Commentary

Pharmacogenomics

Population pharmacogenomics: impact on public health and drug development

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"a promising outlook, which coupled with population-based cost–effectiveness analyses may catalyze the integration of genome-guided drug interventions into routine clinical care"

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In humans, like every other organism, there is huge interindividual variability, resulting in approximately 3.5–5 million naturally occurring genomic variants observed per genome. These variants are discoverable by next-generation sequencing (NGS) methods and by means of comparison with the reference genome. From these variants, a significant proportion is rare and occasionally results in an observable phenotype [1]. Like in every gene, the same situation has been observed in the genes that are involved in encoding the various enzymes involved in absorption, distribution, metabolism, excretion and toxicity of medicines, also known as ADMET genes or pharmacogenes. Mizzi *et al.* have shown that every individual bears, on average, approximately 18,000 variants in their 231 pharmacogenes that can only be identified by NGS technologies, most of which are rare variants that may occasionally lead to rare drug outcomes [2].

Notably, apart from the interindividual differences observed in the pharmacogenes, there are remarkable interethnic differences in the prevalence, that is, allele frequencies of pharmacogenes that have been reported in various studies. These differences are of fundamental importance not only to prescribe tailor-made theranostics, with direct impact on public health [3], but also to empower drug discovery [4]. In other words, it is of utmost importance that we gradually shift from personalized to 'populationalized' medicine with the prospect of enjoying numerous tangible benefits not only for individual patients but also for the entire healthcare system and society as a whole. At the same time, genome-guided clinical trials can help toward reducing the immense drug development cost and the overall length of clinical trials that a drug may need to find its way to the market.

Impact on public health

The advent of high-throughput genomics technologies, such as microarrays and NGS technologies, has significantly contributed toward boosting the genomics discipline and the establishment of genotype–phenotype correlations. Pharmacogenomics (PGx) could have not possibly lagged behind this revolution. Not only has the PGx discipline gained significant insights into the correlation of genomic variants with drug efficacy and toxicity, leading to the establishment of pharmacogenomic biomarkers, but has also benefited from the development of tools for the rapid and cost-effective screening of these biomarkers to rationalize drug treatment in clinical settings. To this end, several microarray-based approaches have been developed.

Recently, these platforms were used to demonstrate that the PGx biomarker allele frequencies vary significantly among different populations around the globe. In particular, by analyzing over 1800 individuals from 22 different European, Asian and South African populations, Mizzi *et al.* demonstrated significant differences in several PGx biomarker allele frequencies, which was also the case when comparing individuals from European populations that all belong to the same racial group [5]. Similar findings were also reported from other population groups [6]. These

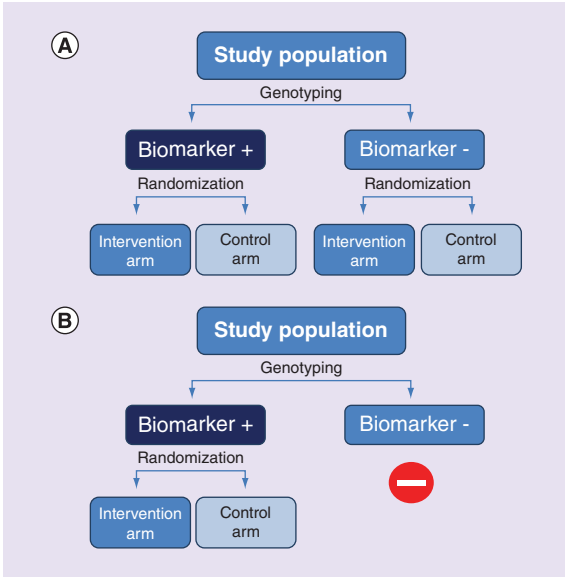

Figure 1. Concept for the alternative designs of randomized controlled trials for evaluating pharmacogenomic biomarkers.
(A) Conventional unselected RCTs. **(B)** Enriched RCTs.
RCT: Randomized clinical trial.

findings have clear implications for public health policies, since prior knowledge of PGx biomarker allele frequencies in a certain population, particularly for those biomarkers with high prevalence, may help toward establishing medication prioritization guidelines, which could not only improve the quality of life of the patients but also minimize the national healthcare expenditure by reducing possible adverse drug reactions (ADR). Such an example would be the screening for the *HLA*1502* variant in southeast Asian populations, leading to Stevens–Johnson Syndrome/toxic epidermal necrolysis [7], which was previously shown to be cost effective in these populations [8,9]. A similar example is tamoxifen, a drug that is used to treat breast cancer patients and whose pharmacological activity depends on CYP2D6 enzyme function. Approximately 6–10% of Europeans are considered to be poor CYP2D6 metabolizers, as compared with less than 1% of east Asians [10]. Recently, Lakiotaki *et al.* revealed significant differences of pharmacogenomic variants allele frequencies that directly reflect on the genomic structure of the 28 populations comprising the 1000 genome project [11].

