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Title:

Economics of pharmacogenetic-guided treatments: Underwhelming or overstated?

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Introduction:

Economic evaluations have dispelled a perception that precision medicine, achieved through pharmacogenetic testing, reduces healthcare costs. For many tests aimed at preventing adverse drug reactions, cost-effectiveness analyses predict modest improvements in health benefits and increases in total costs. While there are many uncertainties in estimating the value of testing, factors which influence cost-effectiveness include the rarity of the outcome, the effectiveness of alternative treatments, and the scope and perspective of analysis.

Cost-effectiveness analyses of pharmacogenetic-guided treatments estimate the value of testing by assessing the incremental health benefits in relation to the costs. Improvements in health – often considered in terms of quality-adjusted life-years (QALYs) – may arise from avoidance of adverse drug reactions (ADRs) and /or improvement in efficacy. Evaluations must consider costs and QALYs that extend beyond those related directly to testing, to also include the costs of alternative treatments that may be indicated by the presence of an allele, and the clinical consequences of prescribing alternative treatments which may be less effective, require more intensive monitoring or associated with different ADRs. Given the comparatively low (and decreasing) cost of genetic testing, however, there is often a presumption that pharmacogenetic tests reduce healthcare costs while improving health outcomes. An economic evaluation from the Office of Policy and Planning at the Food and Drug Administration, for instance, estimated that testing for variants in the *CYP2C9* and *VKORC1* genes to guide initial dosing of warfarin therapy could save the US healthcare system $1.1bn, and avoid 85,000 serious bleeding events and 17,000 strokes each year [1]. While this analysis was based on flawed assumptions, there are a number of reasons why economic evaluations of pharmacogenetic-guided therapy may predict modest health improvements [2] and marginal cost-effectiveness [3].

Firstly, are the costs and consequences of alternative treatment pathways – less effective or more expensive alternatives are likely to result in tests being less cost-effective. The relationship of the incremental costs ($\Delta\mathrm{Cost}$) and QALYs ($\Delta\mathrm{QALY}$) of single-gene tests aimed to reducing the likelihood of ADRs can be approximated by:

$$\Delta\mathrm{Cost}_{\mathrm{Testing/No\ testing}} = \mathrm{Cost}_{\mathrm{Test}} + \mathrm{P(allele)}\{\Delta\mathrm{Cost}_{\mathrm{Alternative/index}} - \mathrm{Cost}_{\mathrm{ADR}} * \mathrm{PPV}\}$$

$$\Delta\mathrm{QALY}_{\mathrm{Testing/No\ testing}} = \mathrm{P(allele)}\{\Delta\mathrm{QALY}_{\mathrm{Alternative/index}} + \mathrm{QALY}_{\mathrm{ADR}} * \mathrm{PPV}\}$$

Where, $\mathrm{Cost}_{\mathrm{Test}}$ is the cost of testing; $\mathrm{P(allele)}$ is the probability of the allele (positive test result); $\Delta\mathrm{Cost}_{\mathrm{Alternative/index}}$ and $\Delta\mathrm{QALY}_{\mathrm{Alternative/index}}$ are the incremental costs and QALYs, respectively, when comparing the alternative therapeutic option (which, for simplification, is assumed to carry no risk of ADR) with the index drug; $\mathrm{Cost}_{\mathrm{ADR}}$ and $\mathrm{QALY}_{\mathrm{ADR}}$ are the costs and QALY decrement associated with the ADR; and PPV is the positive predictive value of genotyping.

