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Cost–effectiveness analysis in pharmacogenomics

The existence of finite healthcare budgets drives the need to consider opportunity cost and demonstrate that pharmacogenomic interventions offer added value, in terms of the relative costs and benefits, compared with current practice. This is where the framework of cost–effectiveness analysis is useful. Existing systematic reviews of economic evaluations of genetic technologies have all highlighted the need to improve the quality of the economics evidence base. More recent cost–effectiveness analyses of pharmacogenomics are generally of higher quality. The future will see an increase in the number of published cost–effectiveness analyses. Critical appraisal of these analyses is necessary to ensure the evidence base is sufficiently robust to inform resource allocation decisions at local and national levels.

KEYWORDS: cost–effectiveness analysis ■ critical appraisal ■ pharmacogenomics

“The past is of no importance. The present is of no importance. It is with the future that we have to deal...”

Oscar Fingal O’Flahertie Wills Wilde
16 October 1854 to 30 November 1900

Oscar Wilde was generally a man of wise words. However, in the context of cost–effectiveness analysis in pharmacogenomics, there is clearly much to learn from the past. The future of cost–effectiveness analysis in pharmacogenomics will only be improved if we recognize what has been achieved to date and move to build on the past. This is the rationale behind the iterative approach to the design and conduct of economic evaluations of healthcare interventions, whereby simple models are constructed when technologies are first introduced and expanded into more complex models as additional data emerges [1].

Pharmacogenomics has introduced the concept of using a companion diagnostic to safely, effectively and cost-effectively target a medicine to a prespecified patient population. The enduring perception is that pharmacogenomics offers potential benefits of decreasing risk of adverse drug events, lowering treatment costs and improving response. The existence of finite healthcare budgets drives the need to consider the opportunity cost of decisions about which healthcare interventions to use. There is a need to demonstrate that pharmacogenomic interventions offer added value, in

terms of the relative costs and benefits, compared with current practice. This is where the framework of cost–effectiveness analysis is useful [2], and is used to assess whether an intervention is technically efficient, which can inform the best way of introducing an intervention into practice. Cost–effectiveness analysis is the most commonly used method of economic evaluation [3], and in the literature the term is often used interchangeably with cost–utility analysis. The methods share the same analytical framework but differ in terms of how benefit is measured, which is an important consideration when designing an economic evaluation [4]. Either method can provide information on the incremental costs and (dis)benefits of a pharmacogenomic intervention.

Past: 2000–2008

A number of overviews of the economic evidence for pharmacogenomic interventions have provided illustrative examples and outlined the key issues to consider when conducting an economic evaluation [5,6]. Between 2003 and 2008, three systematic reviews of economic evaluations of genetic health technologies [7–9] and two systematic reviews with a specific focus on pharmacogenomic interventions [10,11] were conducted (see TABLE 1). All the reviews used different inclusion criteria and assessed the quality of included studies using different approaches. All highlighted the need to improve the quality of the evidence base. In addition, two systematic reviews looking at

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Table 1. Summary of systematic reviews of economic evaluations of genomic health technologies.

Focus of reviews	Study	Date searched	Focus of systematic review	Total studies identified	Pharmacogenomics studies identified	Assessment conducted	Ref.
Economic studies of pharmacogenomics	Phillips and van Beber (2004)	1950 to July 2004	Cost-effectiveness analyses of pharmacogenomic interventions	11 studies	11 studies	Assessment of studies' quality by stringent inclusion criteria and clear description of studies Identification of key drivers of cost-effectiveness and future research priorities	[10]
	Vegter <i>et al.</i> (2008)	2000 to Dec 2007	Economic evaluations of pharmacogenetic and genomic screening program	20 studies	20 studies	Discussion of contents of reviewed studies and adherence to pharmaco-economic guidelines	[11]
Economic studies of genomics	Giacomini <i>et al.</i> (2003)	Oct 1997 to Oct 2002	Economic evaluations of molecular genetic tests	14 studies	Two studies	Detailed discussion on contents of reviewed studies and key issues for economic evaluations of genetic tests	[7]
	Carlson <i>et al.</i> (2005)	1990 to August 2004	Economic evaluations of genetic services	63 studies	Not reported	Assessment of quality of reviewed studies using a published quantitative grading system	[8]
	Jarrett and Mugford (2006)	Jan 1983 to Sept 2005	Economic evaluations of genetic health technologies	37 studies	Not reported	Discussion of contents of reviewed studies	[9]

economic analyses of genetic screening tests [12] and cost-effectiveness studies of TPMT testing for azathioprine [13] have been published. The most recent systematic review by Vegter *et al.* found that 17 of the 20 studies identified were cost-effectiveness (utility) analyses [11]. Most of the 20 studies reported that the pharmacogenomic intervention was cost effective but had poor consistency in adherence to guidelines for conducting economic evaluation, which is in part, but not entirely, explained by country-specific differences in design and reporting requirements. All past studies use retrospective data [10]. Notably, only one published study used clinical evidence from a randomized controlled trial of a pharmacogenomic intervention to populate the economic model [14].

