Pharmacogenetic tests: the need for a level playing field

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The delivery of more personalized medicine could be accelerated by addressing the substantial differences in the level of evidence required for the inclusion of pharmacogenetic tests in treatment guidelines, drug labelling and reimbursement schemes compared with that needed for non-genetic diagnostic tests.

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There is an increasing drive, within both drug development and clinical practice, to stratify or personalize medicines to improve clinical outcomes for patients. Pharmacogenetics is perhaps the most well-developed of the various technologies that can be used to personalize medicines, but it has been criticized for not delivering on this promise. There are several science-related reasons why many pharmacogenetic studies do not progress beyond the stage of biomarker discovery, such as inadequate sample sizes, poor clinical phenotype or poor study design. However, we would also strongly argue that the slow progress in the implementation of pharmacogenetic (and indeed other genetic) tests can partly be explained by the fact that different criteria are applied when considering genetic testing compared with non-genetic diagnostic tests. Three specific areas are highlighted below.

First, drug response (efficacy or toxicity) is related to the dose administered, but more importantly to the systemic and cellular exposure to the drug and its metabolites. As most drugs and/or metabolites are eliminated via the kidney and/or the liver, there are numerous regulatory documents that provide guidance on performing pharmacokinetic and pharmacodynamic assessments on patients with impaired liver or kidney function and using this data to develop dosing recommendations. For example, the UK summary of product characteristics (SmPC) for aztreonam states: "after an initial usual dose, the dosage of aztreonam should be halved in patients with estimated creatinine clearances between 10 and 30 mL/min/1.73 m^2". There are many other drugs that contain similar recommendations within their labelling. Of course, this is logical in order to prevent variability in exposure and thus in the efficacy and/or toxicity of a drug. There is no regulatory requirement to undertake clinical trials to show that the dosing recommendations for patients with, for example, renal impairment are equivalent in terms of clinical outcomes to those for patients with normal renal function. Indeed, such a stipulation would be impractical and costly, and would never be done during the drug development process, potentially disadvantaging vulnerable patient populations.

Another major determinant of variability in drug exposure is genetic polymorphisms in drug-metabolizing enzymes and drug transporters. For example, cytochrome P450 2D6 (CYP2D6) is responsible for the metabolism of ~25% of drugs, but ~7% of the Caucasian population (termed poor metabolizers (PMs)) lack this enzyme, whereas another 2% of Northern Europeans, 10% of Southern Europeans and up to 30% of some African populations carry more than two copies of the gene, and are termed ultra-rapid metabolizers (URMs). Atomoxetine, a drug widely used for attention deficit hyperactivity disorder, is metabolized in the liver by CYP2D6. The SmPC for atomoxetine states that the dose should be reduced by 50% in patients with hepatic impairment (Child-Pugh class B), as drug exposure goes up by twofold. It is also known that drug exposure is increased by a similar amount in CYP2D6 PMs; however, although the SmPC for atomoxetine mentions the effect of CYP2D6 polymorphisms, it does not mandate testing for their presence. It has been stated that atomoxetine is equally efficacious and well tolerated among patients with the different CYP2D6 genotypes[1], but given the occurrence of numerous adverse effects in children, including arrhythmias and hepatotoxicity, can we be sure? The role of such polymorphisms in predisposing to toxicity from increased drug and/or metabolite exposure is only now becoming clear, even with old drugs such as codeine; there is increasing concern about the risk of respiratory depression in children who are CYP2D6 URMs because of increased conversion of codeine to morphine[2]. Notably, the new European Medicines Agency guidance on pharmacogenetic effects on drug pharmacokinetics has recommendations on

dosing evaluation in patients with polymorphisms in known metabolic pathways, an important pioneering development that will begin to ensure harmonization of dosing strategies as part of drug development.

