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Prioritizing the detection of rare pathogenic variants in population screening

Paul Lacaze, Ranjit Manchanda & Robert C. Green

Population genomic screening to detect carriers of rare monogenic variants for medically actionable conditions is supported by substantial evidence of clinical utility and cost effectiveness. Much less evidence supports screening by polygenic risk scores, which do not detect rare variants. Using only polygenic scores in population screening initiatives, while ignoring the detection of higher-risk rare monogenic variants, is ill-advised.

Prioritizing the detection of rare, clinically significant pathogenic variants for penetrant, medically actionable, monogenic conditions represents an evidence-based, appropriate and justifiable strategy for large-scale population screening. Polygenic risk scores (PRS), calculated using genotyping arrays, have been proposed as a possible alternative for population screening to identify individuals at high risk. However, such an approach would miss carriers of rare monogenic variants for medically actionable genomic conditions. These individuals are among those at highest risk in the general population, and their identification should be prioritized in screening programmes.

Modern medical genetics has largely emerged in the context of molecular diagnosis of persons with inherited conditions. But the potential for using genomic technologies to screen certain segments of the population, or even the general population, has considerable provenance and tremendous appeal. Screening occurs routinely today within affected families for hereditary forms of cancer, cardiovascular disease and other highly penetrant conditions, affording an opportunity for enhanced surveillance and risk-reducing interventions among those carrying gene variants. Building upon this precedent, it has been proposed that population screening to identify high-risk individuals from the general population carrying pathogenic or likely pathogenic variants in a limited set of genes for highly penetrant inherited conditions would be a substantial opportunity for public health[1,2]. The genes most often mentioned in the context of population genomic screening include high-risk cancer susceptibility genes such as *BRCA1*, *BRCA2* and *PALB2* for hereditary breast and ovarian cancer (HBOC), *MLH1*, *MSH2* and *MSH6* for Lynch syndrome, as well as the lipid metabolism genes *LDLR*, *APOB* and *PCSK9* for familial hypercholesterolaemia[3]. For those identified to be at high risk of these conditions, there is consensus that effective risk management interventions are available to prevent disease and reduce risk[2,3].

Population-based *BRCA* testing in Jewish populations has already provided an evidence-based model for clinical implementation of such screening[4]. Israel recently implemented such a programme, and the UK National Health Service Cancer Programme team is launching its Jewish population-based *BRCA* programme in early 2023. There is also evidence from modelling studies that population-based screening for a limited set of high-risk monogenic genes will be cost-effective from payer and societal perspectives in the broader general population[5,6]. General population screening for targeted detection of rare pathogenic variants in this limited set of high-risk genes (monogenic screening) therefore represents a tractable strategy with rational precedent for the medical management of individuals who are so identified from the general population.

There is enthusiasm for implementing PRS-based population screening initiatives within medicine and public health. The increasing popularity of PRS is likely owing to low cost, improved accessibility, potential to generate risk prediction on large populations, and the potential for population stratification for risk-adapted screening and prevention. Indeed, PRS will certainly be an important screening tool, and there is good evidence and emerging applicability of PRS for risk stratification in some diseases, the prime example being in risk-adapted screening for breast cancer. However, making clinical decisions based on PRS alone, without undertaking monogenic testing, may provide false reassurance of low genetic risk to some and be potentially harmful in that respect.

A PRS calculates the collective influence of many common genetic variants on the risk of a particular disease, typically calculated as a weighted sum of trait-associated alleles. Population-based PRS estimates of disease risk have been available to the public through direct-to-consumer (DTC) testing companies since 2007, at times attracting fierce criticism for omitting rare monogenic risk variants[7]. Moreover, several population-based studies and biobanking initiatives have begun to undertake PRS testing in the absence of monogenic testing for rare variants. A recent example is the UK Our Future Health initiative, proposing to screen 5 million individuals using PRSs for common disease. In a cohort of this size, using DNA sequencing for the detection of rare pathogenic variants would identify ~50,000 high-risk monogenic carriers for HBOC, Lynch syndrome and familial hypercholesterolaemia alone. Most of these genetically high-risk individuals would be missed by PRS testing, as the underlying technology predominantly used for calculating PRSs (genotyping microarrays) does not typically detect rare monogenic variants.

The existing evidence base regarding the clinical utility of using PRSs for population screening is less robust than monogenic screening, where clinical benefits within affected families are well established. Validation of predictive models using PRSs, including defining absolute

risk thresholds for effective clinical interventions, is still lacking for most disease states[8], especially as PRSs ideally require integration with other risk factors into a combined disease risk model. Unlike clinical monogenic testing, reporting of PRSs is not yet standardized for most diseases, nor are there well-aligned clinical guidelines for action. Furthermore, PRS are subject to well-recognized ancestry-specific biases. In comparison, clinical gene panels based on targeted sequencing of known disease-associated genes are currently offered clinically to patients of all genetic ancestries, and the downstream clinical implications of monogenic testing are more likely to be consistent across ancestries. For population genomic screening to maximize opportunities for prevention and cost effectiveness for health systems in the future, this aspect of population-scale testing and implementation must be given careful consideration.

