GPS for navigating healthcare

Precision genomic medicine is now technically feasible. Just as global positioning systems revolutionized the logistics of travel, so genome-wide polygenic risk scores (GPSs) now have the potential to inform our trajectories of health and to serve in the prevention and mitigation of many common and complex diseases. We welcome research into the implementation of—and equity of access to—genetic predictors and their integration into clinical and evidence-based medical practice.

Thousands of constitutional genetic variants throughout the genomes of all people influence most of our traits as well as our susceptibilities to complex diseases (those determined by environmental factors acting via our genetic predispositions). After over a decade of well-powered genome-wide association studies (GWAS), we have gained not only many molecular clues as to the operation of mechanisms of differential susceptibility to a wide range of common health conditions, but also statistical polygenic predictors (the GPS) of the distribution of genetic risk in the population. In a [new study](#), Amit Khera, Mark Chaffin and colleagues show that, for populations of European ancestry where healthcare data have been systematically collected, such polygenic predictors can identify subsets of the population who are very likely to be at a threefold higher risk of a common disease relative to the remaining majority of the same population. These authors argue that not only are their GPSs classifying more of the higher-risk individuals than would be identified by genotyping rare monogenic causes of the same disease, but that for coronary artery disease the GPS identifies at-risk individuals whom it was not possible to identify using existing clinical measurements such as cholesterol, blood pressure or family history. This method was here shown to work reproducibly for five different diseases, with the group at threefold greater risk of disease ranging from 8% of the population (coronary artery disease) to 1.5% (breast cancer). Clearly, it will be some time before sufficient numbers are genotyped across the genome to provide risk prediction for a larger proportion of the population, even for common cancers.

Following up the implications of the small proportion of cancer risk so far predicted by common variants identified in GWAS, Clare Turnbull, Amit Sud and Richard Houlston offer a [Perspective](#) highlighting the strategies most needed to provide clinical benefit for population-wide cancer prevention programs informed by genetics of cancer predisposition. They point out that identification of familial mutations in DNA repair pathways (homologous repair deficiency in breast cancer and mismatch repair deficiency in colorectal cancer) still provides the best opportunity for early detection and intervention. These variants, some of the first predisposition mutations to be identified, are outliers on the graph of effect size versus allele frequency, either because they confer large relative risk or are over-represented in founder populations, or both. However, this Perspective emphasizes that there is a big opportunity left on the table: “... even in countries with well-developed genetics services, we have identified less than 10% of prevalent BRCA and MMR mutation carriers.” This failing means that even the real risk conferred by mutations in these genes is biased by ascertainment in cancer pedigrees and founder populations, meaning that real clinical benefit could be obtained by targeted, systematic sequence-based screening of whole populations. The Perspective emphasizes this aim at the expense of the much more difficult task of establishing the significance of novel rare constitutive variants in heretofore unstudied genes ascertained by systematic population sequencing of exomes or whole genomes.

In their [News & Views](#) on the GPS study, Andrew Schork, Anthony Schork

and Nicholas Schork are enthusiastic about the use of precision medicine via genomic prediction and raise most of the remaining issues that need to be addressed societally and experimentally if we are to make economic and health gains from the decades of highly reproducible genomic epidemiology research. First and foremost in our opinion is the issue of genomic equity: we need to know which variants and predictors work for which populations and which variants to use to characterize the effects of the trellis-like demographics of the human race on the risk profile of people of different combinations of ancestries. Secondly, they rightly highlight the use of existing diagnostics and biomarkers in the concept of time-limited risk prediction. Although the DNA variants each of us carries are preexisting at our birth, it is unlikely that they exert their effects evenly throughout our lives, so some of the harmonization of predictions based on clinical measurement and on GPSs will need to take into account age and disease courses.

So, we are open to publish research that not only extends the base of genomic variation that we can use in prediction, but also research into implementation of these GPS methods that demonstrably adds useful information for healthcare and economic planning, for clinical decision making, for medical education, and above all for the mechanistic understanding of, prevention and management of common and complex diseases. □

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