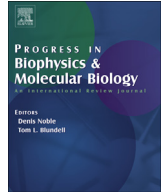




Contents lists available at ScienceDirect

## Progress in Biophysics and Molecular Biology

journal homepage: [www.elsevier.com/locate/pbiomolbio](http://www.elsevier.com/locate/pbiomolbio)

## 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 GBD, 2018](#)).

## References

- [Baverstock, K., 2019](#). Polygenic scores: a public health hazard? *Prog. Biophys. Mol. Biol.* (in press).
- [Cecile, A., Janssens, J.W., Joyner, M.J., 2019](#). Polygenic risk scores that predict common diseases using millions of single nucleotide polymorphisms: is more, better? *Clin. Chem.* 65 (5), 609–611. <https://doi.org/10.1373/clinchem.2018.296103>. Epub 2019/02/28, PubMed PMID: 30808642.
- [Collaborators GBD, 2018](#). Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 392 (10159), 1923–1994. [https://doi.org/10.1016/S0140-6736\(18\)32225-6](https://doi.org/10.1016/S0140-6736(18)32225-6). Epub 2018/11/30, PubMed PMID: 30496105; PMID: PMC6227755.
- [Hollands, G.J., French, D.P., Griffin, S.J., Prevost, A.T., Sutton, S., King, S., Marteau, T.M., 2016](#). The impact of communicating genetic risks of disease on risk-reducing health behaviour: systematic review with meta-analysis. *BMJ* 352, i1102. <https://doi.org/10.1136/bmj.i1102>. Epub 2016/03/17, PubMed PMID: 26979548; PMID: PMC4793156.
- [Joyner M.J., Paneth N, Janssens AC, Cooper R. Associations of Combined Genetic and Lifestyle Risks with Incident Cardiovascular Disease and Diabetes in the UK Biobank Study.](#) <https://www.acc.org/latest-in-cardiology/articles/2018/12/11/12/10/associations-of-combined-genetic-and-lifestyle-risks-with-incident-cv-disease>. American College of Cardiology: CardioSource Plus for Institutions 2018.
- [Said, M.A., Verweij, N., van der Harst, P., 2018](#). Associations of combined genetic and lifestyle risks with incident cardiovascular disease and diabetes in the UK biobank study. *JAMA Cardiol.* 3 (8), 693–702. <https://doi.org/10.1001/jamacardio.2018.1717>. Epub 2018/06/30, PubMed PMID: 29955826; PMID: PMC6143077.
- [Saracci, R., 2018](#). Epidemiology in wonderland: big Data and precision medicine. *Eur. J. Epidemiol.* 33 (3), 245–257. <https://doi.org/10.1007/s10654-018-0385-9>. Epub 2018/04/07, PubMed PMID: 29623670.
- [Wright, C.F., West, B., Tuke, M., Jones, S.E., Patel, K., Laver, T.W., Beaumont, R.N., Tyrrell, J., Wood, A.R., Frayling, T.M., Hattersley, A.T., Weedon, M.N., 2019](#). Assessing the pathogenicity, penetrance, and expressivity of putative disease-causing variants in a population setting. *Am. J. Hum. Genet.* 104 (2), 275–286. <https://doi.org/10.1016/j.ajhg.2018.12.015>. Epub 2019/01/23, PubMed PMID: 30665703; PMID: PMC6369448.

Michael J. Joyner

Department of Anesthesiology and Perioperative Medicine, Mayo Clinic, Rochester, MN, 55902, USA

E-mail address: [joyner.michael@mayo.edu](mailto:joyner.michael@mayo.edu).

Available online xxx