For treatments where the alternative (second-line) treatment is of comparable cost ($\Delta\mathrm{Cost}_{\mathrm{Alternative/index}} = 0$) but is more effective ($\Delta\mathrm{QALY}_{\mathrm{Alternative/index}} > 0$), the incremental cost of pharmacogenetic testing will be low, and the benefits high (making testing cost-effective). However, if the alternative is associated with higher healthcare costs ($\Delta\mathrm{Cost}_{\mathrm{Alternative/index}} > \mathrm{Cost}_{\mathrm{ADR}} * \mathrm{PPV}$), but is similarly or less effective ($\Delta\mathrm{QALY}_{\mathrm{Alternative/index}} \leq 0$) then the incremental cost of testing will be high and the QALY gain low, resulting in testing being non-cost effective. Thus

the health benefits (and hence cost-effectiveness) of pharmacogenetic testing are highly sensitive to the effectiveness (and cost) of alternative courses of action.

In the case of screening for *HLA-B*15:02* to avoid carbamazepine-induced Stevens-Johnson syndrome (SJS) and toxic-epidermal necrolysis (TEN), for instance, sodium valproate may be a valid alternative for patients with the allele. However, as sodium valproate is less effective than carbamazepine in achieving seizure remission, unnecessary changes in prescription (i.e. because of false-positive test results) will lead to less effective control of epilepsy in some patients. An economic analysis of *HLA-B*15:02* testing in Malaysian populations predicted that one case of SJS/TEN would be avoided for every 222 patients screened; but 3 additional patients would experience seizure relapse owing to the reduced effectiveness of the alternative antiepileptic drug [4]. The benefit-risk assessment concerns the differential impacts on health of the avoidance of SJS/TEN versus the seizure breakthrough; while the economic consideration is whether this can be justified based on the costs of screening 222 patients, at $59 each. The QALY, which allows for the health impacts of ADRs and seizures to be assessed on the same scale, yields a positive, but small incremental benefit of 9 quality-adjusted days over a lifetime.

A second reason relates to rarity. For less common alleles, and rare ADRs in particular, the incremental benefit of testing becomes diminishingly small as the numbers needed to be screened to prevent one case is high. Consequently, many single-gene tests may not be cost-effective because of the magnitude of the denominator of the incremental cost-effectiveness ratio (ICER). While a very small number of patients will benefit (through the avoidance of a severe ADR), others will have their medication changed unnecessarily to an alternative which may be less effective, more costly and /or associated with other ADRs.

Genotyping for *HLA-B*58:01* prior to allopurinol being prescribed for patients with gout is a case in point. The presence of *HLA-B*58:01* is associated with SJS/TEN and drug reaction with eosinophilia and systematic symptoms (DRESS) in patients taking allopurinol, with incidences of 2 and 11 in 10,000, respectively. The majority of patients (99.87%) would never experience a severe ADR and would be prescribed allopurinol with no health benefits from testing but having incurred the extra cost. Based on allele prevalence in European populations, testing would require 1.1% of patients to switch to febuxostat as an alternative urate-lowering drug. To avoid one case of ADR, 11,286 patients would need to be screened [5]. That one individual will avoid losses of 3.43 QALYs and a healthcare cost of £17,250 ($22,800). However, the other 11,285 patients, on average, will gain just 0.0025 QALYs (about 1 additional quality-adjusted day) while incurring an additional cost of £105 ($140). These QALY gains reflect the increased benefit (0.22 QALYs) in those prescribed febuxostat, while the added costs result from everyone being tested, and some receiving the more expensive alternative. A key point here is that the ICER is based on the differences in mean costs and QALYs which is appropriate for decision-making, but which is not representative of the underlying distributions, as the benefits of testing are experienced in a few and the costs are effectively spread across many.

A third influence on the estimated health benefits of pharmacogenetic testing concerns the scope and perspective of economic evaluations. There may be consequences of pharmacogenetics testing, especially in moving from single-gene testing to panels, next generation sequencing and whole-genomic sequencing, which extend beyond the immediate benefit to the patient. These include the

incidental findings from test results: A test requested for one diagnostic or prognostic purpose will yield information for others. Genome sequencing of patients and their families for hereditary rare diseases or the use of a panel of multiple pharmacogenes, for instance, could reveal incidental findings with important clinical applications. In these cases, the health benefits of testing extend beyond the initial test to include all future uses of the genetic information (i.e. pre-emptive testing). An economic evaluation with a narrow focus will therefore underestimate the health benefits, and result in an ICER which is higher than if the entire range of applications were considered, each at zero marginal cost. A lack of consideration of the impacts of future treatment options for family members or intergenerational effects may also underestimate the overall health benefits and cost-effectiveness of testing.

