Rare disease prevention and treatment

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Title:

Rare disease prevention and treatment: the need for a level playing field

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Economics of pharmacogenetics

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Abstract:

Pharmacogenetics tests are being used increasingly to prevent rare and potentially life-threatening adverse drug reactions. For many tests, however, cost-effectiveness is hard to demonstrate and, with the exception of a few cases, widespread implementation remains a distant prospect. Many orphan drugs for rare diseases are also not cost-effective but are nonetheless normally reimbursed. In this article, we argue that the health technology assessment of pharmacogenetics tests aimed to prevent rare but severe adverse drug reactions should be on a level playing field with orphan drugs. This is supported by a number of arguments, concerning the severity, rarity and iatrogenic nature of adverse drug reactions, the distribution of benefits and costs, and the preference placed on prevention over treatment.

Article:

Pharmacogenetics tests are being used increasingly to prevent or pre-empt rare and potentially life-threatening adverse drug reactions (ADRs) [1]. Examples where pre-prescription genotyping is required or recommended by the European Medicines Agency or the US Food and Drug Administration (FDA) include *HLA-B*57:01* for the prevention of abacavir-induced hypersensitivity reactions; *HLA-A*15:02* to prevent Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) relating to carbamazepine, and *HLA-DQA1*02:01* or *HLA-DRB1*07:01* to prevent lapatinib-induced hepatotoxicity. For each of these, identified carriers may be offered alternative treatments with reduced risks of harm. In the case of abacavir, routine testing for *HLA-B*58:01* has effectively eliminated hypersensitivity reactions [2].

However, evidence on the clinical effectiveness of pharmacogenetics testing for preventing ADRs is variable. While randomised controlled trials support testing in relation to treatment with abacavir [3], clopidogrel [4] and warfarin [5,6], the majority of labelling recommendations and actionable notices are based on studies of association. Moreover, evidence supporting the cost-effectiveness of introducing pharmacogenetics testing into clinical practice is sparse, with as few as one in ten drugs with FDA labels which include genetic information having associated economic data [7]. For many single-gene tests, cost-effectiveness is hard to demonstrate, not only because of the lack of definitive clinical evidence, but also because of the rarity of the ADR being avoided, the allele frequency, the positive and negative predictive value of testing, and the costs, effectiveness and safety of alternative treatment options [8].

Demonstration of cost-effectiveness requires that the incremental costs of testing are justified by the additional benefits. In the National Health Service (NHS) in the UK, the threshold is set at £20,000 to £30,000 per quality-adjusted life-year (QALY) gained [9]. Health technologies are considered to offer good value for money if their incremental cost-effectiveness ratios (ICER) are below this range, but are generally not recommended for use if they are higher. For drugs associated with more common ADRs and with a high negative predictive value (NPV) of testing, such as in the example of *HLA-B*57:01* genotyping prior to abacavir (ADR ~6%, NPV ~100%) [3], the number of patients needed to be screened is comparatively low making the test cost effective [10]. To prevent one case of abacavir hypersensitivity, 8 *HLA-B*57:01* positive patients would be denied abacavir, and to identify them, 48 patients would require testing [11]. Similarly, many genetic and biomarker screening tests for more prevalent diseases may be cost-effective in certain populations [12-14]. However for the avoidance of many rare events, such as many severe ADRs, a far greater number of patients need to be screened, rendering the test less cost-effective. Allopurinol causes SJS/TEN in about 7 patients for every 10,000 treated [15]. This requires that 11,286 patients need to be screened for *HLA-B*58:01* in order to prevent one case of ADR [16]. Consequently, at around £50 for a single-gene test, the screening of patients with gout is not cost-effective – either in the UK, at £44,954 per QALY gained [16] – or in many other jurisdictions [17-19].

An important consideration here concerns the distribution of costs and benefits. The great majority of patients tested for *HLA-B*58:01* would never experience a severe ADR and so would continue on allopurinol with no additional health benefit from testing, but having incurred the extra cost of testing. Others will have their prescription unnecessarily changed to febuxostat, a more expensive, but possibly more effective drug for gout. As the ICER for testing is based on the average of all patients, it fails to reflect the distribution of costs and consequences among those tested. For every 11,286 patient screened, all bar one will gain 0.0025 QALYs (about 1 additional quality-adjusted day) while costing the NHS an additional £105 over a lifetime. The one patient who averts the ADR avoids losses of 3.43 QALYs, and a cost to the NHS of £17,250 [16].

This presents an interesting contrast with the cost-effectiveness of drugs developed for rare diseases. Regulation 141/2000 of the European Commission [20] defines an orphan medicinal product as the first to represent a satisfactory treatment (or to provide a significant additional benefit to an existing treatment) of a life-threatening or chronically debilitating condition affecting not more than five in 10,000 persons. A treatment of SJS/TEN would thus qualify for orphan designation (general population incidence of around 6 cases per million person-years [21]), but a pharmacogenetic test aimed to prevent SJS/TEN might not. This has implications in terms of the incentives available to manufacturers for developing interventions for rare diseases, and also in terms of healthcare system reimbursement.

The similarities and differences between the treatment and prevention of rare disease are illustrated in Table 1, comparing genotyping for *HLA-B*58:01* to prevent allopurinol induced SJS/TEN with afamelanotide, an orphan drug for the management of erythropoeitic protoporphyria. Afamelanotide has been approved in Europe and is currently reimbursed in Austria, Germany, Italy, Netherlands and Switzerland, and will be evaluated by the UK National Institute for Health and Care Excellence in May 2018. Testing for *HLA-B*58:01* by contrast, is recommended by the Taiwan Department of Health, but not by other regulators, and is not considered to be cost-effective [16-19].

