Addressing the challenges of polygenic scores in human genetic research

John Novembre,[1,2,3,15,*] Catherine Stein,[1,4,15,*] Samira Asgari,[1,5] Claudia Gonzaga-Jauregui,[1,6] Andrew Landstrom,[1,7] Amy Lemke,[1,8] Jun Li,[1,9] Chloe Mighton,[1,10,11] Matthew Taylor,[1,12] and Sarah Tishkoff[1,13,14]

Summary

The genotyping of millions of human samples has made it possible to evaluate variants across the human genome for their possible association with risks for numerous diseases and other traits by using genome-wide association studies (GWASs). The associations between phenotype and genotype found in GWASs make possible the construction of polygenic scores (PGSs), which aim to predict a trait or disease outcome in an individual on the basis of their genotype (in the disease case, the term polygenic risk score [PRS] is often used). PGSs have shown promise for studying the biology of complex traits and as a tool for evaluating individual disease risks in clinical settings. Although the quantity and quality of data to compute PGSs are increasing, challenges remain in the technical aspects of developing PGSs and in the ethical and social issues that might arise from their use. This ASHG Guidance emphasizes three major themes for researchers working with or interested in the application of PGSs in their own research: (1) developing diverse research cohorts; (2) fostering robustness in the development, application, and interpretation of PGSs; and (3) improving the communication of PGS results and their implications to broad audiences.

Introduction

One of the major growth areas in human genetics over the past decade has been the development and application of polygenic scores (PGSs). PGSs aim to provide an indicator of the genetic propensity of an individual to manifest a particular disease or trait relative to other individuals in the cohort on the basis of his or her DNA variants across the genome. As a statistical instrument derived solely from a person's genotypes, a PGS does not depend on phenotype data of family members. Because most associated variants are not causal variants, a PGS goes beyond using high-impact variants for understanding monogenic diseases and does not depend on the characterization of causal genetic variants or the disease mechanisms. Commonly, PGSs are generated by using variants discovered in one or several genome-wide association studies (GWASs). Although more statistically advanced approaches have been developed,[1] in the simplest form, a PGS is a sum of trait-associated alleles, one for each independently associated region, weighted by estimates of their average effect size in a "Discovery GWAS." The conceptual foundation of PGSs has its roots in approaches developed in quantitative genetics, especially for applied problems in plant and animal breeding.[2] The development and use of PGSs in humans presents both new opportunities and challenges. We discuss these here and offer several recommendations for future research and use (see Box 1).

This ASHG Guidance was developed by a writing group led by members of the Professional Practice and Social Implications Committee to discuss and provide recommendations on three major issues related to the technical, ethical, and social considerations of PGSs. It was approved by the ASHG Board of Directors for publication in October, 2022. A series of related, independent guidances on PGSs in clinical practice is in development by colleagues in the American College of Medical Genetics and Genomics (ACMG), and we also refer readers to other recently published commentaries.[3,4]

Develop diverse research cohorts and analyses

Several limitations of PGSs arise from the lack of diverse cohort data in PGS development. The accuracy of a PGS

[1]Professional Practice and Social Implications Committee Polygenic Scores Guidance Writing Group, American Society of Human Genetics, Rockville MD, USA; [2]Department of Human Genetics, University of Chicago, Chicago, IL, USA; [3]Department of Ecology and Evolution, University of Chicago, Chicago, IL, USA; [4]Department of Population and Quantitative Health Sciences, Case Western Reserve University, Cleveland, OH, USA; [5]Institute for Genomic Health, Icahn School of Medicine at Mount Sinai, New York, NY, USA; [6]International Laboratory for Human Genome Research, Laboratorio Internacional de Investigación sobre el Genoma Humano, Universidad Nacional Autónoma de México, Juriquilla, Querétaro, México; [7]Department of Pediatrics, Division of Cardiology, Duke University School of Medicine, Durham, NC, USA; [8]Norton Children's Research Institute, affiliated with the University of Louisville School of Medicine, Louisville, KY, USA; [9]Department of Human Genetics, University of Michigan, Ann Arbor, MI, USA; [10]Genomics Health Services Research Program, St. Michael's Hospital, Unity Health Toronto, Toronto, ON, Canada; [11]Institute of Health Policy, Management and Evaluation, Dalla Lana School of Public Health, University of Toronto, Toronto, ON, Canada; [12]Adult Medical Genetics Program, Department of Medicine, University of Colorado Anschutz Medical Campus, Aurora, CO, USA; [13]Department of Genetics, Center for Global Genomics and Health Equity, University of Pennsylvania, Philadelphia, PA, USA; [14]Department of Biology, Center for Global Genomics and Health Equity, University of Pennsylvania, Philadelphia, PA, USA
[15]These authors contributed equally
*Correspondence: jnovembre@uchicago.edu (J.N.), cmj7@case.edu (C.S.)
https://doi.org/10.1016/j.ajhg.2022.10.012.

