Health Technology Assessment 2010; Vol. 14: No. 3

The clinical effectiveness and cost-effectiveness of testing for cytochrome P450 polymorphisms in patients with schizophrenia treated with antipsychotics: a systematic review and economic evaluation

N Fleeman, C McLeod, A Bagust, S Beale, A Boland, Y Dundar, A Jorgensen, K Payne, M Pirmohamed, S Pushpakom, T Walley, P de Warren-Penny and R Dickson

January 2010
DOI: 10.3310/hta14030

Health Technology Assessment
NIHR HTA programme
www.hta.ac.uk

How to obtain copies of this and other HTA programme reports
An electronic version of this title, in Adobe Acrobat format, is available for downloading free of charge for personal use from the HTA website (www.hta.ac.uk). A fully searchable DVD is also available (see below).

Printed copies of HTA journal series issues cost £20 each (post and packing free in the UK) to both public **and** private sector purchasers from our despatch agents.

Non-UK purchasers will have to pay a small fee for post and packing. For European countries the cost is £2 per issue and for the rest of the world £3 per issue.

How to order:

– fax (with **credit card details**)
– post (with **credit card details** or **cheque**)
– phone during office hours (**credit card** only).

Additionally the HTA website allows you to either print out your order or download a blank order form.

Contact details are as follows:

Synergie UK (HTA Department)
Digital House, The Loddon Centre
Wade Road
Basingstoke
Hants RG24 8QW

Email: orders@hta.ac.uk

Tel: 0845 812 4000 – ask for 'HTA Payment Services' (out-of-hours answer-phone service)

Fax: 0845 812 4001 – put 'HTA Order' on the fax header

Payment methods

Paying by cheque
If you pay by cheque, the cheque must be in **pounds sterling**, made payable to *University of Southampton* and drawn on a bank with a UK address.

Paying by credit card
You can order using your credit card by phone, fax or post.

Subscriptions

NHS libraries can subscribe free of charge. Public libraries can subscribe at a reduced cost of £100 for each volume (normally comprising 40–50 titles). The commercial subscription rate is £400 per volume (addresses within the UK) and £600 per volume (addresses outside the UK). Please see our website for details. Subscriptions can be purchased only for the current or forthcoming volume.

How do I get a copy of *HTA on DVD*?

Please use the form on the HTA website (www.hta.ac.uk/htacd/index.shtml). *HTA on DVD* is currently free of charge worldwide.

The website also provides information about the HTA programme and lists the membership of the various committees.

The clinical effectiveness and cost-effectiveness of testing for cytochrome P450 polymorphisms in patients with schizophrenia treated with antipsychotics: a systematic review and economic evaluation

N Fleeman,[1] C McLeod,[1] A Bagust,[1] S Beale,[2] A Boland,[1] Y Dundar,[1,3] A Jorgensen,[4] K Payne,[5] M Pirmohamed,[6] S Pushpakom,[6] T Walley,[1] P de Warren-Penny[7] and R Dickson[1]*

[1]Liverpool Reviews and Implementation Group (LRiG), University of Liverpool, UK
[2]York Health Economics Consortium, University of York, UK
[3]Health Methodology Research Group, School of Community Based Medicine, University of Manchester, UK
[4]Medical Statistics, University of Liverpool, UK
[5]The Hesketh Centre, Merseyside NHS Trust, Southport, UK
[6]Department of Pharmacology and Therapeutics, University of Liverpool, UK
[7]North Devon District Hospital, Barnstaple, UK

*Corresponding author

Declared competing interests of authors: Professor Tom Walley is Editor-in-Chief of *Health Technology Assessment*, although he was not involved in the editorial processes for this report.

Published January 2010
DOI: 10.3310/hta14030

This report should be referenced as follows:

Fleeman N, McLeod C, Bagust A, Beale S, Boland A, Dundar Y, *et al.* The clinical effectiveness and cost-effectiveness of testing for cytochrome P450 polymorphisms in patients with schizophrenia treated with antipsychotics: a systematic review and economic evaluation. *Health Technol Assess* 2010;**14**(3).

Health Technology Assessment is indexed and abstracted in *Index Medicus*/MEDLINE, *Excerpta Medica*/EMBASE, *Science Citation Index Expanded* (*SciSearch*®) and *Current Contents*®/Clinical Medicine.

NIHR Health Technology Assessment programme

The Health Technology Assessment (HTA) programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

The research findings from the HTA programme directly influence decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC). HTA findings also help to improve the quality of clinical practice in the NHS indirectly in that they form a key component of the 'National Knowledge Service'.

The HTA programme is needs led in that it fills gaps in the evidence needed by the NHS. There are three routes to the start of projects.

First is the commissioned route. Suggestions for research are actively sought from people working in the NHS, from the public and consumer groups and from professional bodies such as royal colleges and NHS trusts. These suggestions are carefully prioritised by panels of independent experts (including NHS service users). The HTA programme then commissions the research by competitive tender.

Second, the HTA programme provides grants for clinical trials for researchers who identify research questions. These are assessed for importance to patients and the NHS, and scientific rigour.

Third, through its Technology Assessment Report (TAR) call-off contract, the HTA programme commissions bespoke reports, principally for NICE, but also for other policy-makers. TARs bring together evidence on the value of specific technologies.

Some HTA research projects, including TARs, may take only months, others need several years. They can cost from as little as £40,000 to over £1 million, and may involve synthesising existing evidence, undertaking a trial, or other research collecting new data to answer a research problem.

The final reports from HTA projects are peer reviewed by a number of independent expert referees before publication in the widely read journal series *Health Technology Assessment*.

Criteria for inclusion in the HTA journal series

Reports are published in the HTA journal series if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The research reported in this issue of the journal was commissioned and funded by the HTA programme on behalf of NICE as project number 06/28/01. The protocol was agreed in October 2007. The assessment report began editorial review in December 2008 and was accepted for publication in April 2009. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

The views expressed in this publication are those of the authors and not necessarily those of the HTA programme or the Department of Health.

ISSN 1366-5278

Published by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk), on behalf of NETSCC, HTA.

Printed on acid-free paper in the UK by Henry Ling Ltd, The Dorset Press, Dorchester.

Abstract

The clinical effectiveness and cost-effectiveness of testing for cytochrome P450 polymorphisms in patients with schizophrenia treated with antipsychotics: a systematic review and economic evaluation

N Fleeman,[1] C McLeod,[1] A Bagust,[1] S Beale,[2] A Boland,[1] Y Dundar,[1,3] A Jorgensen,[4] K Payne,[5] M Pirmohamed,[6] S Pushpakom,[6] T Walley,[1] P de Warren-Penny[7] and R Dickson[1]*

[1]Liverpool Reviews and Implementation Group (LRiG), University of Liverpool, UK
[2]York Health Economics Consortium, University of York, UK
[3]Health Methodology Research Group, School of Community Based Medicine, University of Manchester, UK
[4]Medical Statistics, University of Liverpool, UK
[5]The Hesketh Centre, Merseyside NHS Trust, Southport, UK
[6]Department of Pharmacology and Therapeutics, University of Liverpool, UK
[7]North Devon District Hospital, Barnstaple, UK

*Corresponding author

Objective: To determine whether testing for cytochrome P450 (*CYP*) polymorphisms in adults entering antipsychotic treatment for schizophrenia leads to improvement in outcomes, is useful in medical, personal or public health decision-making, and is a cost-effective use of health-care resources.

