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Towards an economic evidence base for pharmacogenetics: consideration of outcomes is key

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'In the absence of a robust alternative, QALYs are currently widely used by UK decision-makers trying to make difficult decisions about how best to use healthcare resources for maximum patient benefit.'

Using genetic information to target the safe and effective use of medicines offers potential patient benefits but will also have an impact on the use of healthcare resources. Pharmacogenetics has been viewed as something for the future [1], but real clinical examples now exist [2,3]. Some pharmacogenetic tests, such as the thiopurine methyltransferase (TPMT) test that aims to predict the risk of severe neutropenia for the purine drugs azathioprine and 6-mercaptopurine, have relatively low unit costs of approximately £28 [101]. Even low unit cost tests may have a significant cost impact if they have a high volume of uptake in a healthcare system. In England, two clinical laboratories currently offer routine TPMT-enzyme level testing for purine drugs. In 2006, one laboratory reported analyzing 11,167 samples [101] and the second 10,931 samples [A Marinaki, Pers. Comm. 2007]. Assuming both laboratories charge £28 [101] a test, the total cost of testing to the NHS is currently £0.6 million. As pharmacogenetic tests are provided from finite healthcare budgets, there is an opportunity cost associated with diverting funding towards them. Two important issues need to be considered. First, the cost of introducing a pharmacogenetic test includes more than just the cost of the test itself, and the impact on other healthcare resources, such as managing adverse drug reactions and frequency of blood monitoring, needs to be quantified. The types of cost to consider are driven by the perspective of the decision-maker who is responsible for how to spend a given budget. Second, there may be added value associated with introducing a pharmacogenetic test to guide a prescribing decision, in terms of improved health-related quality of life resulting from fewer severe side effects and

improved treatment response in the patient population taking the medicine. This is a complex issue for decision-makers as they have to decide whether to divert scarce healthcare resources to pharmacogenetic testing. It is not clear that decision-makers currently have sufficient robust information on costs and patient benefits to allow an informed trade off.

Pharmacogenetic tests broadly fall into one of two types, those provided through clinical laboratories, such as the TPMT test, and those for which a product license has been granted in a similar way to new medicines, such as Third Wave Technologies' (WI, USA) Invader® UGT1A1 Molecular Assay, which was approved by the US FDA in 2005. For all new medicines, a product licence must be granted before they can be prescribed. The licence will be awarded once the regulatory body is satisfied that there is sufficient information on the product's quality, safety and efficacy. In some countries, specific medicines are selected for further evaluation of evidence of clinical and cost-effectiveness. In England, this appraisal process is carried out by NICE. Laboratories providing genetics and pharmacogenetic tests are required to meet external quality assessment standards, but such tests do not go through the same licensing process as medicines and may emerge into clinical practice without supportive evidence on clinical utility or cost effectiveness.

'Decision makers need to consider which outcomes they deem most useful in the context of pharmacogenetic testing.'

Robust evidence on the economic impact of services and technologies is now considered by health departments and others to be a necessary prerequisite to inform clinical decision making, local and national policy. Economic evaluations potentially provide decision makers with such information and are formally defined as: 'the comparative analysis of alternative courses of action in terms of both their costs and consequences' [4]. It is clear, therefore, that the evaluation involves comparing a minimum of two interventions, one of which

should be current practice, to allow the added value of the new technology to be appraised. The type of economic evaluation is defined by the approach taken to measure the consequences or outcomes in terms of the impact on the patient population receiving the technologies under comparison.

In the UK, NICE uses cost-effectiveness data and asks for outcome measures that are generic [5], rather than ones specific to particular conditions or alleviation of symptoms, to allow direct comparison of interventions with different effects. Examples of generic health status measures include the EQ-5D [6] and the SF-6D [7]. The outcome generally used by NICE is the quality-adjusted life year (QALY), which is the product of quality-of-life and survival [8]. Weightings (utilities) are assigned to the quality-of-life associated with being in a particular health state for each year of survival. Preference-based methods are used to calculate these utilities [5]. Healthcare technologies are then prioritised in terms of those that maximise the improvement in QALYs for a given cost. The use of QALYs to prioritise resources is not without some problems and there have been a number of criticisms [9,10].

‘...we need economic evaluations to inform the appropriate use of pharmacogenetic testing in clinical practice.’