Box 1. Recommendations for future development and use of PGSs

1. Develop diverse research cohorts and analyses.
2. Foster robustness in scientific development, validation, application, and interpretation of PGSs.
3. Accompany research products with communications materials for broad, non-specialist audiences.

might be compromised when applied to a cohort that differs in key demographic characteristics from the discovery cohort(s) used to develop the PGS.[5–7] This is known as the PGS portability problem (sometimes also called the generalizability problem or transferability problem). Several factors contribute to the portability problem—although the relative importance of each is still an open topic of research. First, linkage disequilibrium (LD) varies across human populations, and because PGSs are based on marker loci that are in LD with the as-yet-unknown causal loci, inaccuracies will be introduced if one assumes the GWAS marker loci have the same LD with causal loci in different populations.[8] Fine-mapping approaches that aim to identify causal loci can help ameliorate this problem.[9] Second, different causal alleles will be at different frequencies (or even absent) in different populations. At a global scale, a variant common in one region is more likely to be found in several others, whereas rare variants are more likely to be localized.[10,11] Third, even causal variants that are shared might have differing average effect sizes in different populations (e.g., see Shi et al.[12]). One potential cause is differing genetic backgrounds between discovery and application cohorts, which might give rise to different average effect sizes as a result of gene-gene interactions (i.e., epistasis, e.g., see Patel et al.[13]). Another potential cause is a different distribution of non-genetic individual risk factors between the discovery and implementation cohorts, when such factors moderate the effect of a genotype. Such factors are varied and phenotype dependent; examples include age, sex, diet, pollutant exposure, access to healthcare, and gut microbiome composition. In quantitative and statistical genetics, these factors are often collectively referred to as "environment," and they induce what are known as "genotype-by-environment interactions" or "context-dependent effects." In the context of PGSs, exposures to different environmental backgrounds, perhaps because of sex, age, or socioeconomic status, have been shown to impact the accuracy of some PGSs,[6] and some traits appear to show context-dependent heritability,[14] which implies variable predictive ability of PGSs.

As a result of the portability problem, there might be diminished applicability of PGSs for individuals under-represented in genetic studies, potentially misrepresenting disease risk and exacerbating health inequities.[5,15–17] Lower accuracy and higher bias of PGSs might arise for individuals whose genetic and environmental backgrounds are not well represented in the GWASs that underlie a particular PGS. This variation in the usefulness of a PGS for particular individuals might lead to varied opportunities to realize potentially beneficial management strategies. For instance, as a result of better representation in GWASs to date, individuals of European ancestry can expect a higher predictive accuracy from PGSs for phenotypes such as cardiovascular disease, breast and prostate cancer, and diabetes, resulting in better clinical surveillance and management as well as targeted therapy recommendations.[5,16,18–21] Furthermore, under-represented and marginalized groups often experience environmental health disparities, such as pollutant exposures, nutrition deficits, or lack of access to clean water or basic healthcare. These environmental backgrounds can potentially exacerbate portability challenges due to genotype-environment interactions,[22] in turn accentuating equity concerns in the applicability of PGSs.[4]

Given these problems, we recommend that future development of PGSs incorporate increased cohort diversity along multiple dimensions (e.g., ancestry, age, sex, healthcare access, and other environmental variables relevant to focal phenotypes). Specifically, funding agencies and researchers should aim to build more diverse cohorts and make the best use of such resources via collaborative data sharing.[3] Over the past few years several such efforts, including the *All of Us*, *H3Africa*, and the *Trans-Omics for Precision Medicine* (*TOPMed*) programs (see Web Resources), have been launched with the goal of increasing the diversity and representation of previously understudied groups in human genomics research and better understanding the contribution of genetic and environmental factors on disease risks.