Data sources: The following electronic databases were searched for relevant published literature: Cochrane Controlled Trials Register, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effectiveness, EMBASE, Health Technology Assessment database, ISI Web of Knowledge, MEDLINE, PsycINFO, NHS Economic Evaluation Database, Health Economic Evaluation Database, Cost-effectiveness Analysis (CEA) Registry and the Centre for Health Economics website. In addition, publicly available information on various genotyping tests was sought from the internet and advisory panel members.

Review methods: A systematic review of analytical validity, clinical validity and clinical utility of *CYP* testing was undertaken. Data were extracted into structured tables and narratively discussed, and meta-analysis was undertaken when possible. A review of economic evaluations of *CYP* testing in psychiatry and a review of economic models related to schizophrenia were also carried out.

Results: For analytical validity, 46 studies of a range of different genotyping tests for 11 different *CYP* polymorphisms (most commonly *CYP2D6*) were included. Sensitivity and specificity were high (99–100%). For clinical validity, 51 studies were found. In patients tested for *CYP2D6*, an association between genotype and tardive dyskinesia (including Abnormal Involuntary Movement Scale scores) was found. The only other significant finding linked the *CYP2D6* genotype to parkinsonism. One small unpublished study met the inclusion criteria for clinical utility. One economic evaluation assessing the costs and benefits of *CYP* testing for prescribing antidepressants and 28 economic models of schizophrenia were identified; none was suitable for developing a model to examine the cost-effectiveness of *CYP* testing.

Conclusions: Tests for determining genotypes appear to be accurate although not all aspects of analytical validity were reported. Given the absence of convincing evidence from clinical validity studies, the lack of clinical utility and economic studies, and the unsuitability of published schizophrenia models, no model was developed; instead key features and data requirements for economic modelling are presented. Recommendations for future research cover both aspects of research quality and data that will be required to inform the development of future economic models.

Contents

Glossary and list of abbreviations

Glossary

5-HT (5-hydroxytryptamine or serotonin) A monoamine neurotransmitter that plays an important role in the modulation of mood.

ACCE An acronym for a model process developed by the Foundation for Blood Research through a cooperative agreement with the Centers for Disease Control and Prevention in the USA for evaluating data on emerging genetic tests, taken from the four components of genetic testing evaluation – *a*nalytical validity, *c*linical validity, *c*linical utility and *e*thical, legal and social implications.

Active metabolite This is when the metabolite of a drug produces a therapeutic effect.

ADME A common acronym used to describe the manner in which an agent is processed within an organism – *a*bsorption, *d*istribution, *m*etabolism and *e*xcretion.

Allele In humans an allele is a member of a pair of different forms of a gene.

DNA (deoxyribonucleic acid) A nucleic acid which contains the genetic instructions that make up living organisms.

DNA sequence A DNA sequence consists of a double strand of DNA molecules, which are made up of even smaller molecules known as nucleotides.

Enzyme A protein molecule produced by living organisms that catalyses chemical reactions of substances (including drugs).

False-positive case A misclassified case in which the case is classified as positive for a condition (or particular genotype) by a test instead of being classified as negative.

Gene The basic biological unit of heredity – a segment of DNA that contributes to phenotype/function.

Genome Sum total of the genetic material included in every cell of the human body, apart from the red blood cells.

Genotype The genetic constitution of an individual, i.e. the specific allelic makeup of an individual.

Heterozygote A person who has two copies of an allele that are different.

Homozygote A person who has two copies of an allele that are the same.

Locus A specific position on the genome, e.g. where a particular nucleotide is located.

Metabolite A substance produced during metabolism (when it is drugs being metabolised, this usually refers to the end product that remains after metabolism).

Nucleotide Small molecules that are the basic constituents of DNA.

Penetrance The proportion of individuals carrying a particular genotype who also express a particular phenotype.

Pharmacogenetics A term used to define inherited variability in response to drug treatment.

Phenotype The observable physical or behavioural traits of an organism, largely determined by the organism's genotype but also influenced by environmental factors.

Predictive value Ratio of true-positive cases to combined true- and false-positive cases.

Prodrug An agent that is administered in a significantly less active form, which, once administered, is metabolised in vivo into the active compound (active metabolite).

continued

Protein molecule A complete biological molecule made up of amino acids arranged in a linear chain defined by a gene and encoded in the genetic code. Types of proteins include enzymes and receptors.

Receptor A protein molecule embedded in a membrane to which a signal molecule (ligand) such as a pharmaceutical drug may attach itself to and which usually initiates a cellular response (although some ligands merely block receptors without inducing any response).

Sensitivity The proportion of true-positive cases that are correctly identified by a test.

Single-nucleotide polymorphism (SNP) The most common type of genetic variation in humans, which occurs when a single nucleotide [adenosine (A), guanine (G), cytosine (C) or thymine (T)] in the genome sequence is changed.

Specificity The proportion of true-negative cases that are correctly identified by a test.

Substrate A substance that is acted upon by an enzyme.

True-positive case A case correctly identified by a test as possessing a particular condition (or genotype).

List of abbreviations

5-HT	5-hydroxytryptamine
ADR	adverse drug reaction
AHRQ	Agency for Healthcare Research and Quality
AIMS	Abnormal Involuntary Movement Scale
AS-PCR	allele-specific polymerase chain reaction
BPRS	Brief Psychiatric Rating Score
CATIE	Clinical Antipsychotic Trials in Intervention Effectiveness
CI	confidence interval
CL/F	oral clearance
CUtLASS	Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study
CYP	cytochrome P450
CYP450	cytochrome P450
DALY	disability-adjusted life-year
EM	extensive metaboliser
EPS	extrapyramidal symptoms
ESRS	Extrapyramidal Symptoms Rating Scale
FDA	Food and Drug Administration
IM	intermediate metaboliser
HTA	Health Technology Assessment
IPD	individual patient data
mut	mutant type
NICE	National Institute for Health and Clinical Excellence
NIHR	National Institute for Health Research
NSF	National Service Framework
OR	odds ratio

PANSS	Positive and Negative Syndrome Scale
PCR	polymerase chain reaction
PCR-RFLP	polymerase chain reaction–restriction fragment length polymorphism
PM	poor metaboliser
QALY	quality-adjusted life-year
QTc	QT interval
SAS	Simpson–Angus Scale
SD	standard deviation
SMR	standardised mortality ratio
SNP	single-nucleotide polymorphism
SSRIs	selective serotonin reuptake inhibitors
TD	tardive dyskinesia
TDL	The Doctors Laboratory
TDRS	Tardive Dyskinesia Rating Scale
TRS	treatment-resistant schizophrenia
UM	ultrarapid metaboliser
WMD	weighted mean difference
wt	wild type

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has only been used once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure or table legend.

