**TITLE:** Cost-effectiveness of a multi-gene panel in the context of reducing adverse drug reactions

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**OBJECTIVES:** Adverse drug reactions (ADRs) are a major causes of iatrogenic morbidity and mortality. Genetic variations, which can be identified through prospective genotyping may predispose a patient to ADRs. We aimed to develop an evaluation framework for assessing the cost-effectiveness of multiple-gene testing in the context of ADR reduction, taking into consideration the benefits of incidental findings.

**METHODS:** We developed a decision-analytic framework for combining results from existing cost-effectiveness evaluations of single-gene tests. The framework is underpinned by a series of logical assumptions relating to their cost-effectiveness, both inclusive and exclusive of the cost of genotyping. Weighted combinations of costs and QALYs from existing analyses of single-gene tests provide a basis for estimating the outcomes of incidental findings, which are combined to provide an overall estimate of cost-effectiveness for the multi-gene test.

We present an example based on existing studies of genotyping for *HLA-A\*31:01* prior to prescription of carbamazepine, and *HLA-B\*58:01* prior to prescription of allopurinol.

Scenario analyses examine the complex relationship between the inclusion of single gene tests in the panel, the cost-effectiveness threshold, and the cost of the panel. Probabilistic sensitivity analysis explores parameter uncertainty.

**RESULTS:** Independently, single-gene tests for *HLA-A\*31:01* but not *HLA-B\*58:01* are cost-effective. *HLA-B\*58:01* was cost-effective as an incidental finding. The incremental cost-effectiveness ratio for the panel was £13,464, based on a panel test cost of £50. In the sensitivity analysis, for 82% of replications, at least one test was cost-effective prospectively. As the test cost decreases, or the cost-effectiveness threshold increases, the likelihood that both single-genes were cost-effective increases.

**CONCLUSIONS:** We present a framework for assessing the cost-utility of multiple gene testing for predicting and pre-empting ADRs. For a case study of two single-gene tests, we show that a cost-ineffective test becomes cost-effective when the results are revealed as the incidental finding of a panel test result.