We also recommend more research efforts directed toward developing and implementing computational methods that address issues associated with the inclusion of diverse and heterogeneous datasets. Pan-ancestry or meta-ancestry GWASs are helping to identify trait-associated variants that are more likely to replicate broadly; these variants can then be used for PGS construction.[23] As mentioned above, fine-mapping approaches can help mitigate one aspect of the portability problem.[24] Further, given the potential for gene-environment interactions, more effort on understanding and incorporating these interactions is needed.[25] Assessing and reporting the accuracy of a PGS across different subsets within a test sample is one means to understanding whether problems of generalizability in a PGS might exist.[5,6]

When one increases diversity in research cohorts, there is the potential for unintended group harm. Efforts should be made to avoid the application of genetics study results that might stigmatize or discriminate against vulnerable populations. Guidance on this topic is presented in a recent Perspective article by ASHG[26] and in another ASHG Guidance for researchers on effective community engagement.[27]

Foster robustness in scientific development, validation, application, and interpretation of PGSs

Numerous technical challenges arise when developing and applying PGSs for research, and researchers are encouraged to consider them each carefully in their work.

First, the accuracy of the effect size estimates used in a PGS depend on the sample size of the reference GWAS, the genotyping (or imputation) accuracy, the precision of the trait measurement, and GWAS modeling decisions, such as those regarding batch-correction and adjustment for covariates.[1,28–31] During estimation of effect sizes in the reference GWAS, a correlation between a variant genotype and unobserved environmental factors ("environmental confounding") or between a variant genotype and genetic background ("genetic confounding") can lead to inaccurate effect-size estimates.[32–34] In addition, traits that serve as a basis for assortative mating (such as height and other physical traits, educational attainment and other behavioral traits, and traits correlated with those traits) are especially prone to biases in effect-size estimates because assortative mating induces a correlation between causal variants for different traits, as well as between variants and unobserved shared environments between parents.[35,36] Importantly, commonly accepted methods of addressing these confounders, such as including principal components (PCs) based on common variants as covariates, are not always effective at preventing all confounding effects (for example, effects of recent, rare variants and more localized environmental effects,[37,38] differences in local LD among groups,[39] and confounding of direct and indirect genetic effects).[40]

Second, most PGS calculations assume a lack of interaction and correlation between genetic and non-genetic factors. Such genotype-by-environment interactions and correlations create two major limitations for the use of PGSs: (1) a difference in environmental backgrounds between the GWAS cohort and target individuals can have unpredictable effects on PGS accuracy and biases[6]; and (2) the interaction and correlation between a PGS and environmental variables can induce a "collider bias" that undermines the use of the PGS as a covariate in modeling a trait.[41] For complex social and environmentally mediated traits, interactions of genotype and environment (as well as indirect genetic effects) might be particularly important, and thus we recommend special care in interpreting PGSs for such traits[42,43]).

Third, in many cases there are multiple reference GWASs available for the same trait, and new ones are emerging.[44] In such cases, one might choose to build a PGS on the basis of the single "best" GWAS or attempt a meta-analysis approach to building the PGS.[45,46] Meta-analysis brings its own set of technical challenges, such as variation across studies in cohort definitions, trait definitions, trait measurement procedures, genotyping strategies, and corrections for confounding factors made in earlier steps of each GWAS. Often the same set of environmental covariates is not available, or the covariates are not measured in the same way in the reference studies and in the individual for whom the PGS is being calculated, making the resulting PGS vulnerable to the unknown contributions of these factors even within individuals of similar genetic ancestry.[6]

Fourth, specific challenges arise in using PGSs to study how specific traits have differentiated across groups. Such studies are often undertaken to address evolutionary questions, such as whether traits have changed as a result of directional selection, genetic drift, or stabilizing selection in changing environments.[47,48] However, largely as a result of several of the technical challenges already described, to date, robust interpretations of such results are limited,[33,47,49,50] and the methodological and interpretation challenges of these approaches are still being understood.[48,51]

Although the issues described above are diverse, we recommend a concerted effort by researchers developing and applying PGSs to consider these issues in their analyses. In particular, careful attention to emerging best practices and standards is highly recommended,[46,52,53] and while reviewing research manuscripts and grants, scientists should be cognizant of the challenges described above and encourage authors to address limitations of these approaches. Because many of these issues will most likely require additional methodological development, we strongly recommend further research in this area.