Executive summary

Objectives

The overarching questions that this review aimed to answer were:

- Could testing for cytochrome P450 (*CYP*) polymorphisms in adults entering antipsychotic treatment for schizophrenia lead to improvement in outcomes?
- Are testing results for *CYP* polymorphisms useful in medical, personal or public health decision-making?
- Is testing for *CYP* polymorphisms in schizophrenia patients treated with antipsychotics a cost-effective use of health-care resources?

Background

Mental health is recognised as a major challenge in UK clinical practice and as such it is one of the nine National Service Frameworks. Schizophrenia is a condition requiring immediate attention but it is complex both to diagnose and to treat. Treatment of schizophrenia is especially difficult because of the large amount of interindividual variability in patient response to therapy. This high degree of heterogeneity is associated with adverse drug reactions (ADRs) or therapeutic failure, which has important implications for both the patient and the UK NHS.

The interindividual variability to therapy may in part be explained by differences in the enzymes responsible for metabolising drugs to their excretable forms, in particular the CYP enzyme system. A number of antipsychotics (both typical and atypical) are metabolised by CYP2D6 and CYP3A4, and to a lesser extent CYP1A2, including haloperidol, risperidone and clozapine.

Diagnostic genotyping tests for certain CYP enzymes are now available. The first licensed test is the AmpliChip® CYP450 test, which tests for both *CYP2D6* and *CYP2C19*. *CYP* testing for prescribing antipsychotics to schizophrenia patients would be attractive if it could improve response rates or reduce side effects from treatment.

Methods

A systematic review of the analytical validity, clinical validity and clinical utility of *CYP* testing was undertaken. A review of economic evaluations of *CYP* testing in the field of psychiatry was also undertaken, as was a review of schizophrenia models.

Several search strategies were used in various databases including EMBASE, MEDLINE and the Cochrane Library. Searches related to analytical and clinical validity were carried out up to January 2008, whereas searches for clinical utility were carried out up to March 2008.

Data were extracted into structured tables and are narratively discussed in the relevant sections of the report. Meta-analysis was also undertaken where possible. For the purpose of meta-analysis, patients with multiple copies (more than two) of *wt* alleles were considered to be *wt*/*wt*, which it should be noted may dilute effects, given that such patients are ultrarapid metabolisers (UMs) and so will metabolise drugs quicker than patients with just two *wt* alleles. Given data limitations, economic modelling was not feasible, therefore key issues relating to the existing evidence base and future research needs were narratively discussed.

Inclusion criteria

For the reviews of analytical validity, clinical validity and clinical utility any study design except single case studies was included. In the case of analytical validity any patient population was accepted, whereas in the case of clinical validity and clinical utility only adults with schizophrenia receiving treatment were included. Outcome measures included accuracy of the test, measures of pharmacokinetic bioavailability, efficacy, ADRs and clinical outcomes.

For the economic literature review, economic evaluations that considered both the costs and the benefits of *CYP* testing were included in the review. For the review of schizophrenia models, models were included if they modelled antipsychotic therapy in any schizophrenia population and if they were published in English.

Results

Clinical evaluation

For analytical validity, 46 studies of a range of different genotyping tests for 11 different *CYP* polymorphisms (most commonly *CYP2D6*) were included. Sensitivity and specificity was typically found to be 99–100%. For clinical validity, 51 studies were found in which very few patients had either the *mut/mut* genotype or multiple copies (more than two) of the *wt* allele. These studies mainly focused on ADRs; there was some evidence from prospective studies of patients tested for *CYP2D6* that, compared with those with the *wt/wt* genotype, patients with the *wt/mut* and *mut/mut* + *wt/mut* genotypes were at increased risk of tardive dyskinesia (TD) [odds ratio (OR) 2.08, 95% confidence interval (CI) 1.21 to 3.57, and OR 1.83, 95% CI 1.09 to 3.08 respectively]. In cross-sectional studies, those with the *mut/mut* genotype also had higher Abnormal Involuntary Movement Scale (AIMS) scores (measuring TD severity) than those with the *wt/wt* genotype [weighted mean difference (WMD) 1.80, 95% CI 0.40 to 3.19]. The only other significant finding was that patients with the *CYP2D6 mut/mut* + *wt/mut* genotype were significantly more likely to develop parkinsonism than those with the *wt/wt* genotype (OR 1.64, 95% CI 1.04 to 2.58). No published studies were found that met the inclusion criteria for clinical utility.

Economic evaluation

Only one economic evaluation assessing the costs and benefits of *CYP* testing for prescribing antidepressants was identified from our search and subsequently included in our review. Although not directly relevant to our decision problem the study did highlight the difficulties in undertaking an economic analysis in this area. Results from our search for a suitable schizophrenia model for adaptation and use in our review identified a total of 28 models, none of which was suitable for our purposes.

The absence of published economic studies of *CYP* testing for schizophrenia, the lack of evidence from the clinical component of this review and the unsuitability of published schizophrenia models meant that no model was developed; instead, the key features and data requirements of an economic model were discussed. This identified that there are still a number of factors that are unknown both for schizophrenia as a condition and in relation to the *CYP* pharmacogenetic test.

Conclusions

From this review of the literature, tests for determining genotypes appear to be highly accurate. However, not all aspects of analytical validity have been reported in the studies (quality control and assay robustness being commonly neglected). In terms of clinical validity, research is being conducted to assess the links between genotype and metabolism and ADRs. However, to date the research is limited and no firm conclusions can be drawn. No studies assessing clinical utility have been reported.

In terms of assessing the cost-effectiveness of using such pharmacogenetic testing, in the opinion of the authors it is too soon to tell. An economic model was not developed as a part of this report but, from previous work carried out in the area of pharmacogenetic testing in depression and through the assessment of published economic models of schizophrenia, a suggested model framework has been developed.

Our proposed model framework consists of four main modules: pharmacogenetic test module (assigning patient to phenotype), clinical effects module (linking phenotype to outcomes), transitional module (effect of test results on clinical decision) and the schizophrenia module (projecting treatment effects over a patient's lifetime). Without all four components and the information to populate them it is not possible to determine the cost-effectiveness of *CYP* testing in schizophrenia.

However, on the basis of a single test per patient costing around £300, the expected lifetime benefit per patient need be only about 0.01 quality-adjusted life-years (QALYs) to achieve cost-effectiveness of ≤ £30,000 per QALY gained. If any survival improvement can be shown to be supported by evidence then this level of gain appears to be modest, particularly if opportunities arise to target testing to those patients most likely to show improvements in their care and expected outcomes. Therefore, *CYP* pharmacogenetic testing still shows promise, but further research is needed.

Recommendations for future research

Although the current evidence base does not support the use of pharmacogenetic testing in this area, it does indicate that further study in each of the key areas is needed to either demonstrate

or refute the ability of pharmacogenetic testing to assist in the development of individualised patient care in the area of schizophrenia. Recommendations for future research cover both aspects of research quality and data that will be required to inform the development of future economic models.

Analytical validity

- Studies of analytical validity need to be explicit about patient selection, quality control, assay robustness and the sensitivity and specificity of tests. Study findings should not only report on allele frequencies but also report appropriate genotype data.