Present: 2009–2010

Recent cost-effectiveness analyses of pharmacogenomics are generally of higher quality, with robust design, use of appropriate analytical methods and clear reporting compared with earlier examples. Some good examples include Meckley *et al.* [15], Carlson *et al.* [16] and Vegter *et al.* [17], which have all incorporated robust sensitivity analyses in the study design.

The primary aim of a cost-effectiveness analysis is to provide sufficiently robust information for decision-makers charged with allocating resources to healthcare interventions [18,19]. The usefulness of results from economic models is determined by the quality of the data used to populate the model, and relevance of the model structure to current and proposed clinical practice. Model structure and data quality have a direct bearing on the degree of uncertainty inherent in the model findings. This uncertainty is formally quantified using sensitivity analysis, and, ideally, probabilistic sensitivity analysis [19].

Currently, there are no prospective economic evaluations of pharmacogenomics that collected economic and outcome data within a randomized controlled trial. The lack of prospective pharmacogenomics economic studies reporting empirical evidence is often cited as a problem with the current evidence base [6]. However, the use of economic decision models are preferred by some decision-making bodies, such as the National Institute for Health and Clinical Excellence (NICE) in the UK, as they facilitate systematic evidence-based analyses of incremental costs and benefits of healthcare interventions [20]. Ideally, model inputs should consist of good quality data collected prospectively.

It is necessary to critique the quality of a cost–effectiveness analysis to be certain that the findings are useful to decision-makers and directly relevant to current and proposed new practice. A number of tools to critique the quality of economic evaluations are available. UK-relevant examples include NHS Economic Evaluation Database criteria [21] and the NICE Reference Case [20], with Philips *et al.* providing criteria to examine the robustness of economic modeling studies [22]. The basic framework of all economic evaluations is the same, but technicalities of the model structure, inputs and interpretation of the findings are country specific. Reviews of the current situation are, in some ways, of limited use, unless the review identifies studies with relevant comparators, and cost and benefit inputs for a clinical setting applicable to the decision-makers.

Future: 2010–2020

Although the quality of the evidence base is improving, the future holds further challenges for economic evaluations of pharmacogenomics. To date, cost–effectiveness analyses have focused on single-gene tests, but high-throughput sequencing methods potentially allow multiple genes to be tested within a short timeframe. More complex models will be required to accurately reflect the number of potential treatment pathways resulting from a multiple-gene pharmacogenomic test.

Understanding the current situation can improve designs of future cost–effectiveness analyses. Existing models can be critically appraised and their structures and inputs modified to more accurately match the research questions of specific decision-makers. Furthermore, simple models can be expanded as additional clinical, cost and patient outcome data become available.

While economic evidence is currently not a criterion for the reimbursement of pharmacogenomics [23], this is likely to change in some jurisdictions. In 2010, NICE will form a Diagnostics Advisory Committee, which is expected to be a key stimulus for manufacturers and academic groups to produce a robust evidence base [101], including improved design and data sources for economic models. Furthermore, the promise of funding specific to the health technology assessment of diagnostics in the UK [24] and increased federal support in the US for comparative effectiveness research [25] may potentially resolve the paucity of data presently troubling the evaluation of pharmacogenomic interventions.

The fundamental aim should be to improve study quality. Acquiring more evidence can reduce uncertainty by providing more precise estimates of effectiveness and costs [18,26]. Diverting funds towards additional research may not be an efficient use of scarce resources if the additional research informs parameters that do not contribute to uncertainty in the model or do not generate data that reduces imprecision of a key parameter. Formal methods, such as value of information, are being increasingly used to explicitly quantify the cost of reducing decision uncertainty for key parameters [26]. Future analyses must also accurately quantify how subsequent treatment pathways and associated costs and outcomes are changed and explore the impact of structural uncertainty using appropriate methods [19] when assessing the added value of pharmacogenomics.

The future may also emphasize additional methodological challenges. For example, an increase in data volume will necessitate robust assimilation of data on pharmacogenomic test accuracy to populate economic models. Meta-analysis of genotype–phenotype association studies pose design and statistical challenges. Sutton *et al.* demonstrated how using different meta-analysis methods to summarize accuracy data of diagnostic tests can affect the results of an economic evaluation [27]. Similar considerations are needed for pharmacogenomic interventions.

The future is expected to see continued efforts to develop a good quality evidence base, which will be the foundation for robust cost–effectiveness analyses of pharmacogenomics. There will be an increase in the number of published cost–effectiveness analyses. Clinicians and decision-makers charged with resource allocation decisions for pharmacogenomics need to understand that economic evaluations are not always designed well or analyzed appropriately, and be ready to critically appraise, either themselves or via a friendly health economist, whether the evidence is sufficiently robust and relevant to inform resource allocation decisions in their locality.

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