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.

"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.


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.

<table>
<thead>
<tr>
<th>Focus of reviews</th>
<th>Study</th>
<th>Date searched</th>
<th>Focus of systematic review</th>
<th>Total studies identified</th>
<th>Pharmacogenomics studies identified</th>
<th>Assessment conducted</th>
<th>Ref.</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Carlson et al. (2005)</td>
<td>1990 to August 2004</td>
<td>Economic evaluations of genetic services</td>
<td>63 studies</td>
<td>Not reported</td>
<td>Assessment of quality of reviewed studies using a published quantitative grading system</td>
<td>[8]</td>
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</table>

**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. The usefulness of results from economic models is determined by the quality of the data used to populate the model and the 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. Currently, there are no prospective economic evaluations of pharmacogenomic interventions that consider the use of some decision-analysis models, such as the National Institute for Health and Clinical Excellence (NICE) in the UK, as they facilitate systematic evidence-based analyses of interventions. 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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No writing assistance was utilized in the production of this manuscript.
**Systematic review summarizes economic analyses of pharmacogenomic interventions up until December 2007.**


**Discusses the concept of understanding whether there is economic evidence sufficient to inform decision-making.**


**Describes the complexities of performing meta-analyses of diagnostic data.**

### Website

101. National Institute for Health and Clinical Excellence


(Accessed 21 January 2010)