Clinical validity

- Further evidence is required to link phenotype to genotype. Such studies need to include larger numbers of patients with the UM (multiple copies of the *wt* allele) and poor metaboliser (*mut*/*mut*) phenotypes and be prospective in design.
- Studies need to consider the impact of environmental factors such as smoking, concomitant medicines, medication adherence and ethnicity. In relation to medication adherence, genotypes need to be related not only to clinical parameters but also to pharmacokinetic parameters.
- Studies need to ensure that all currently used antipsychotics are investigated. However, given the uncertainty about the full extent of the role played by CYP2D6, further studies focusing on patients taking risperidone and olanzapine would also be useful.
- Future research will need to consider a comprehensive approach that considers not only CYP isoforms involved in the metabolism of antipsychotics but also other targets such as dopamine and 5-hydroxytryptamine receptors.

Clinical utility

- Prospective clinical utility studies are needed. As with clinical validity they should ensure that all currently used antipsychotics are investigated although, given their importance to the NHS (and the uncertainty about the full extent of the role played by CYP2D6), further studies focusing on patients taking risperidone and olanzapine would be particularly useful.

Economic evaluation

- Improved evidence should be sought on the link between improved schizophrenia care and life expectancy.
- Collection of longitudinal data that identify patterns of adherence, length of time in relapse and cost of care (including care provided in the community) is required.
- A common approach to the measurement and reporting of adherence, relapse and quality of life in schizophrenia is needed.

Chapter 1

Assessment aims

The review evaluated the clinical effectiveness and cost-effectiveness of testing for cytochrome P450 (hereafter abbreviated to *CYP*) polymorphisms in patients with schizophrenia treated with antipsychotics.

The overarching questions that this review aimed to answer were:

- Could testing for *CYP* polymorphisms in adults entering antipsychotic treatment for schizophrenia lead to improvement in outcomes?
- Are testing results for *CYP* polymorphisms useful in medical, personal or public health decision-making?
- Is testing for *CYP* polymorphisms in schizophrenia patients treated with antipsychotics a cost-effective use of health-care resources?

To answer the clinical overarching questions, three key clinical areas were considered:

- Analytical validity:
  - What is the analytical validity of tests that identify key *CYP* polymorphisms?
- Clinical validity:
  - How well do particular *CYP* genotypes predict metabolism of particular antipsychotics?
  - How well does *CYP* testing predict drug efficacy and adverse drug reactions (ADRs)?
- Clinical utility:
  - Does *CYP* testing influence disease management decisions by patients and providers in ways that could improve or worsen outcomes?
  - Could the identification of *CYP* genotype in adults entering treatment lead to improved clinical outcomes compared with not testing?
  - What are the harms associated with testing for *CYP* polymorphisms and subsequent management options?

Chapter 2
Background

Possibilities for individualised patient care

There is wide variability in the response of individuals to standard doses of drug therapy, which may occur as a result of interindividual differences that may be inherited (pharmacogenetics). Thus, there is growing anticipation among scientists, health-care providers and the general public that tests to identify genetic differences will be available and be used to more specifically direct the prescribing of therapeutic agents (pharmacogenetic testing), improving our ability to personalise therapies and subsequently improving clinical outcomes.[1]

Genetics

There are approximately 50,000 genes in the human genome. Inherited variation in genes coding for metabolising enzymes and drug transporters (polymorphisms) may alter drug response and toxicity. Each gene is made up of a deoxyribonucleic acid (DNA) sequence. A DNA sequence consists of a double strand of DNA molecules, with these molecules made up of even smaller molecules known as nucleotides. Most of the DNA sequence is identical from one individual to the next in that the same type of nucleotide [adenosine (A), guanine (G), cytosine (C) or thymine (T)] occurs at the same locus between individuals. However, there are a small proportion of loci where the type of nucleotide varies from one individual to the next; these parts of the DNA sequence are known as single-nucleotide polymorphisms (SNPs) and they are the most common type of genetic variation in humans. As DNA exists in double strands, these nucleotides exist in pairs (one nucleotide on each strand). Alternative forms of a nucleotide that can occur at a particular locus of the genome are known as alleles.

Loci usually have two possible alternative alleles commonly known as wild type (*wt*) or mutant (*mut*), with the *wt* allele being the most common allele found in the general population. Thus, for example, at a given locus where it is possible to have either an adenosine or a thymine nucleotide, if the adenosine nucleotide is the most common then this would be identified as the *wt* allele. Genotypes are derived from the alleles [e.g. *wt/wt* (also known as homozygous wild type) or *wt/mut* (also known as heterozygous wild type)] and thus these SNPs give rise to the variation in genotype and phenotype across individuals.

Pharmacogenetic testing

Technologies used for genetic testing (commonly called genotyping) have undergone a revolution in recent years. Since the discovery of DNA, scientists have been trying to unravel the genetic knowledge and find ways of applying it for the benefit of mankind. The problem of obtaining sufficient quantities of DNA for genetic manipulation, which was the single biggest obstacle faced by molecular biologists, was solved by the very significant development of the polymerase chain reaction (PCR) by Kary Mullis in 1983. This discovery, coupled with the advent of DNA sequencing (first developed by Frederick Sanger), significantly accelerated genetic research and discovery.

Attainment of rapid speeds of DNA sequencing by modern technologies led to the complete sequencing of the human genome (Human Genome Project) and shed more light on variations that exist in individual genomes such as SNPs and copy number variations. Recent years have seen major strides taken in genotyping technologies, thus making them more robust and easier to use as well as costing less per SNP genotyped. In addition, point-of-care tests are also being developed, which in some cases may facilitate translation into a clinical environment. A summary of the most common genotyping techniques available is provided in *Table 1*.

To assist policy-makers in the process of making decisions regarding the use of genetic testing in the delivery of patient care, the ACCE model has been developed. Based on previously published methodologies and terminology, this collaboration between the Foundation for Blood Research and the Centers for Disease Control and Prevention (CDC) in the USA includes four key components that are required for evaluating any genetic

TABLE 1 *Common genotyping techniques*

Genotyping platforms	Principle involved	Throughput	Advantages/disadvantages
AS–PCR	Hybridisation with allele-specific probes	Low	Only singleplex possible (one SNP at a time)
Bead arrays	Sequence-coded microspheres/fluorimetric detection	High	Can multiplex Quantification of allelic ratios possible Limitations in availability of unique microspheres Costly dedicated equipment required
Invader assay	Enzymatic cleavage followed by FRET-based estimation	High	Multiplex formats available Requires larger amounts of DNA
Microarrays (gene chips)	Allele-specific hybridisation/ fluorescence detection	Very high (500,000 SNPs at a time; Affymetrix)	Very high probe density Built-in probe features (mismatch probes) to minimise false calls Dedicated expensive equipment required Complex software required to interpret data
Molecular beacons	Non-linear allele-specific probes/FRET-based estimation	Medium	Multiplex up to 10 SNPs Use of non-linear probes increases probe specificity
PCR-RFLP	Enzymatic cleavage of restriction sites followed by electrophoretic detection	Low	Singleplex only Time-consuming setup Incomplete enzyme digestion leads to false genotype calls
Pyrosequencing™	Primer extension followed by enzyme-mediated luminometric detection	Medium	Dedicated equipment (Pyrosequencer) required Time-consuming setup Limited scope for multiplexing
Sequenom	Primer extension/MALDI-TOF (matrix-associated laser desorption time-of-flight) mass spectrometry	High	Multiplex up to 40 SNPs at a time Relatively cheap Requires well-purified PCR products Requires dedicated expensive equipment
SNaPshot®	Electrophoretic size separation	High	Relatively cheap Can be performed on 96-channel sequencers common in genotyping laboratories Multiplex up to 6 SNPs Time-consuming
TaqMan®	FRET	Medium	Useful for genotyping larger sample sizes Robust Automated calling Only singleplex available Costly if only for smaller sample sizes