Accompany research products with communications materials for broad, non-specialist audiences

In order to mitigate unintended consequences of research and downstream application of PGSs, researchers should make directed efforts to communicate limitations when sharing and reporting results. This is especially important because genetic concepts and genetic risk information can be misunderstood by the public.[54–57] One strategy for addressing this could include an online frequently asked questions (FAQs) resource to accompany an original manuscript to guide journalists, lay people, and other researchers regarding the scope of application of the PGS developed and its limitations (for examples see Clarke and van El[58]). Researchers should also engage the communities being studied and their university or institutional press office to produce targeted press releases that help to address common misunderstandings and prevent potential individual and group harms,[59] such as negative psychosocial effects and genetic discrimination,[60] that might arise from such misunderstandings.[61] We recommend engaging community stakeholders and colleagues dedicated to ethical, legal, and social issues during the development of communication materials to improve the relevance and readability of these materials for broad audiences, especially in light of recent negative impacts on communities studied or affected by genetics research that utilized PGSs.[62,63] Adopting principles of user-centered design[64–66] might also promote the development of effective communication materials tailored to the needs of members of the relevant audience.[67–70]

In certain cases, a research team might wish to indicate in its publications or other online summaries of their GWAS results that these are intended for research purposes only, to discourage inappropriate or premature application of these metrics by, for example, direct-to-consumer genetic-testing companies.[71,72] In addition, within research papers and derivative works, researchers should adopt data-visualization and -reporting practices that clearly convey individual-level error across the whole sample and within substrata of the data (age, gender, ethnicity/race/ancestry categories, SES groupings) or indicate when such stratified analyses are not feasible. If the PGS shows between-group differences, it must be reported with caution, especially if the trait has strong social repercussions. There is the potential that variation in the PGS across populations could be used in a racist, sexist, or otherwise discriminatory way to explain differences between populations.[4] Other potential risks associated with inappropriate communication of PGSs include promoting attitudes of genetic determinism and de-emphasizing the role of social determinants of health[4,59]).

Conclusion

The development of methods to derive and improve PGSs and the application of these methods for numerous clinical outcomes and phenotypes of interest are ongoing and very active areas of research. Therefore, strategies and considerations aimed at improving the appropriate and equitable implementation of PGSs in research and clinical care will continue to evolve. However, given the increasing use of PGSs in both clinical and research applications, it is important for researchers to examine the current challenges and limitations of working with PGSs. This ASHG Guidance proposes three major recommendations to help address some of these challenges. As future work moves forward in this area, it is critical for researchers to pro-actively consider, apply, and build upon these recommendations in order to avoid misapplication of PGSs. Overall, a more comprehensive approach addressing increased diversity in human genetics and genomics studies, improved methodology in PGS development, and more clear communication with the public will help achieve the promise of PGSs in basic and clinical research.

Acknowledgments

Many thanks to Kiran Musunuru, who was the ASHG Board of Directors liaison in preparing this ASHG Guidance, and also thanks to Derek Scholes, Lyly Luhachack, and Karina Miller for their invaluable contributions during their time at ASHG. We also thank our consultants, who provided insightful feedback into an earlier version of this piece: Dalton Conley, Arbel Harpak, Iain Mathieson, Anya Prince, Jennifer Wagner, and Alicia Zhou.

Web resources

All of Us Research Program, https://allofus.nih.gov/
H3Africa consortium, https://h3africa.org/
Trans-Omics for Precision Medicine (TOPMed), https://www.nhlbi.nih.gov/science/trans-omics-precision-medicine-topmed-program