The second example relates to the use of diagnostic tests. In general, the evidence required for implementation of non-genetic tests in clinical practice seems to be relatively haphazard and varies between genetic and non-genetic tests. For example, renal impairment is widely regarded as a risk factor for hypersensitivity to the gout drug allopurinol, with drug package inserts recommending the use of lower doses in patients with renal impairment. The origin of this association is from case reports and case series in the 1970s and 1980s, and it has become widely accepted despite the fact that other studies have shown no differences in adverse events according to creatinine clearance, and there have been concerns about under-dosing to control urate levels in clinical practice. By contrast, there is now extensive evidence showing that the presence of the *HLA-B*58:01* allele predisposes to serious cutaneous adverse drug reactions to allopurinol[3], but this has not been implemented in guidelines or as yet in drug package inserts. Prospective studies are quoted as being necessary to demonstrate evidence of clinical utility. Indeed, this has been done for two other drugs that can cause severe hypersensitivity reactions: the anti-HIV drug abacavir[4] (for which the presence of the *HLA-B*57:01* allele has been associated with hypersensitivity) and the anti-epileptic drug carbamazepine[5] (for which the presence of the *HLA-B*15:02* allele has been associated with a life-threatening hypersensitivity disorder known as Stevens–Johnson syndrome). Part of the reason for differences in evidential standards may be the familiarity and availability of non-genetic tests, and the perceived low costs of these tests. However, it is important to note that genetic tests only need to be done once, whereas protein- or metabolite-based tests, such as renal function tests, need to be performed repeatedly. So, over a lifetime, the costs of the non-genetic tests may be equivalent and indeed may become greater as the costs of genetic tests fall.

A final difference between genetic and other health technologies is apparent with respect to legislation on orphan drugs in various regions. Such legislation provides incentives for manufacturers to develop treatments for life-threatening or chronically debilitating diseases that are rare (in the European Union, diseases that affect no more than 5 in 10,000 people). The incentives range from reductions in regulatory fees to 10 years of market exclusivity once authorized (7 years in the United States). However, manufacturers of genetic tests that prevent equally severe and rare conditions — such as testing for the presence of *HLA-B*15:02* to avoid the development of Stevens–Johnson syndrome in patients treated with carbamazepine — do not enjoy these benefits. Subsidizing treatments to manage, but not tests to prevent, serious conditions appears inconsistent. Moreover, many treatments for rare diseases are very expensive and exceed conventional thresholds of cost-effectiveness. However, these are still available in most markets, implying that more lenient criteria are applied for reimbursement. Pharmacogenetic tests typically cost less than their value-based price (that is, the price that results in a cost-effectiveness ratio of £30,000 per quality-adjusted life-year in the United Kingdom), and much less than the premium prices of many orphan drugs. As with other diagnostics, however, their value is appropriated to the treatments they accompany. Whereas the annual cost of abacavir is ~£6,100, for instance, the cost of *HLA-B*57:01* testing is £50 (less than 1% of the cost of abacavir). However, the value of testing is not limited to the reduction in the incidence of hypersensitivity reactions: it also increased HIV clinicians' confidence in the drug and therefore led to more widespread use of abacavir. Different strategies for setting the price of pharmacogenetic tests may therefore be warranted, such that their true value is reflected in their price.

Our arguments here are not meant to suggest that special consideration should be given to genetic tests, but more that the same level of evidence needs to be applied to genetic and non-genetic tests for adoption into guidelines and drug package inserts. Incentives for the development of genetic tests, their pricing and reimbursement arrangements must also be aligned with other health technologies.

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Competing financial interests

The authors declare no competing financial interests.

FURTHER INFORMATION

European Medicines Agency publishes guideline on use of pharmacogenetics in evaluating pharmacokinetics of medicines: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2012/02/news_detail_001434.jsp&mid=WC0b01ac058004d5c1

SmPC for atomoxetine: http://www.medicines.org.uk/EMC/medicine/14482/SPC/Strattera+10mg%2c+18mg%2c+25mg%2c+40mg%2c+60mg%2c+80mg+or+100mg+hard+capsules

SmPC for aztreonam: http://www.medicines.org.uk/EMC/medicine/549/SPC/Azactam+1g+or+2g+Powder+for+Solution+for+Injection+or+Infusion%2c+vial

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