AS-PCR, allele-specific PCR; FRET, fluorescence resonance energy transfer; PCR-RFLP, polymerase chain reaction–restriction fragment length polymorphism; SNP, single-nucleotide polymorphism.

test (and which thus give the model its name): *a*nalytical validity; *c*linical validity; *c*linical utility; and *e*thical, legal and social implications (*Figure 1*).

Although many genetic tests are concerned with testing for diseases, increasingly pharmacogenetic tests are also being developed to predict the probability of an individual's response to drug treatment in terms of efficacy and ADRs and as such the key components should also be generally applicable to pharmacogenetic tests.

Analytical validity in the process includes evaluation of all aspects related to the accuracy and reliability of genotype testing and includes sensitivity, specificity, quality control and robustness

of the assessment process. Assessment of clinical validity begins with linking the four components of analytical validity and then assessing the other five elements identified in *Figure 1*. In relation to pharmacogenetics, the important outcomes to consider are the relationships between genotypes and phenotypes, with outcomes arising from the treatments currently being used in the clinical condition being considered, specifically efficacy and ADRs. Clinical utility refers to the ability to use the information from analytical and clinical validity in clinical practice. Establishing clinical utility is therefore important and should consider evidence for the use of pharmacogenetic testing to prospectively predict clinical outcomes and to modify clinical management (e.g. changing doses or switching drugs based on genotype tests). Harms associated with tests also need to be considered. These may include increased cost without impact on clinical decision-making or improvement in patient outcomes, less effective treatment with drugs, or inappropriate use of genotype information in the management of other drugs metabolised by particular enzymes.

To date, studies and reviews of pharmacogenetic tests have yielded insufficient evidence for any unequivocal benefit in terms of clinical validity or utility in a wide range of clinical areas including psychiatry (selective serotonin reuptake inhibitors for patients with non-psychotic depression[3]). Part of the difficulty in establishing an evidence base may be attributed to the fact that response may be multifactorial and multigenic, being dependent not only on CYP enzymes but also on phase II enzymes and differences in the drug targets. Thus, recent evidence-based recommendations issued in this field have urged further studies to be completed before testing can be recommended.[4]

Nevertheless, in December 2004 the AmpliChip,® which is a microarray-based test, became the first test to be granted market approval in the USA by the Food and Drug Administration (FDA),[5] as well as in the EU.[5,6] This test is intended to identify a patient's *CYP2D6* and *CYP2C19* genotype from genomic DNA extracted from a whole blood sample and thus provide a predicted metabolic phenotype. There are other technologies also

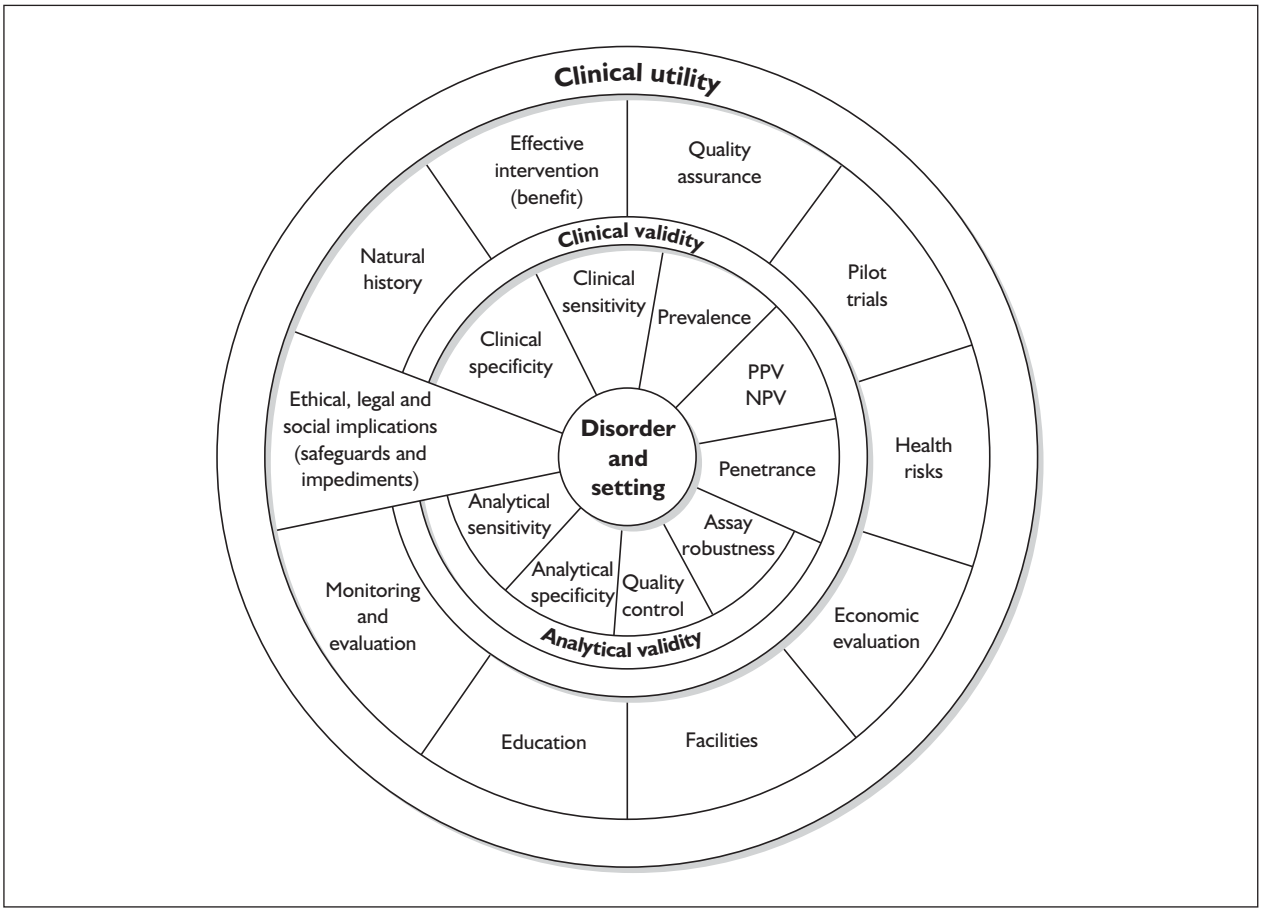


FIGURE 1 *ACCE evaluation process for genetic testing taken from Palomaki et al.[2] PPV, positive predictive value; NPV, negative predictive value.*

available for genotyping of CYP enzymes, as well as the other genes that can influence drug response, and there is no doubt that other genotyping technologies will follow, including point-of-care tests. Currently the tests available for pharmacogenetics include *HER2* (herceptin), *HLA-B*5701*, thiopurine methyltransferase, *G6PD*, factor V Leiden, the caffeine contracture test (for malignant hyperthermia) and pseudocholinesterase deficiency. Not all of these are genotypic tests; some are phenotypic.

