Ethical Implications of Disparities in Translation Genomic Medicine – from research to practice

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Genomic medicine has the potential to contribute to the development of an array of novel technologies within the clinical armoury, making possible early detection and management of high-risk conditions such as cancer. Whilst significant impact has already been felt in the context of rare inherited single gene disorders, much of the advancement in patient care through genomic medicine more broadly is going to be made possible by research involving large data sets that enable analyses of multiple genetic variants that contribute to risk of common diseases (1). As well as informing diagnosis and treatment of these diseases, these advances will support prediction and prevention. Considering risk prediction, combining data from multiple variants can produce a polygenic (or integrated) score (PGS/IGS). This will provide more accurate prediction than simply relying on environmental risk factors. While still in their early stages of development and implementation, it is clear that translation of these genomic advances into clinical practice has the potential to improve health outcomes. However, as in other areas of genomic medicine, such benefits will be limited if important weaknesses in the datasets underpinning the development of PGS/IGS are not addressed as a matter of urgency. One important weakness is that such datasets are significantly under-representative of population diversity and there is data to suggest that the evidence of PGS/IGS association with common chronic disease is not generalizable to the whole population.(2)

Translational research progresses from "discovery" to "evaluation" through to "adoption".(3,4) Few studies have explored what the implications are of a disparities lens being absent across these three stages of research translation with respect to development of data and knowledge informing PGS/IGS. Here we explore how a disparities lens is essential, throughout the translation process, to ensure early detection and mitigation of disparities downstream.

Assessing disparities within the "discovery phase" of PGS/IGS technologies

The basic science discovery phase involves identification of disease susceptibility genes using, for example, high throughput technologies. Genome Wide Association Studies (GWAS) that lead to PGS/IGS rely on big genomic datasets, such as the UK Biobank, the US based "All of Us" Biobank and the Finland based nationwide network of FinnGen biobanks. Several studies have shown that these 'biobanks' lack sociodemographic diversity and are not representative of the sampling population.(5) Others have highlighted that the paucity of diverse data sets and samples, within genomic medicine, mean that the development and implementation of PGS technologies may result in the exacerbation of health inequalities, particularly amongst the most underserved communities, such as low socioeconomic and ethnic minority communities.(6) For example, there are several examples of studies looking at PGS/IGS of various diseases, such as hypocholesterolaemia(7), breast cancer(8), coronary heart disease(9), where the cohorts are not representative of the UK population. Disparities in the discovery phase of research are important in their own right. They also have implications for subsequent phases.

Implications for disparities within the "evaluation phase" of PGS/IGS technologies

For the evaluation phase, studies seeking to further develop and validate PGS/IGS for a range of diseases have largely involved data sets that are also mainly comprised of European ancestry cohorts(10) through, for example, the use of data subsets from the aforementioned biobanks. Such approaches will likely further exacerbate inequity. For example, one of the earliest hypercholesterolaemia PGS was developed from the Whitehall study cohort, which is predominantly of European ancestry. An increased inherited risk of hypercholesterolemia (High PGS) may reduce the threshold at which patients are prescribed lipid lowering treatment to prevent future cardiovascular disease. A study assessing the predictive utility of the hypercholesteraemia PGS in different ethnic groups, unsurprisingly has found the PGS to be most relevant for individuals of European ancestry.(11) They also came to the conclusion that the PGS may not be relevant for or may under or overestimate the risk of hypercholesterolaemia in ethnic minority communities.(11) Such assessments will have implications for individual as well as population level management of hypercholesteraemia. Several studies have looked at the association between PGS and coronary heart disease, with the proposal that the PGS would inform cardiovascular risk prediction. However, the association is stronger in

individuals of European ancestry than those of African ancestry.(12) Such analyses indicate that in the absence of diverse data to corroborate the validity of PGS/IGS studies, the risk prediction tools should be used with caution.

Furthermore, in cohorts where there are efforts to include and utilise diverse data, there is still a lack of "true representativeness"(13). It is important to assess the implications of this including the risk of skewing data further away from being applicable for diverse groups and such approaches preventing comprehensive efforts towards representative diverse data.

To demonstrate health impact of such risk prediction, intervention trials are performed. But these trials can exacerbate socioeconomic biases, by recruiting study participants with better opportunities for good health through better housing, employment, food and financial security. Such groups are already accessing disease prevention such as better diet, lifestyle changes and lower stress. These kinds of 'intersectional' factors must also be a component of the disparities lens that is applied to translational research. Preventative measures in "well-served" populations to assess impact on modifiable risk are likely to be subject to "ceiling effects" where further addition of preventative measures may lead to little or no improvement in outcomes.(14) Diverse data including study participants that are socioeconomically and racially disadvantaged will not only afford better insights through valid representation but more accurately identify the intervention's true effect size in the general population.

Implications for disparities within the "adoption phase" of PGS/IGS technologies

As we await the adoption of PGS/IGS in practice it is crucial to consider the in-built inequities that have informed their development and their consequences for diagnosis through to treatment. A hypercholesteraemia PGS/IGS that is less relevant for and may under/over-estimate risk in patients of diverse ancestry will require careful appraisal in terms of its application. Some authors suggest that such PGS/IGS may still have relevance but will require adjustment.(11) It is still unclear how such adjustment ought to be calculated and validated. One approach would be to dedicate data collection to track, for example, assessment of risk, prescription of intervention (statin dosage and frequency) with rigorous follow up of outcomes, to inform adjustment methods. Such approaches may also aid in assessments of how valid the initial PGS/IGS are for diverse cohorts.

A well-recognised observation is that uptake of emerging technologies is worse amongst low socioeconomic and ethnic minority populations. Developing and adopting technologies that may have little/no relevance to such groups may be inappropriate and even harmful e.g. may lead to adverse outcomes. One proposal could be a stratified method of adoption or patient care i.e. offering different groups different technologies and services. Such an approach could be justifiable if it is meeting patient needs. However, this method fails to address the lack of representative diverse data in the discovery and evaluation of PGS/IGS technologies.

Conclusion

There is a great deal of excitement about the potential for genomic medicine to transform the prevention, diagnosis, and treatment of diseases with significant benefits for patients, families, and society. Much of this is justified. However, unless the three phases of research – discovery, evaluation, adoption – are better informed and transformed by paying closer attention to diversity and disparities, these benefits will be inequitably distributed with implications not only for underserved communities but for all.

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