One specific criticism of QALYs for genetic-based technologies is they may not capture all the potential benefits. Focussing on improved health status alone misses key benefits, such as the ability to make an informed life decision for the individual and family members [11]. Cost-benefit analysis uses a monetary valuation of outcome that allows consideration of such nonhealth and process attributes. Process attributes relate to benefits that accrue to patients as a result of how a service is provided, such as the value attached to who explains a particular pharmacogenetic test, and interprets the implications for prescribing [12]. Contingent valuation methods, such as willingness to pay (WTP) or the human capital approach, are used to attach a monetary value to the benefit. Collating WTP data involves asking a sample of respondents to value a hypothetical scenario describing the technology [13]. The relevance of WTP has been criticised in the UK where people are not used to paying for their healthcare, but the approach is used in countries with privately

financed healthcare systems. Further criticisms of WTP center on the hypothetical nature of the exercise [14]. In the absence of a robust alternative, QALYs are currently used widely by UK decision-makers trying to make difficult decisions about how best to use healthcare resources for maximum patient benefit.

Pharmacogenetic tests will also compete for scarce healthcare resources and may also be subject to robust evaluation. Published economic evaluations of pharmacogenetic technologies are notable by their absence [15,16] but the TPMT test is one example where there have been a number of published studies [17–22]. The primary aim of the TPMT test is to reduce the incidence of severe neutropenic episodes associated with purine drugs, and published economic evaluations have generally used this as the primary outcome measure. This is an intermediate rather than a final outcome because it does not tell a decision-maker the impact on overall benefit for a patient population who are tested. Five of the six published evaluations used a measure of ‘neutropenia avoided’ as the prime outcome of interest [17–19,21,22]. Dubinsky *et al.* used time to an initial or sustained response to azathioprine in people with Crohn’s disease [20]. Frequency of leucopenic events was also estimated but there was no real observable difference in this outcome. Marra *et al.* estimated a number needed to treat of 20 to avoid one adverse event over 6 months [17]. Oh *et al.* assumed the probability of not stopping treatment in the first year due to serious adverse events was 99.9% for genotype-based dosing compared with 97.06% for conventional dosing of azathioprine [19]. Two of the models reported cost-per-life years gained by making assumptions, which were not based on data, about the number of deaths averted by introducing TPMT testing [18,22]. Winter *et al.* assumed that one death would be avoided by screening a population of 1000 people with inflammatory bowel disease [18]. Van den Akker-van Marle *et al.* applied the same value and estimated that one death per 1000 children with acute lymphoblastic leukemia would be avoided by TPMT genotyping [22]. Priest *et al.* was the only model to include an estimate of the impact on QALYs [21]. Clinical opinion rather than data from patients was used to describe the EQ-5D health states associated with neutropenia and New Zealand social tariffs were used to estimate weightings for each of the health states [21]. This analysis assumed that no deaths would be avoided from TPMT testing. The enzyme level

(phenotype) test was superior and avoided an estimated 71 cases of neutropenia compared with 40 neutropenias avoided by a genotype test. Small improvements in QALYs were assumed using a phenotype test or genotype test compared with no testing.

All of the published economic evaluations reported TPMT testing to be a cost-effective use of healthcare resources, but it is important to note these were retrospective modeling studies that used existing data to populate a model. Models represent simplifications of clinical pathways involved in the choice of whether or not to use a technology, such as pretreatment TPMT testing. None of the studies identified any actual data that measured the impact of the TPMT test on the number of deaths averted (improved survival) or health-related quality-of-life. The analysts who populated these models therefore had to make assumptions and extrapolate from the assumed number of cases of neutropenia avoided by using the test to estimate the impact on life-years gained. Dubinsky *et al.* discussed how a calculation of QALYs gained was not possible due to lack of data [20]. Priest *et al.* described how they chose to use health-related quality-of-life estimates from clinical experts rather than patients because of convenience [21].

Commentators agree that we need economic evaluations to inform the appropriate use of pharmacogenetic testing in clinical practice

[15,23,24]. There is clearly also a need to consider which outcomes are to be used in such economic evaluations. The QALY has currently been labeled in the UK as the ideal outcome since it allows comparison between interventions used for different conditions and due to the absence of a more robust alternative measure to use. Decision makers need to consider which outcomes they deem most useful in the context of pharmacogenetic testing and whether it is sufficient to know the number of side-effects avoided by introducing the test. One could argue that this information alone is not sufficient to divert healthcare resources to a pharmacogenetic technology and robust information that shows the link between averting side effects and improving the quantity and quality of life years compared with current clinical practice is also necessary. The question that remains unanswered is who will fund the research that is necessary to provide this information.

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