This report has been commissioned by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme to address the issues of pharmacogenetic testing related to the use of antipsychotics for schizophrenia. Specifically the report addresses the issues related to the clinical and cost-effectiveness of testing for *CYP* polymorphisms in patients treated with antipsychotics. As such, the remainder of this report deals with the issues of pharmacogenetics related to this specific area. The report uses as its base the ACCE process and then goes on to discuss the economic implications of this new and evolving technology.

CYP enzyme system

A link between drug metabolism and drug response has been widely discussed in the literature and a significant proportion of this literature is focused on the CYP enzyme system, which has been identified as a major metabolic pathway for many drugs and a source of interindividual variability in patient response.[7,8] The CYP enzyme system contains major phase I enzymes involved in the metabolism of a number of substrates. There are 57 *CYP* genes in humans with each gene being named with *CYP*, indicating that it is part of the *CYP* gene family, a number associated with a specific group within the gene family, a letter representing the gene's subfamily and a number assigned to the specific gene within the subfamily.[9] Thus, for example, *CYP2D6* is gene 6 in group 2, subfamily D.

A number of SNPs in various *CYP* genes have been identified in recent years and several studies have shown how these SNPs affect the metabolism, safety and efficacy of various drugs, with CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4 accounting for over 90% of drugs metabolised by the CYP enzyme system. Different *CYP* genes are involved in the metabolism of different types of drugs. For example, in oncology, the three major genes accounting for over 85% of hepatic activity are *CYP1A2*, *CYP2D6* and *CYP3A4*;[10] in psychiatry, several studies[11–13] have shown a link between genetic polymorphisms and response to antidepressants with regards to *CYP2C9*, *CYP2C19* and *CYP2D6*; whereas, for antipsychotics, *CYP1A2*, *CYP2D6* and *CYP3A4* again seem to be the most important.[14]

Indeed, the *CYP2D6* gene plays a primary role in the metabolism of drugs used to treat severe depression, schizophrenia, bipolar disorder and cardiovascular diseases.[15] CYP2D6 is responsible for the metabolism of 25% of all drugs on the market and polymorphisms in its gene significantly affect the metabolism of about 50% of these drugs.[16] Thus, it is of little surprise that it is probably the most extensively studied gene with regard to its impact on the metabolism of antipsychotics.[17]

Drug/enzyme interactions generally result from one of two processes, enzyme inhibition or enzyme induction. The majority of drugs act as inhibitors, that is, they decrease the metabolism of substrates, which generally leads to an increase in the effect of the drug. Inducers, on the other hand, increase the metabolism of substrates, generally resulting in a decreased drug effect.[18] The CYP2D6 enzyme is the only one among the drug-metabolising CYP enzymes that cannot undergo induction and therefore genetic variation contributes largely to the interindividual variation in enzyme activity.[16]

The prevalence of *CYP* gene polymorphisms varies across populations. *Table 2* presents a summary of the frequencies of *CYP2D6* alleles in various populations and also describes each allele's predicted enzymatic function. As can be seen from *Table 3*, it is with reference to these classifications that the anticipated phenotype is commonly determined (when the CYP2D6 enzyme is the primary metabolic route) although it should be noted that there are a number of other classification systems being used.[19,20] Nevertheless, according to this classification system, drugs should have the intended effect in individuals with two copies of the normal functional allele. At the same dose, suboptimal responses would be expected in individuals with deficient or differing copies of functional alleles. Thus, individuals who carry copies of decreased activity or loss of function alleles are defined as poor metabolisers (PMs).

Given that the four most common loss of function alleles (**3*, **4*, **5* and **6*) are associated with up

TABLE 2 *Allele frequencies of CYP2D6 variants in selected populations*

CYP2D6 variant[a]	Predicted enzymatic function	Caucasian (Europe)	Caucasian (US)	African American	Swedish
**1*	Normal	33–36%	27–40%	29–35%	36.7%
**2*	Normal	22–33%	26–34%	18–27%	32.4%
**3*	Loss of function	1–4%	1–1.4%	< 1%	1.4%
**4*	Loss of function	12–23%	18–23%	6–9%	24.4%
**5*	Loss of function	2–7%	2–4%	6–7%	4.3%
**6*	Loss of function	1–1.4%	1%	< 1%	0.9%
**7*	Loss of function	–	–	–	–
**8*	Loss of function	–	–	–	–
**9*	Decreased activity	0–2.6%	2–3%	< 1%	–
**10*	Decreased activity	1.4–2%	2–8%	3–8%	–
**11*	Loss of function	–	–	–	–
**12*	Loss of function	–	–	–	–
**13*	Loss of function	–	–	–	–
**14*	Loss of function	–	–	–	–
**15*	Loss of function	–	–	–	–
**16*	Loss of function	–	–	–	–
**17*	Decreased activity	< 1%	< 1%	15–26%	–
**18*	Decreased activity	–	–	–	–
**21*	Loss of function	–	–	–	–
**29*	Decreased activity	–	–	–	–
**33*	Normal	–	–	–	–
**35*	Normal	–	–	–	–
**36*	Decreased activity	–	–	–	–
**41*	Decreased activity	–	–	–	–
**1XN*	Increased activity (where $N \geq 2$)	< 1%	< 1%	1.3%	–
**2XN*	Increased activity (where $N = 2, 3, 4, 5$ or 13)	1.5%	< 1%	1.3%	–
**4XN*	Loss of function (where $N \geq 2$)	< 1%	< 1%	2.3%	–
**10XN*	Loss of function (where $N \geq 2$)	–	–	–	–
**17X2*	Normal	–	–	–	–
**35X2*	Increased activity	–	–	–	–
**41X2*	Normal	–	–	–	–

Adapted from Matchar *et al.*[24] and Ingelman-Sundberg *et al.*,[16] in which all prevalence figures are taken from Bradford[22] or Zackrisson *et al.*[25]

a Not all alleles are presented here. All currently recognised alleles can be found on the home page of the Human Cytochrome P450 Allele Nomenclature Committee.[26]

to 98% of the PM phenotypes, it is no surprise to find that there are ethnic differences in metaboliser status. For example, a number of studies have found that around 7% of Caucasians are PMs compared with 1% of Asians, with data for other ethnic groups less cogent.[21] However, fewer Asians metabolise CYP2D6 normally, largely because of high frequencies of the **10* allele,[22] resulting in a

