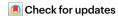# Editorial

# Genetic futurism

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**Large-scale genotyping and phenotyping efforts, including biobanks, have revolutionized our understanding of the genetic architecture of human traits and diseases. Years of ever-larger genome-wide association studies (GWAS) have produced a catalog of genetic variants that contribute to complex traits. A corollary of this research has been the development of personalized polygenic scores (PGS) or polygenic risk scores (PRS).**

PGS/PRS are calculated as a weighted sum of the genome-wide risk variants that are carried by a specific individual for a particular trait, and they provide a quantitative estimate of the likelihood that the individual will manifest the trait. Despite their potential utility for disease prediction and prevention, among other uses, PGS/PRS have notable limitations.

Typically, complex traits are influenced by thousands of variants, each of which makes only a small contribution to the overall variance of the trait. Furthermore, variants influencing complex traits are often identified by studying populations with specific characteristics (for example: genetic ancestry, sex/gender, or age biases), and the derived PGS/PRS may not generalize to other populations.

Finally, complex traits are influenced not only by genetics but also by environmental factors. Thus, great care must be used when producing, applying and interpreting PGS/PRS across populations, particularly in clinical settings.

This month, *Nature Genetics* is hosting a webcast that focuses on the development of new analytical tools and concepts in PGS/PRS research, as well as current challenges in using these tools, and future opportunities to augment their clinical and societal utility globally. After presentations by two leading researchers in this field, Michael Inouye and Naomi Wray, there will be an open discussion session, including questions from the audience.

In a thematically related Comment in this issue, Dov Greenbaum and Mark Gerstein present their thoughts on the predictive power of genetics and its potential societal implications. This piece was motivated by the 25th anniversary of the film *GATTACA*, which portrays a futuristic and dystopian society where every individual's role is determined at birth by analyzing their DNA and inferring their potential traits. In essence, in the world of *GATTACA*, life opportunities are strongly conditioned by PGS/PRS.

While the predictive accuracy of current PGS/PRS methods is far from the one depicted in *GATTACA*, the potential future misuse of PGS/PRS raises serious concerns, for example, by limiting individual freedoms and rights in an extreme scenario like *GATTACA*'s and by undervaluing the important contribution that the environment has in sculpting the phenotypic raw material provided by our genomes.

The debate regarding nature versus nurture is not new and is still ongoing. From a mechanistic perspective, our understanding of how genetic information interacts with external stimuli in a context-specific manner is far from complete. There is a growing appreciation that the functional impact of a given genetic variant often depends on its context. Key variables such as genomic background, cellular identity and state, developmental or physiological cues, age, sex and so on can modulate the activity of our genes. This view may seem obvious to some but it is not held universally. Many in the scientific and lay communities continue to see genetics as an essentially deterministic science. Fortunately, there are signs that the field is moving toward more nuanced context-aware approaches that are still firmly grounded in quantitation and statistical analysis.

Going forward, all branches of society will need to think deeply and broadly about how to leverage a growing body of genetic information to the benefit of all. New laws and regulations will likely need to be crafted to ensure that genetic data and PGS/PRS results do not transform into scientifically and morally dubious hurdles but instead contribute to improving people's lives and to building a more inclusive future.