References

1. Ma, Y., and Zhou, X. (2021). Genetic prediction of complex traits with polygenic scores: a statistical review. Trends Genet. *37*, 995–1011.
2. Wray, N.R., Kemper, K.E., Hayes, B.J., Goddard, M.E., and Visscher, P.M. (2019). Complex Trait Prediction from Genome Data: Contrasting EBV in Livestock to PRS in Humans: Genomic Prediction. Genetics *211*, 1131–1141.
3. McCarthy, M., and Birney, E. (2021). Personalized profiles for disease risk must capture all facets of health. Nature *597*, 175–177.
4. Polygenic Risk Score Task Force of the International Common Disease Alliance (2021). Responsible use of polygenic risk scores in the clinic: potential benefits, risks and gaps. Nat. Med. *27*, 1876–1884.
5. Martin, A.R., Kanai, M., Kamatani, Y., Okada, Y., Neale, B.M., and Daly, M.J. (2019). Clinical use of current polygenic risk scores may exacerbate health disparities. Nat. Genet. *51*, 584–591.
6. Mostafavi, H., Harpak, A., Agarwal, I., Conley, D., Pritchard, J.K., and Przeworski, M. (2020). Variable prediction accuracy of polygenic scores within an ancestry group. Elife *9*, e48376. https://doi.org/10.7554/eLife.48376.
7. Privé, F., Aschard, H., Carmi, S., Folkersen, L., Hoggart, C., O'Reilly, P.F., and Vilhjálmsson, B.J. (2022). Portability of 245 polygenic scores when derived from the UK Biobank and applied to 9 ancestry groups from the same cohort. Am. J. Hum. Genet. *109*, 12–23.
8. Carlson, C.S., Matise, T.C., North, K.E., Haiman, C.A., Fesinmeyer, M.D., Buyske, S., Schumacher, F.R., Peters, U., Franceschini, N., Ritchie, M.D., et al. (2013). Generalization and dilution of association results from European GWAS in populations of non-European ancestry: the PAGE study. PLoS Biol. *11*, e1001661.
9. Amariuta, T., Ishigaki, K., Sugishita, H., Ohta, T., Koido, M., Dey, K.K., Matsuda, K., Murakami, Y., Price, A.L., Kawakami, E., et al. (2020). Improving the trans-ancestry portability of polygenic risk scores by prioritizing variants in predicted cell-type-specific regulatory elements. Nat. Genet. *52*, 1346–1354.
10. 1000 Genomes Project Consortium, Auton, A., Brooks, L.D., Durbin, R.M., Garrison, E.P., Kang, H.M., Korbel, J.O., Marchini, J.L., McCarthy, S., McVean, G.A., and Abecasis, G.R. (2015). A global reference for human genetic variation. Nature *526*, 68–74.
11. Biddanda, A., Rice, D.P., and Novembre, J. (2020). A variant-centric perspective on geographic patterns of human allele frequency variation. Elife *9*, e60107. https://doi.org/10.7554/eLife.60107.
12. Shi, H., Gazal, S., Kanai, M., Koch, E.M., Schoech, A.P., Siewert, K.M., Kim, S.S., Luo, Y., Amariuta, T., Huang, H., et al. (2021). Population-specific causal disease effect sizes in functionally important regions impacted by selection. Nat. Commun. *12*, 1098.
13. Patel, R.A., Musharoff, S.A., Spence, J.P., Pimentel, H., Tcheandjieu, C., Mostafavi, H., Sinnott-Armstrong, N., Clarke, S.L., Smith, C.J.; and V.A. Million Veteran Program (2022).