TABLE 3 *Effects of genetic polymorphisms of CYP2D*

Phenotype (metaboliser status)[a]	Genotype	Expected drug effects
Extensive metaboliser (EM)	Two copies of normal function allele	Usual doses lead to expected drug concentrations and response
Intermediate metaboliser (IM)	Two copies of reduced activity allele or one copy of loss of function allele and one copy of decreased activity allele	Drug effects between those of EMs and PMs
Ultrarapid metaboliser (UM)	Multiple copies of functional allele or of the whole gene itself (gene duplications)	Usual doses may not lead to therapeutic drug concentration, possible non-response
Poor metaboliser (PM)	Two copies of loss of function allele	Usual doses may lead to higher than expected drug concentrations and possibly adverse drug reactions

Adapted from Matchar *et al.*[24]

a Some studies make no distinction between EMs and IMs whereas others classify these as homozygous EMs and heterozygous EMs respectively (but not all heterozygous EMs will necessary be IMs). Similarly, not all studies make distinctions with ultrarapid metabolisers (and not all pharmacogenetic tests are capable of detecting patients with multiple copies of alleles and thus making this distinction).

higher prevalence of intermediate metabolisers (IM). This decreased activity allele, which is rare in Caucasian populations, has been estimated to be as high as 55% in Chinese populations.[21,23]

The classification used in *Table 3* is the one that is used by the first approved pharmacogenetic test, the AmpliChip. This test also tests for *CYP2C19* and patients are given either an extensive metaboliser (EM) or a PM phenotype, reflecting the fact that the **1* allele is a normal activity allele whereas **2* and **3* are associated with loss of function. Other *CYP2C19* alleles exist that are not tested for by the AmpliChip including **4*, **5*, **6*, **7* and **8*, and **17*, which are loss of function and increased activity alleles respectively.[26]

However, as noted above, *CYP1A2* and *CYP3A4* appear to be relatively more important genes than *CYP2C19* with regard to antipsychotics. With regard to *CYP1A2*, the **1* allele is associated with normal activity, **1C* and **1K* with decreased activity and **1F* with higher inducibility.[26] For *CYP3A4*, the **1A* allele is associated with normal activity whereas data on the function of other alleles are currently lacking.

Current costs of *CYP* tests to the NHS

The Doctors Laboratory (TDL)[15,27] currently provides the Roche AmpliChip *CYP2D6/2C19* testing facility to the NHS at a cost of £300, including any administration fees and platform costs (TDL, April 2008, personal communication). The turnaround time is stated as 1–2 weeks.

It was not possible to obtain costs for other tests including any in-house laboratory tests although these are thought to be less than that of the AmpliChip.

Current usage of *CYP* tests in the NHS

The use of *CYP* tests in the NHS has not been documented but it is thought that currently they are likely to be available only on a research basis.

Schizophrenia

Mental health is recognised as a major challenge in UK clinical practice and as such it is one of the nine National Service Frameworks (NSFs).[28] Schizophrenia is described in the NSF for mental health as a severe psychotic mental illness. Although there are no symptoms that in themselves are pathognomonic of schizophrenia, it can be viewed as a clinical syndrome within which is a broad spectrum of symptoms. Schizophrenia is viewed variably as a single disease or a group of heterogeneous disorders due to the variability of presentation and patterns within its diagnostic criteria, both currently and historically. The 10th version of the International Classification of Diseases and Related Health Problems (ICD-10)[29] describes schizophrenic disorders as being 'characterised in general by fundamental

and characteristic distortions of thinking and perception, and by inappropriate or blunted affect'. These have been further described as 'positive' symptoms such as delusions and hallucinations (reality distortion) and 'negative' symptoms such as lack of emotional responsiveness and lack of volition.

Schizophrenia is associated with increased mortality compared with that of the general population, with individuals with schizophrenia having an 'all-cause' standardised mortality ratio (SMR) of between 2 and 3.[30,31] Suicide has been shown to have a large impact on the all-cause SMR, with an SMR for suicide or unexplained violence being greater than 10, with the prevalence of suicide amongst those with schizophrenia being currently estimated at around 5%.[30,32]

The lifetime prevalence of schizophrenia is currently estimated to be between 0.34% and 1%,[33–35] with annual prevalence and incidence rates of around 500 per 100,000 population (0.5%)[34,35] and 10–20 per 100,000 population[34,36] respectively. Overall, the rates are similar in men and women but the peak incidence of onset is between 15 and 25 years in men (where the incidence rate is twice that for women) and 25 and 35 years in women (where the incidence rate is higher among women).[33,35]

Although the aetiology of schizophrenia is not clear, it almost certainly involves dopamine, specifically the D2 receptor. Thus, pharmacological agents that act as dopamine antagonists (with the exception of aripiprazole, a dopamine partial agonist) and which have actions on a number of other neurotransmitters and their receptors [e.g. 5-hydroxytryptamine (5-HT)] are used alongside a number of other strategies and interventions to treat schizophrenia, comprising a total care package.

Drugs for schizophrenia can be classified into typical (first generation) and atypical (second generation) antipsychotic agents. The historical difference between the two classes is the propensity of the older typical agents to cause catalepsy [a severe extrapyramidal symptom (EPS) characterised by muscular rigidity and fixity of posture with decreased pain sensation] in rats, whereas the newer atypical agents do not. In clinical practice risperidone, olanzapine, amisulpride and quetiapine are most commonly used as first-line treatment as recommended by the National Institute for Health and Clinical Excellence (NICE).[37] Typical antipsychotics are now more commonly used as second-line treatment, either as oral medication or in depot form, or to assist in the management of severe behavioural disturbance.

Atypical antipsychotics initially appeared to have the benefit of lower levels of some ADRs, most notably movement disorders, elevation of prolactin and sedation,[38,39] although this has been increasingly challenged.[40,41] The atypicals have been associated with a metabolic syndrome including weight gain, diabetes and abnormal blood lipid profiles.[42,43]

Clozapine is clinically in a separate class from typical and atypical antipsychotics. Although theoretically an atypical in that it does not cause catalepsy, its ADR profile includes a significant risk of agranulocytosis to the degree that mandatory monitoring of blood counts for neutropenia are part of its licensing requirements.[44] It remains available in the UK for use in treatment-resistant schizophrenia only.[37] It produces few acute EPS and has a lower incidence of tardive dyskinesia (TD) than other antipsychotics, although other ADRs include sedation, hypersalivation and hypertension.[44–46]

Regarding efficacy, the HTA review of atypical antipsychotics in schizophrenia[47] noted that evidence for the effectiveness of the atypicals compared with typicals was 'in general of poor quality, based on short term trials and difficult to generalise to the whole population of people with schizophrenia'. The more recent Clinical Antipsychotic Trials in Intervention Effectiveness (CATIE)[43] and Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS) trials[48] have led the chief investigators of these trials to conclude that typical antipsychotics are as good as atypical antipsychotics for many patients.[49]

