive perspective are oligogenic medical conditions – that lie between complex and Mendelian diseases – that are likely to be amenable to GRS-based predictions.^{3,10} For example, auto-immune diseases may represent one such category where ROC curve values of around 0.9 from a GRS may be feasible.^{17,18} Of note, while the high C-statistic does not mean that such a GRS can automatically translate into clinical utility,

it is likely a prerequisite for population screening.^{3,9} Regarding the potential of genetic prediction, it is notable that studies of monozygotic twins can provide an ‘upper limit’ of what can be achieved; this information may guide which traits and diseases have sufficient genetic attributes that a GRS could be of potential clinical value.¹⁹ Finally, a GRS captures risk (arising from genetic variants and gene-by-environment interactions) that occurs over a lifetime, and thus while violating conventional prevention paradoxes that would argue that the focus of preventative strategies should be the entire population rather than just high risk individuals, the identification of those at high genetic risk may facilitate timely prevention targeted to those who would develop early onset disease: it might therefore be feasible that, for example, a population-wide treatment with e.g. a polypill given to everyone at say at the age of 40 and above might be enhanced with earlier targeted treatment in those at high genetic risk. We note that the availability of genome-wide genotyping facilitated by technological advances and massive reductions in cost are likely to make genotype a readily available trait at the population-level (thus facilitating translational opportunities). Widespread availability of genotyping is likely to occur (at least initially) in high- and middle-income countries, which, together with the predominance of genetic studies being conducted in European populations, may have the net effect to further increase global health inequalities.

In conclusion, we recognise and celebrate the incontrovertible role that genomics research has, and will continue to provide in our understanding of the molecular basis of common diseases, in elucidating the mechanisms by which diseases occur, and in identifying new therapeutic targets.^{9-13,20} Nonetheless, the inconvenient truth is that for common diseases, no combination of normally-distributed biomarkers, each modestly associated with disease, is likely to lead to clinically-relevant improvements in risk prediction. Geoffrey Rose stated¹⁶ that for common diseases, “a large number of people at a small risk may give rise to more cases of disease than the small number who are at a high risk”, which notably relates to examining the upper quantiles of a GRS, and concluded that the underlying motivation “should always be to discover and control the causes of incidence”. This elegant elaboration on sick individuals and sick populations by Rose¹⁶ over 30 years ago was prescient to the contemporary era of big data and genome-wide analysis studies.

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