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Current Controversy

Comment on *"polygenic scores: A public health hazard?"*

In his terrific essay ***"Polygenic Scores: a public health hazard?"*** Keith Baverstock (2019) takes a step by step approach and explains the many intellectual issues associated with using information technology analogies to describe how DNA sequence variation contributes to phenotypic variation in complex biological systems. He then goes on to discuss how gene scores derived from huge numbers of small effect size DNA sequence variants are unlikely to shed much causal light on complex phenotypes and also the common diseases that afflict most of humanity. In this brief commentary I want to wear my "clinical hat" and amplify what he has written with four additional points.

1) Most polygenic scores have very modest receiver operator curves and so-called C-statistics. This means that a gene score associated with higher than average risk for disease is likely to do a poor job of predicting who in fact gets the disease. It also means that most people with a high gene score will not become cases and most cases will occur in people with average or even lower risk gene scores (Cecile et al., 2019; Joyner et al., 2018; Saracci, 2018). Thus, generating useful gene score centric screening paradigms for large populations will be challenging.
2) In study after study, individuals in the top quartile or quintile of gene score "risk" do have greater disease risk. However, polygenic risk estimates are typically dwarfed by the effects of lifestyle factors on overall risk (Said et al., 2018). This means that a person with a "high" gene score risk but a healthy lifestyle is at lower risk than a person with a "low" gene score risk and an unhealthy lifestyle.
3) Even when there is evidence that a specific variant can have a large effect size in specific patients or families, when viewed in a larger population such variants frequently show declining penetrance (Wright et al., 2019).
4) There is little evidence that informing people about their genetic risk for a given disease leads to durable individual behavior change (Hollands et al., 2016).

Taken together these practical limitations amplify the deep intellectual and experimental critique of gene scores provided by Baverstock. They also support the idea that broad based, population wide interventions are the route to better public health. Gene scores simply are not going to solve the massive public health problems associated with hypertension, obesity, inactivity, smoking, violence, dirty water and air pollution along with the many other potentially actionable things that shorten the lives of many humans (Collaborators GBDRF, 2018).

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