Emerging population screening initiatives

Despite the availability of effective interventions for monogenic conditions such as HBOC, Lynch syndrome and familial hypercholesterolaemia, these conditions remain chronically underdiagnosed. Over 95% of those carrying pathogenic variants in the *BRCA1/2* genes remain unidentified in the general UK population, despite more than 25 years of genetic testing based on clinical presentation or family history[9]. Similar circumstances hold in the USA[10], and the rates for testing and detection of Lynch syndrome and familial hypercholesterolaemia variants are even lower[3]. Unfortunately, an estimated 50–80% of pathogenic variant carriers for these conditions in the general population do not fulfil current clinical genetic testing criteria[3,4,9]. The system for proactive screening in most countries is plagued by restricted access and underutilization of testing. Finding unaffected rare pathogenic variant carriers for highly penetrant monogenic conditions in the general population should be an upfront priority of population genomics.

Some recent population genomic screening studies have indeed been designed specifically to prioritize the detection of highly penetrant, rare pathogenic variants in medically actionable genes using targeted sequencing. The recently launched Australian 'DNA Screen' national pilot study is offering preventive DNA screening for 10 medically actionable genes to 10,000 adults aged 18–40 years[3]. Similarly, the recently announced PROTECT (population-based germline testing for early detection and cancer prevention) trial is offering DNA screening for nine (HBOC and Lynch syndrome) cancer susceptibility genes to over 5,000 women in the UK. In PROTECT, PRS will be utilized concurrently to provide personalized breast and ovarian cancer risk prediction for risk-adapted breast cancer screening and breast/ovarian cancer prevention. Importantly, polygenic testing will not replace monogenic testing.

To maximize the preventive potential and public health impact of population genomic screening, initiatives should prioritize monogenic testing for medically actionable conditions before or concurrently with polygenic testing. It is important to prioritize the identification of the most genetically high-risk individuals in the general population and provide them with access to risk management and preventive care based on current guidelines. Using PRS alone without monogenic testing, long considered a major limitation of low-cost DTC approaches, will miss the most clinically significant genetic risk information associated with rare high-risk pathogenic variants for heritable conditions. This would be a missed opportunity for genomic medicine and prevention. Using PRSs 'alone' is therefore misguided as a population screening strategy and will not maximize benefits at a critical inflection point for population genomics.

Paul Lacaze [1] ✉, **Ranjit Manchanda** [2,3,4,6] **& Robert C. Green** [5,6]
[1]Public Health Genomics, Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Australia. [2]Wolfson Institute of Population Health, CRUK Barts Centre, Queen Mary University of London, London, UK. [3]Department of Gynaecological Oncology, St Bartholomew's Hospital, London, UK. [4]Department of Health Services Research, Faculty of Public Health & Policy, London School of Hygiene & Tropical Medicine, London, UK. [5]Mass General Brigham, Broad Institute, Ariadne Labs and Harvard Medical School, Boston, MA, USA. [6]These authors contributed equally: Ranjit Manchanda & Robert C. Green.
✉e-mail: paul.lacaze@monash.edu

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References

1. Bean, L. J. H. et al. DNA-based screening and personal health: a points to consider statement for individuals and health-care providers from the American College of Medical Genetics and Genomics (ACMG). *Genet. Med.* **23**, 979–988 (2021).
2. Murray, M. F., Evans, J. P. & Khoury, M. J. DNA-based population screening: potential suitability and important knowledge gaps. *JAMA* **323**, 307–308 (2020).
3. Lacaze, P. A., Tiller, J. & Winship, I., Group, D. N. A. S. I. Population DNA screening for medically actionable disease risk in adults. *Med. J. Aust.* **216**, 278–280 (2022).
4. Manchanda, R. et al. Randomised trial of population-based BRCA testing in Ashkenazi Jews: long-term outcomes. *BJOG* **127**, 364–375 (2020).
5. Zhang, L. et al. Population genomic screening of all young adults in a health-care system: a cost-effectiveness analysis. *Genet. Med.* **21**, 1958–1968 (2019).
6. Manchanda, R. et al. Cost-effectiveness of population-based BRCA1, BRCA2, RAD51C, RAD51D, BRIP1, PALB2 mutation testing in unselected general population women. *J. Natl Cancer Inst.* **110**, 714–725 (2018).
7. The New York Times. Don't Count on 23andMe to Detect Most Breast Cancer Risks, Study Warns. https://www.nytimes.com/2019/04/16/health/23andme-brca-gene-testing.html (2019).
8. Ding, Y. et al. Large uncertainty in individual polygenic risk score estimation impacts PRS-based risk stratification. *Nat. Genet.* **54**, 30–39 (2022).
9. Manchanda, R. et al. Current detection rates and time-to-detection of all identifiable BRCA carriers in the Greater London population. *J. Med. Genet.* **55**, 538–545 (2018).
10. Manickam, K. et al. Exome sequencing-based screening for BRCA1/2 expected pathogenic variants among adult biobank participants. *JAMA Netw. Open* **1**, e182140 (2018).

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Competing interests

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