Genetic interactions drive heterogeneity in causal variant effect sizes for gene expression and complex traits. Am. J. Hum. Genet. *109*, 1286–1297.
14. Dahl, A., Nguyen, K., Cai, N., Gandal, M.J., Flint, J., and Zaitlen, N. (2020). A Robust Method Uncovers Significant Context-Specific Heritability in Diverse Complex Traits. Am. J. Hum. Genet. *106*, 71–91.
15. Bustamante, C.D., Burchard, E.G., and De la Vega, F.M. (2011). Genomics for the world. Nature *475*, 163–165.
16. Popejoy, A.B., and Fullerton, S.M. (2016). Genomics is failing on diversity. Nature *538*, 161–164.
17. Ju, D., Hui, D., Hammond, D.A., Wonkam, A., and Tishkoff, S.A. (2022). Importance of Including Non-European Populations in Large Human Genetic Studies to Enhance Precision Medicine. Annu. Rev. Biomed. Data Sci. *5*, 321–339. https://doi.org/10.1146/annurev-biodatasci-122220-112550.
18. Need, A.C., and Goldstein, D.B. (2009). Next generation disparities in human genomics: concerns and remedies. Trends Genet. *25*, 489–494.
19. Maas, P., Barrdahl, M., Joshi, A.D., Auer, P.L., Gaudet, M.M., Milne, R.L., Schumacher, F.R., Anderson, W.F., Check, D., Chattopadhyay, S., et al. (2016). Breast Cancer Risk From Modifiable and Nonmodifiable Risk Factors Among White Women in the United States. JAMA Oncol. *2*, 1295–1302.
20. Knowles, J.W., and Ashley, E.A. (2018). Cardiovascular disease: The rise of the genetic risk score. PLoS Med. *15*, e1002546.
21. Khera, A.V., Chaffin, M., Aragam, K.G., Haas, M.E., Roselli, C., Choi, S.H., Natarajan, P., Lander, E.S., Lubitz, S.A., Ellinor, P.T., and Kathiresan, S. (2018). Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations. Nat. Genet. *50*, 1219–1224.
22. Favé, M.J., Lamaze, F.C., Soave, D., Hodgkinson, A., Gauvin, H., Bruat, V., Grenier, J.C., Gbeha, E., Skead, K., Smargiassi, A., et al. (2018). Gene-by-environment interactions in urban populations modulate risk phenotypes. Nat. Commun. *9*, 827.
23. Ruan, Y., Lin, Y.-F., Feng, Y.-C.A., Chen, C.-Y., Lam, M., Guo, Z., Stanley Global Asia Initiatives, He, L., Sawa, A., Martin, A.R., et al. (2022). Improving polygenic prediction in ancestrally diverse populations. Nat. Genet. *54*, 573–580.
24. Weissbrod, O., Kanai, M., Shi, H., Gazal, S., Peyrot, W.J., Khera, A.V., Okada, Y., Biobank Japan Project, Martin, A.R., Finucane, H.K., and Price, A.L. (2022). Leveraging fine-mapping and multipopulation training data to improve cross-population polygenic risk scores. Nat. Genet. *54*, 450–458.
25. Domingue, B.W., Trejo, S., Armstrong-Carter, E., and Tucker-Drob, E.M. (2020). Interactions between polygenic scores and environments: Methodological and conceptual challenges. Sociol. Sci. *7*, 465–486.
26. (2020 Sep 3). Advancing Diverse Participation in Research with Special Consideration for Vulnerable Populations. Am. J. Hum. Genet. *107*, 379–380. https://doi.org/10.1016/j.ajhg.2020.08.011.
27. Lemke, A.A., Esplin, E.D., Goldenberg, A.J., Gonzaga-Jauregui, C., Hanchard, N.A., Harris-Wai, J., Ideozu, J.E., Isasi, R., Landstrom, A.P., Prince, A.E.R., et al. (2022). Addressing underrepresentation in genomics research through community engagement. Am. J. Hum. Genet. *109*, 1563–1571.
28. Dudbridge, F. (2013). Power and predictive accuracy of polygenic risk scores. PLoS Genet. *9*, e1003348.
29. Roshyara, N.R., Horn, K., Kirsten, H., Ahnert, P., and Scholz, M. (2016). Comparing performance of modern genotype imputation methods in different ethnicities. Sci. Rep. *6*, 34386.
