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Are randomized controlled trials necessary to establish the value of implementing pharmacogenomics in the clinic?

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Introduction

Pharmacogenomics can personalize drug prescribing to individual patients, increasing drug efficacy and reducing incidence of adverse drug reactions (ADRs). Despite a substantial evidence base and published pharmacogenomic guidelines, a lack of evidence from randomized controlled trials (RCTs) is frequently cited as a reason to delay implementation of pharmacogenomics in the clinic. We believe that this argument is misguided as RCTs are unnecessary for implementation and can obscure important pharmacogenomic factors which may affect drug response.

RCTs aren't always necessary, practical or possible

Although RCTs are considered the gold standard in evidence-based medicine, many prescribing decisions, including drug selection and dose adjustments, are made without supporting evidence from clinical studies, let alone RCTs. Rather, these decisions must be tailored to the individual patient and take into account many factors, including age and any comorbidities, that may not have been investigated in the setting of an RCT. Pharmacogenomics can help to further refine these prescribing decisions, giving patients a better chance of finding a pharmacotherapy that works first time.

Information about altered drug exposure and dosage changes for patients with hepatic or renal impairments does not require supporting evidence from an RCT to be added to a drug label (1). Yet this is key information used by clinicians to make the appropriate dose adjustments for patients. In the same vein, a patient's drug exposure can also be altered by their metabolizer phenotype for drug-metabolizing enzymes such as CYP2D6 and CYP2C19. In the absence of data from RCTs, the US Food and Drug Administration (FDA)

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Conflicts of Interest

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have already used evidence from non-randomized clinical studies to add pharmacogenomic information to drug labels. We agree with Pirmohamed and Hughes in questioning why genetic exceptionalism is being applied to pharmacogenomics when other tests for clinical features resulting in the same outcome of altered drug exposure do not require RCTs (1).

In a positive development, pharmacogenomic sub-studies are beginning to be included in standard RCT design. However, there are thousands of drugs already on the market with little to no pharmacogenomic evidence available. There is no incentive for pharmaceutical companies to carry out RCTs or pharmacogenomic sub-studies of previous RCTs for these drugs, particularly drugs which are now generic. Of the 43 drugs which are currently covered by pharmacogenomic dosing guidelines from the Clinical Pharmacogenetics Implementation consortium (CPIC; www.cpicpgx.org), at least 39 are generics. Unless companies are incentivized to carry out pharmacogenomic RCTs or significantly more funding and support is made available to researchers to conduct these trials, it is highly unlikely that RCTs covering every possible drug-gene interaction will be carried out.

There are also ethical issues to consider in pharmacogenomic RCTs. The inclusion of a control group is a fundamental feature of an RCT and there are legitimate concerns regarding the confounding factors introduced when pharmacogenomic testing is restricted to the treatment arm of a RCT. This has prompted researchers to suggest that both the treatment and control arms of a pharmacogenomic RCT should undergo pharmacogenomic testing. However, it can be reasonably argued that it is unethical to randomize patients who are known to carry actionable pharmacogenetic variants to a drug choice or drug dose that could cause drug toxicity or an ADR.

RCTs can miss important pharmacogenomic interactions

Many actionable pharmacogenomic variants are only found at low frequencies in populations. As an example, the *HLA-B*57:01* allele, which is associated with an increased risk of abacavir hypersensitivity, has an average frequency of 5% in European populations sampled as part of the 1000 Genomes project and an average of 1.05% in East Asian populations (2). This issue is exacerbated by the lack of diversity seen in RCT cohorts. 86% of RCT participants in 2014 were of European ancestry, with black and Asian patients accounting for 3% and 6%, respectively (3). This can cause particular problems in pharmacogenomics as homogenous cohorts can prevent rare pharmacogenomic variants from being adequately represented in the RCT and potentially means that the effects of rare variants on drug safety and efficacy are missed or, at best, significantly understated. The result of this is that evidence from pharmacogenomic RCTs is unlikely to be directly applicable to a significant number of patients.