-- Insert Table 1 here --

Orphan drugs treat the identifiable few whereas pharmacogenetic tests identify the few who are at risk of a rare ADR. Orphan drugs tend to be very expensive on an individual patient basis but provide significant health benefits to those treated [27]; whereas pharmacogenetic tests are inexpensive for individual patients, but expensive for populations and benefit only a small proportion of those tested. Because of their high costs, economic evaluations of orphan drugs often yield ICERs in the order of hundreds of thousands (if not millions) of pounds per QALY gained [28], far exceeding the cost-effectiveness threshold. Yet despite this, most orphan drugs are approved for use [29], often justified on the grounds of equity [30]. That is, equity considerations (a sense of distributive fairness in access to treatment) outweigh efficiency principles (achieving the greatest benefit from finite resources).

Consequently, non-implementation of pharmacogenetic tests on the grounds of cost-ineffectiveness (such as *HLA-B*58:01* for allopurinol), would be inconsistent with the special funding status given to orphan drugs [31]. While there is considerable empirical evidence showing society's unwillingness to trade extensive health benefits experienced by many, for expensive benefits experienced by a few [32-34], there is evidence that people's evaluation of fairness is influenced when comparing the benefit to an individual patient with the average cost to those who share the cost [35]. When patient numbers are small and the average cost to those who share the cost is small, a well-informed public is likely to support the funding or part-funding of effective services that may not be cost effective.

Many rare diseases are hereditable. The lysosomal storage disorders, for which there are many effective, but highly expensive enzyme replacement therapies, are autosomal recessively inherited and affect 1 in 5,000 to 1 in 10,000 live births. The clustering of LSDs and other inherited metabolic disorders within families, and their early presentation in childhood are further reasons offered to justify funding of non-cost-effective medicines. These characteristics are considered in health technology assessments of orphan drugs but not of pharmacogenetics tests despite the comparable contexts, such as with the significant association between HLA loci (which are hereditary) and the predisposition of immune-mediated ADRs. Mother-to-child transmission of HIV could require both to be treated with abacavir, and risk ADRs if also carriers of *HLA-B*57:01*. Moreover, there are

potentially important incidental findings to genotyping, both in relation to future prescriptions for an individual, and to family members. These are not generally considered in economic evaluations.

ADRs are iatrogenic, and this presents a further challenge regarding social value judgements. It is possible that society values the benefits achieved through implementing methods to avoid iatrogenic harm higher than the health forgone through the disinvestment or displacement of other services which would be necessary to finance them within the confines of a finite budget. While there are no empirical data to support this, it is aligned with the safety agenda of the NHS and other healthcare services internationally and the notion that harm experienced through the course of healthcare is to be prevented at all/any (reasonable) cost.

Preference elicitation studies indicate that for equivalent health gains, the general public strongly prefer prevention over cure [36]. The implied value placed on deaths avoided through preventative strategies is twice that of treatment policies [37]. In the context of pharmacogenetics and ADRs, and drawing on the comparison with orphan drugs, this might indicate an equity balance tipped in favour of testing over treating.

We contend that pharmacogenetics tests aimed to prevent rare but severe and potentially life threatening ADRs should be on a level playing field – not only with other diagnostics in terms of evidential standards [38] – but also with orphan drugs used to treat rare diseases. This is supported by a number of arguments, concerning the severity, rarity and iatrogenic nature of ADRs, the distribution of benefits and costs, and the preference placed on prevention over treatment.

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		Afamelanotide for erythropoeitic protoporphyria	Genotyping (*HLA-B*58:01*) to prevent allopurinol induced SJS/TEN in gout patients
Disease related factors			
	Incidence	Less than 2 in 100,000 people [22]	7 per 10,000 patients prescribed allopurinol [15]
	Clinical features	Most patients experience prodromal symptoms (e.g. itching, tingling) and symptoms of cutaneous phototoxicity (e.g. burning, intense pain) within minutes of sun/light exposure, and erythema and oedema may appear with prolonged exposure	Macules appear and rapidly spread and coalesce, leading to epidermal blistering, necrosis, and sloughing. Epidermal detachment can, in severe cases of TEN, lead to large sheets of epithelium sliding off the entire body
	Prognosis	Prognosis depends on evolution of hepatic disease. Photosensitivity significantly impacts quality of life. Further complications can include gallstones, chronic hepatitis, liver failure and vitamin D deficiency	Patients are at high risk of infection, multi-organ failure, and mortality (26.5% over the first 30 days [16]). Long term sequelae can be ocular, cutaneous, oral, pulmonary, renal, urogenital/gynaecological, gastrointestinal, hepatic, psychiatric and psychosocial [23]
Intervention-related factors			
	Strength of clinical evidence	Clinical development programme, including 3 phase III placebo-controlled randomised controlled trials, inclusive of 259 patients [24]	13 genetic association studies with allopurinol-tolerant controls and 239 cases of SJS/TEN patients [13]
	Cost per patient	€56,404 to €84,606 per annum [25]	£55.50
	Average QALY gain per patient	0.63 to 3.35 [26]	0.0023 [16]
	Average incremental cost per patient	£697,510 [26]	£103 [16]
	Incremental cost effectiveness ratio	£208,000 to £1.1m per QALY gained [26]	£44,954 per QALY gained [16]

Table 1. Comparison of the clinical and economic features of a treatment for a rare disease and pharmacogenetic test to prevent a rare ADR.