30. Chen, S.-F., Dias, R., Evans, D., Salfati, E.L., Liu, S., Wineinger, N.E., and Torkamani, A. (2020). Genotype imputation and variability in polygenic risk score estimation. Genome Med. *12*, 100.
31. Li, J.H., Mazur, C.A., Berisa, T., and Pickrell, J.K. (2021). Low-pass sequencing increases the power of GWAS and decreases measurement error of polygenic risk scores compared to genotyping arrays. Genome Res. *31*, 529–537.
32. Haworth, S., Mitchell, R., Corbin, L., Wade, K.H., Dudding, T., Budu-Aggrey, A., Carslake, D., Hemani, G., Paternoster, L., Smith, G.D., et al. (2019). Apparent latent structure within the UK Biobank sample has implications for epidemiological analysis. Nat. Commun. *10*, 333.
33. Barton, N., Hermisson, J., and Nordborg, M. (2019). Why structure matters. Elife *8*, e45380.
34. Lawson, D.J., Davies, N.M., Haworth, S., Ashraf, B., Howe, L., Crawford, A., Hemani, G., Davey Smith, G., and Timpson, N.J. (2020). Is population structure in the genetic biobank era irrelevant, a challenge, or an opportunity? Hum. Genet. *139*, 23–41.
35. Domingue, B.W., Fletcher, J., Conley, D., and Boardman, J.D. (2014). Genetic and educational assortative mating among US adults. Proc. Natl. Acad. Sci. USA *111*, 7996–8000.
36. Young, A.I., Benonisdottir, S., Przeworski, M., and Kong, A. (2019). Deconstructing the sources of genotype-phenotype associations in humans. Science *365*, 1396–1400.
37. Mathieson, I., and McVean, G. (2012). Differential confounding of rare and common variants in spatially structured populations. Nat. Genet. *44*, 243–246.
38. Zaidi, A.A., and Mathieson, I. (2020). Demographic history mediates the effect of stratification on polygenic scores. Elife *9*, e61548. https://doi.org/10.7554/eLife.61548.
39. Berg, J.J., Harpak, A., Sinnott-Armstrong, N., Joergensen, A.M., Mostafavi, H., Field, Y., Boyle, E.A., Zhang, X., Racimo, F., Pritchard, J.K., and Coop, G. (2019). Reduced signal for polygenic adaptation of height in UK Biobank. Elife *8*, e39725. https://doi.org/10.7554/eLife.39725.
40. Wu, Y., Zhong, X., Lin, Y., Zhao, Z., Chen, J., Zheng, B., Li, J.J., Fletcher, J.M., and Lu, Q. (2021). Estimating genetic nurture with summary statistics of multigenerational genome-wide association studies. Proc. Natl. Acad. Sci. USA *118*. e2023184118. https://doi.org/10.1073/pnas.2023184118.
41. Akimova, E.T., Breen, R., Brazel, D.M., and Mills, M.C. (2021). Gene-environment dependencies lead to collider bias in models with polygenic scores. Sci. Rep. *11*, 9457.
42. Adam, D. (2019). The promise and peril of the new science of social genomics. Nature *574*, 618–620.
43. Harden, K.P. (2021). Reports of my death were greatly exaggerated": Behavior genetics in the postgenomic era. Annu. Rev. Psychol. *72*, 37–60.
44. Lambert, S.A., Gil, L., Jupp, S., Ritchie, S.C., Xu, Y., Buniello, A., McMahon, A., Abraham, G., Chapman, M., Parkinson, H., et al. (2021). The Polygenic Score Catalog as an open database for reproducibility and systematic evaluation. Nat. Genet. *53*, 420–425.
45. Winkler, T.W., Locke, A.E., Mägi, R., Ferreira, T., Fall, T., Graff, M., Justice, A.E., , et al.; The Genetic Investigation of Anthropometric Traits (GIANT) Consortium, Day, F.R., Croteau-Chonka, D.C., Wood, A.R. (2014). Quality control and conduct of genome-wide association meta-analyses. Nat. Protoc. *9*, 1192–1212.