From the above, it is evident that including PGx into national healthcare policies and plans has the potential to make healthcare more cost-effective by ensuring better treatment, proper medication prescription and identification of subpopulations at certain disease and ADR risk [3]. The latter could be particularly helpful for ethnically diverse populations, residing not only in developing but also in developed countries, such as the USA.

Impact on drug development

Apart from integrating PGx into public health, there is a significant role that PGx has to play in drug development. According to the Pharmacogenomics Research Network Translational Pharmacogenetics Program, the lack of prospective genome-guided randomized clinical trials (RCTs) is among the key obstacles that hold back the implementation of PGx into clinical care [12]. In brief, participant selection in these trials is informed by PGx biomarker status, identified by previous exploratory and subsequently confirmatory studies, provided that: there is strong and persuasive clinical evidence to link this PGx biomarker with drug response and/or toxicity; and the PGx biomarker directly influences the therapeutic target. In this study design, also known as enriched design, although the proposed genome-based stratified approach for RCTs may raise ethical, legal and practical concerns, it may be considered a very attractive approach to revisit the current clinical trial design [13]. In other words, by pursuing such a population PGx approach and identifying participants subgroups that are likely to respond better to a given drug, or be more susceptible to a potential ADR, the entire drug development process may become more cost-effective and significantly faster (Figure 1). This can be also applicable to the enrollment, in these RCTs, of participants from diverse racial/ethnic, ancestral and geographic backgrounds, even from the developing world [14], since in several clinical trials, there is often limited ethnic diversity.

Conclusion

From the above, it is evident that PGx biomarkers, like every other genomic variant, are able to distinguish population groups and thus, given their well-documented association with drug response and/or development of ADRs, can be exploited not only for medication prioritization from a population perspective but also to better design and develop genome-based stratified clinical trials. To this end, the scientific community must be equipped with efficient computational tools, enriched with certain analysis features that can accurately and comprehensively translate genotype to the corresponding phenotypic features, also taking into consideration certain environmental modifiers, such as food, comedication, among others, and in concert with well-curated population specific databases (e.g., PharmGKB [15], FINDbase [16] and ClinVar [17]).

Integration of PGx in public health policy is considered a long-term investment for both research and healthcare. Notably, though, there is often a communication and collaboration gap between various stakeholders, such as academics, government and the private sector [18]. Such interactions should be fostered and strengthened so that PGx knowledge transcends from the individual to the population level in a win–win fashion.

Last, population PGx present as yet another opportunity for developing countries and low-resource environments. Until now, the impact of PGx on developing countries has been minimal, since small (sub)populations have historically been ignored by researchers and pharmaceutical companies [19,20]. As such, by investing in PGx, developing countries can focus on their own local healthcare needs, that are so far ignored on the international level, hence prioritizing their local disease and drug metabolism patterns, based on the existing PGx studies, resulting in better healthcare. These efforts can be assisted by using and redistributing their human, technological and financial resources more prudently and cost effectively to maximize their impact on healthcare [21,22]. Ghana represents such an example, where PGx data were used at a population level [23], while the recently completed Euro-PGx project [2] and the ongoing 100 Pharmacogenes resequencing project in southeast Asia can serve as examples of successful international collaborations, and, hence, models for possible replication.

Overall, implementation of population PGx into public health and/or the pharmaceutical industry is a multi-faceted decision and requires the well-orchestrated efforts and fruitful engagement of several stakeholders, always backed up from strong political will. As such, differences in the prevalence of PGx biomarkers in different populations can be translated into findings, which not only enhance the underlying drug development pipelines, but also facilitate the identification of population differences in drug response/toxicity events. Even if the concept and application of population-based PGx is still in its infancy, it clearly demonstrates a promising outlook, which coupled with population-based cost–effectiveness analyses may catalyze the integration of genome-guided drug interventions into routine clinical care.

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