The most obvious example of this is the Hawaiian clopidogrel lawsuit, where the makers of Plavix were sued by the District Attorney of Hawaii for marketing the drug to a population with a high frequency of CYP2C19 poor metabolizers, who do not respond to clopidogrel therapy. The nonfunctional *CYP2C19*2* and **3* alleles are found at high frequencies in Pacific Islanders and East Asians, two of the largest ethnic groups in Hawaii. 95% of participants in the CAPRIE trial, which established the efficacy of Plavix, were Caucasian,

where these alleles and the resulting CYP2C19 poor metabolizer phenotype, are found at much lower frequencies. Consequently, the risk of death from myocardial infarction indicating a lack of response to clopidogrel calculated from the trial data was of questionable relevance to patients who carry nonfunctional *CYP2C19* alleles. Subsequent analysis following the release of Plavix revealed that the rate of death from myocardial infarction in Native Hawaiians was almost twice that found in people of European descent (see https://www.futuremedicine.com/doi/full/10.2217/pme.15.4).

Due to the persistent underrepresentation of rare variants and the prevalence of small study cohorts, many pharmacogenomic studies including sub-studies of RCTs, are underpowered (4, 5). This leads to consistent underestimations about the strength of a relationship between a particular variant and drug. Table 2 from Ross *et al.*'s 2012 publication highlights the logistical issues which force many pharmacogenomic studies to be underpowered. As an example, 1,657 subjects would be required to detect a drug-gene interaction at 80% power with an odds ratio of 2.00 and a minor allele frequency of 0.1 in control participants (4). Recruiting a study cohort of this size is beyond the resources of many individual research groups.

Pharmacogenomic sub-studies of RCTs can be particularly unhelpful in establishing a link between a pharmacogenetic variant and risk of an ADR as RCTs are primarily designed to investigate drug efficacy (5). Retrospective pharmacogenomic sub-studies are also, by their nature, not able to collect evidence on how pharmacogenetic markers can be used to guide drug dosing.

Non-RCT sources of pharmacogenomic evidence

Alternative forms of evidence are available to inform implementation of pharmacogenomics in the clinic. Smaller-scale, non-randomized clinical studies of drug-gene interactions, including retrospective studies, are significantly cheaper and easier to run than RCTs, while still making valuable contributions to the pharmacogenomic evidence base. These real-life clinical studies can also have greater external validity compared to RCTs, resulting in transferable evidence to everyday clinical practice. Evidence from studies such as these, as well as other forms of pharmacogenomics research, is already used by numerous international consortia including CPIC and the Dutch Pharmacogenetics Working Group (DPWG) to produce pharmacogenomic dosing guidelines which are already being implemented in healthcare settings. The aggregation of evidence from smaller studies allows high quality guidelines to be issued to clinicians without having to wait for a relevant RCT to be conducted.

Meta-analyses are also an attractive option for consolidating the evidence and improving the statistical power surrounding a drug-gene pair. Aggregation of studies from diverse populations has the added benefit of producing clinical evidence that is relevant to a larger proportion of the patient population. However, we acknowledge that pharmacogenomic studies can be highly heterogeneous, complicating the ability of researchers to directly compare studies or successfully aggregate them for a meta-analysis. Several papers offering frameworks for pharmacogenomic study standardization have been published and we

strongly encourage the pharmacogenomics community to consider applying these frameworks to their own research and further strengthen the evidence base for implementing pharmacogenomics in the clinic. Resources at the Pharmacogenomics Knowledgebase (PharmGKB; www.pharmgkb.org) and the Pharmacogene Variation Consortium (PharmVar; www.pharmvar.org) can help in these efforts.

Other areas of personalized medicine, such as oncology, are embracing a number of alternative trial designs. This includes n-of-1 trials, where the entire trial cohort is comprised of a single patient. Given the issues relating to the low frequency of many pharmacogenomic variants, it is easy to envision that n-of-1 pharmacogenomic trials of patients carrying rare variants could contribute valuable evidence to drive clinical implementation.

Conclusion

Patients are becoming increasing aware of, and engaged with, pharmacogenomics. As a result, there is rapidly increasing demand for pharmacogenomics to be incorporated into clinical care and there is a significant evidence base, accessible resources and clinical guidelines already available to aid implementation. Why should patients, particularly those in underserved populations, be knowingly exposed to pharmacotherapy failure or potentially fatal ADRs when the information which could lead to their successful treatment is already available?

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