46. Uffelmann, E., Huang, Q.Q., Munung, N.S., de Vries, J., Okada, Y., Martin, A.R., Martin, H.C., Lappalainen, T., and Posthuma, D. (2021). Genome-wide association studies. Nat. Rev. Methods Primers *1*, 59.
47. Berg, J.J., and Coop, G. (2014). A population genetic signal of polygenic adaptation. PLoS Genet. *10*, e1004412.
48. Harpak, A., and Przeworski, M. (2021). The evolution of group differences in changing environments. PLoS Biol. *19*, e3001072.
49. Novembre, J., and Barton, N.H. (2018). Tread lightly interpreting polygenic tests of selection. Genetics *208*, 1351–1355.
50. Rosenberg, N.A., Edge, M.D., Pritchard, J.K., and Feldman, M.W. (2019). Interpreting polygenic scores, polygenic adaptation, and human phenotypic differences. Evol. Med. Public Health *2019*, 26–34.
51. Yair, S., and Coop, G. (2022). Population differentiation of polygenic score predictions under stabilizing selection. Philos. Trans. R. Soc. Lond. B Biol. Sci. *377*, 20200416.
52. Choi, S.W., Mak, T.S.-H., and O'Reilly, P.F. (2020). Tutorial: a guide to performing polygenic risk score analyses. Nat. Protoc. *15*, 2759–2772.
53. Wand, H., Lambert, S.A., Tamburro, C., Iacocca, M.A., O'Sullivan, J.W., Sillari, C., Kullo, I.J., Rowley, R., Dron, J.S., Brockman, D., et al. (2021). Improving reporting standards for polygenic scores in risk prediction studies. Nature *591*, 211–219.
54. Sivell, S., Elwyn, G., Gaff, C.L., Clarke, A.J., Iredale, R., Shaw, C., Dundon, J., Thornton, H., and Edwards, A. (2008). How risk is perceived, constructed and interpreted by clients in clinical genetics, and the effects on decision making: systematic review. J. Genet. Counsel. *17*, 30–63.
55. Leighton, J.W., Valverde, K., and Bernhardt, B.A. (2012). The general public's understanding and perception of direct-to-consumer genetic test results. Public Health Genomics *15*, 11–21.
56. Lautenbach, D.M., Christensen, K.D., Sparks, J.A., and Green, R.C. (2013). Communicating genetic risk information for common disorders in the era of genomic medicine. Annu. Rev. Genom. Hum. Genet. *14*, 491–513.
57. Peck, L., Borle, K., Folkersen, L., and Austin, J. (2022). Why do people seek out polygenic risk scores for complex disorders, and how do they understand and react to results? Eur. J. Hum. Genet. *30*, 81–87.
58. Martschenko, D.O., Domingue, B.W., Matthews, L.J., and Trejo, S. (2021). FoGS provides a public FAQ repository for social and behavioral genomic discoveries. Nat. Genet. *53*, 1272–1274.
59. Clarke, A.J., and van El, C.G. (2022). Genomics and justice: mitigating the potential harms and inequities that arise from the implementation of genomics in medicine. Hum. Genet. *141*, 1099–1107.
60. Green, R.C., Lautenbach, D., and McGuire, A.L. (2015). GINA, genetic discrimination, and genomic medicine. N. Engl. J. Med. *372*, 397–399.
61. Lázaro-Muñoz, G., Sabatello, M., Huckins, L., Peay, H., Degenhardt, F., Meiser, B., Lencz, T., Soda, T., Docherty, A., Crepaz-Keay, D., et al. (2019). International Society of Psychiatric Genetics Ethics Committee: Issues facing us. Am. J. Med. Genet. B Neuropsychiatr. Genet. *180*, 543–554.
62. Mudd-Martin, G., Cirino, A.L., Barcelona, V., Fox, K., Hudson, M., Sun, Y.V., Taylor, J.Y., Cameron, V.A.; and American Heart Association Council on Genomic and Precision Medicine; Council on Cardiovascular and Stroke Nursing; and Council on Clinical Cardiology (2021). Considerations for cardiovascular genetic and genomic research with marginalized racial and ethnic groups and indigenous peoples: a scientific statement from the american heart association. Circ. Genom. Precis. Med. *14*, e000084.
63. Sanderson, K. (2021). High-profile autism genetics project paused amid backlash. Nature *598*, 17–18.
64. Gould, J.D., and Lewis, C. (1985). Designing for usability: key principles and what designers think. Commun. ACM *28*, 300–311.
65. Kujala, S. (2003). User involvement: A review of the benefits and challenges. Behav. Inf. Technol. *22*, 1–16.
66. Vaisson, G., Provencher, T., Dugas, M., Trottier, M.È., Chipenda Dansokho, S., Colquhoun, H., Fagerlin, A., Giguere, A.M.C., Hakim, H., Haslett, L., et al. (2021). User Involvement in the Design and Development of Patient Decision Aids and Other Personal Health Tools: A Systematic Review. Med. Decis. Making *41*, 261–274.
67. Bombard, Y., Clausen, M., Mighton, C., Carlsson, L., Casalino, S., Glogowski, E., Schrader, K., Evans, M., Scheer, A., Baxter, N., et al. (2018). The Genomics ADvISER: development and usability testing of a decision aid for the selection of incidental sequencing results. Eur. J. Hum. Genet. *26*, 984–995.
68. Reumkens, K., Tummers, M.H.E., Gietel-Habets, J.J.G., van Kuijk, S.M.J., Aalfs, C.M., van Asperen, C.J., Ausems, M.G.E.M., Collée, M., Dommering, C.J., Kets, C.M., et al. (2019). The development of an online decision aid to support persons having a genetic predisposition to cancer and their partners during reproductive decision-making: a usability and pilot study. Fam. Cancer *18*, 137–146.
69. Suckiel, S.A., Odgis, J.A., Gallagher, K.M., Rodriguez, J.E., Watnick, D., Bertier, G., Sebastin, M., Yelton, N., Maria, E., Lopez, J., et al. (2021). GUÍA: a digital platform to facilitate result disclosure in genetic counseling. Genet. Med. *23*, 942–949.
70. Brockman, D.G., Petronio, L., Dron, J.S., Kwon, B.C., Vosburg, T., Nip, L., Tang, A., O'Reilly, M., Lennon, N., Wong, B., et al. (2021). Design and user experience testing of a polygenic score report: a qualitative study of prospective users. BMC Med. Genom. *14*, 238.
71. Turley, P., Meyer, M.N., Wang, N., Cesarini, D., Hammonds, E., Martin, A.R., Neale, B.M., Rehm, H.L., Wilkins-Haug, L., Benjamin, D.J., et al. (2021). Problems with Using Polygenic Scores to Select Embryos. N. Engl. J. Med. *385*, 78–86.
72. Forzano, F., Antonova, O., Clarke, A., de Wert, G., Hentze, S., Jamshidi, Y., Moreau, Y., Perola, M., Prokopenko, I., Read, A., et al. (2022). The use of polygenic risk scores in pre-implantation genetic testing: an unproven, unethical practice. Eur. J. Hum. Genet. *30*, 493–495.