A fourth reason relates to the nature of the benefits. The QALY is most often based on utilities derived from the EuroQol-5D, which has many limitations, not least a lack of sensitivity for some outcome domains. It does not, for instance, include a dimension for sensory effects, and so would not directly capture the ocular complications of SJS/TEN. Moreover, non-health benefits such as a person or family having the option for a more informed choice, or having increased certainty from diagnosis – regardless of whether there may be appropriate treatment options – are rarely considered in economic evaluations. In such situations, alternative methods of evaluation, such as the willingness to pay or capability approach have been proposed. Importantly, however, is that the outcome used to capture the benefits of genomic testing is also considered in the benefits forgone.

Finally, most of the uncertainty in estimating the value of pharmacogenetic testing in economic evaluations arises not so much from the cost and health impact of ADRs or the consequences of treatment on disease management, but rather from a lack of definitive evidence on the clinical effectiveness of pharmacogenetics testing in improving treatment efficacy or preventing ADRs – there are only a few randomised controlled trials to support routine genotyping. A key challenge moving forward is to define the evidential standards for routine use of pharmacogenetic tests. Non-genetic prognostic factors enjoy a lower evidential threshold for adoption – there is no regulatory requirement, for instance, to undertake clinical trials to show that dosing recommendations for patients with renal or hepatic impairment are equivalent in terms of clinical outcomes. Yet, the implementation of pharmacogenetic testing has been impeded by concerns about clinical effectiveness, and costs. Even where clinical trial and economic evidence supports pharmacogenetic testing, such as in relation to warfarin dosing, the FDA does not require or recommend genotyping for *CYP2C9* or *VKORC1*.

Within healthcare systems with limited, finite budgets, investment decisions result in opportunity costs in the form of forgone health gains to other patients, and economic evaluations of pharmacogenetic tests are increasingly necessary to inform policy recommendations for adoption in routine practice. Key considerations are necessary to ensure that evaluations are unbiased, appropriately scoped and defined to provide accurate estimates of the clinical benefit and value of testing. In the context of using genotyping to exclude the use of a drug, the health benefits are modest across populations, but significant in those who avoid serious ADRs. With increasing possibilities for pre-emptive testing, the cost-effectiveness of diagnostic panels will become more favourable.

References

1. McWilliam A, Lutter R, Nardinelli C. Health Care Savings from Personalizing Medicine Using Genetic Testing: The Case of Warfarin. AEI-Brookings Joint Center for Regulatory Studies 2006. http://pgxlab.com/wp-content/uploads/2012/06/Health-Care-Savings-from-Personalizing-Medicine_AEI-Brookings.pdf
2. Veenstra DL. The value of routine pharmacogenomic screening-Are we there yet? A perspective on the costs and benefits of routine screening-shouldn't everyone have this done? Clin Pharmacol Ther. 2016;99(2):164-6.
3. Plumpton CO, Roberts D, Pirmohamed M, Hughes DA. A Systematic Review of Economic Evaluations of Pharmacogenetic Testing for Prevention of Adverse Drug Reactions. Pharmacoeconomics. 2016;34(8):771-93.
4. Plumpton C, Hughes D. Cost-effectiveness of HLA-B*15:02 screening in Malaysia. Br J Dermatol. 2017;177(4):904-5.
5. Plumpton CO, Alfirevic A, Pirmohamed M, Hughes DA. Cost effectiveness analysis of HLA-B*58:01 genotyping prior to initiation of allopurinol for gout. Rheumatology (Oxford). 2017;56(10):1729-39.