With advances in treatment, the prognosis of an individual with a first episode of schizophrenia is less bleak than was once thought, with approximately 20–25% of patients having no further episodes.[50–52] However, within the first year, recurrence is observed in up to 25% of patients,[53] rising to almost 50% within 2 years.[50,54,55] Within 12 months it has also been found that 14% of patients are treatment resistant,[56] and over 2 years' duration 20–45% are only partially responsive to antipsychotic medication,[57,58] with 5–10% of patients deriving no benefit at all.[59] However,

the prevalence of treatment resistance is hard to determine given the lack of agreement on defining the term, and, as these figures also reflect treatment outcomes with typical antipsychotics, with atypical antipsychotics now also being widely available, it has been argued there is a need to reconsider what constitutes 'non-response'.[60] Treatment resistance is broadly described in NICE Clinical Guideline 1 (Schizophrenia)[37] as a 'lack of satisfactory clinical improvement despite the sequential use of the recommended doses for 6 to 8 weeks of at least two antipsychotics'. Individuals who receive antipsychotic prophylaxis (maintenance therapy) have been found to have a better outcome than those who have antipsychotics only when symptoms are present.[61,62]

Non-compliance is also often related to efficacy limitations as well as ADRs of antipsychotics,[63] increasing the risk and severity of relapse (with each further episode a decline in baseline functioning can be expected[64]), increasing the length of hospital stay and quadrupling the risk of suicide attempts.[65] It has been found that 10 days after discharge from hospital up to 25% of individuals with schizophrenia are partially or non-compliant, rising to 50% after 1 year and 75% after 2 years.[65] However, instruments for measuring adherence and non-compliance rates have varied across studies,[66] with one recent systematic review of 28 studies finding the weighted non-adherence rate to be 40.6% (weighted mean 25%, 95% CI 17.42 to 32.66)[67] and another finding the mean rate of non-adherence to be between 41.2% and 49.5% in 10 and 5 studies, respectively, depending on the inclusion criteria used.[68]

Factors influencing compliance have also been explored in numerous studies and reviews and, unsurprisingly, many different factors influence compliance including those that affect patient's beliefs that medication will be efficacious and ameliorate symptoms and fears about ADRs.[69] The types of ADRs that are distressing to patients and linked to non-compliance include EPS, neuroleptic dysphoria, akathisia, sexual dysfunction and weight gain.[69]

Extrapyramidal symptoms are relatively common ADRs to antipsychotic medication. They can be severe and disabling and a significant factor in an individual deciding to stop or modify treatment as prescribed.[63] Although easy to recognise, the likelihood of EPS cannot be predicted accurately because they depend on the dose, the type of drug and individual susceptibility.[44] EPS include parkinsonian symptoms (including tremor), dystonia (abnormal face and body movements), akathisia (restlessness) and TD (rhythmic involuntary movements of tongue, face and jaw). TD also reflects the underlying pathology in schizophrenia as it has been established that the presence of TD predates the advent of antipsychotic treatment of schizophrenia[70] and has been observed in older individuals with schizophrenia who have never been treated with antipsychotics.[71] A recent systematic review of TD[72] gave prevalence rates of 13.1% for those treated with atypical antipsychotics, 15.6% for antipsychotic-free patients and 32.4% for those treated with typical antipsychotics.

Pharmacogenetics and schizophrenia

As noted above, a number of antipsychotics (both typical and atypical) are metabolised by the CYP1A2, CYP2D6 and CYP3A4 enzymes (*Table 4*). It should be noted, however, that enzymes other than CYP enzymes are also involved in the metabolism of these drugs. Another key issue for clinical practice is the risk of drug interactions, which although not common have the potential to cause significant harm. Many patients receiving antipsychotics are also likely to be prescribed other medications, including other psychotropic medications, many of which will also be inhibitors of CYP enzymes. Thus, enzyme inhibition may involve competition between drugs for the enzyme binding site, increasing the likelihood or severity of drug–drug interactions. Therefore, knowledge about CYP gene polymorphisms could potentially aid the selection of a specific drug and/or guide decisions about appropriate dosing to optimise efficacy and tolerability for individual patients.

Although CYP3A4 is present in much higher abundance in the liver and is involved in the metabolism of a greater number of drugs than the other CYP enzymes (50% of all marketed drugs[73,74]), its enzyme activity is affected more by environmental factors such as diet and concurrent medications than by inherited variations. For example, human in vivo studies have indicated considerable interindividual variability (fivefold) that can be significantly increased by deliberate modulation, i.e. inhibition and induction.[75]

TABLE 4 *Common antipsychotics metabolised by the CYP enzyme system*

Enzyme	Typical antipsychotics	Atypical antipsychotics
CYP1A2	Haloperidol	Clozapine, olanzapine
CYP2D6	Thioridazine, perphenazine, fluphenazine, zuclopenthixol, haloperidol, chlorpromazine	Risperidone, olanzapine
CYP3A4	Haloperidol	Clozapine, risperidone, quetiapine, ziprasidone, olanzapine

Similarly it remains questionable how much of the interindividual variability in CYP1A2 activity is explained by genetic polymorphisms;[13] smoking in particular is thought to affect the level of CYP1A2.[76] As already noted, CYP2D6 is the only one among the drug-metabolising CYP enzymes that is not inducible but it can be inhibited by a number of drugs and hence this, together with genetic variation, contributes to the interindividual variation in enzyme activity. The association between *CYP2D6* genotype and the risk of having TD has recently been reviewed in a meta-analysis[77] that investigated loss of function alleles (**3*, **4*, **5*, **6* and **7*), decreased activity alleles (**10*) and the **2* allele. This found that patients who were homozygotes for loss of function alleles (PMs) had a 1.64-fold greater chance of suffering TD compared with other patients with schizophrenia, but the effect was not significant (95% CI 0.79 to 3.43).

Current service costs for treating schizophrenia

The cost of care for individuals with schizophrenia is high. Davies[78] estimated that 1.6% of the total national health-care budget was attributable to schizophrenia treatment. On the basis of this figure and estimated government spending on health,[79] NHS expenditure on schizophrenia in 2008–9 is calculated to be in the region of £1.2 million.

Chapter 3
Methods

A systematic review of the clinical and economic literature was conducted to assess the clinical and cost-effectiveness of testing for *CYP* polymorphisms in patients treated with antipsychotics for schizophrenia. The systematic review was guided by the general principles recommended in the QUOROM statement[80] and the HuGENet HUGE Review Handbook,[81] which provides guidelines on undertaking systematic reviews and meta-analyses of genetic association studies.

To ensure that adequate clinical input was obtained, an advisory panel comprising clinicians and experts in the field of pharmacogenetics and schizophrenia was established. The role of this panel was to comment on the draft report and answer specific clinical questions as the review progressed.

Clinical effectiveness

Search strategy

The search incorporated a number of strategies, combining index terms (for the disease) and free text words for the technologies involved (generic and trade names of the drugs) but did not include methodological filters that would limit results to a specific study design. A separate search was conducted for each of the three main components of the clinical review (analytical validity, clinical validity and clinical utility). Details of the search strategies and the number of records retrieved for each search are provided in Appendix 1. All references were exported to an EndNote bibliographic database.

For all searches the following electronic databases were searched (YD) for relevant published literature (for the period 1995 to January Week 2 2008 for analytical validity and clinical validity; 1995 to March Week 2 2008 for clinical utility):

- CCTR (Cochrane Controlled Trials Register)
- CDSR (Cochrane Database of Systematic Reviews)
- DARE (Database of Abstracts of Reviews of Effectiveness)
- EMBASE
- Health Technology Assessment database
- ISI Web of Knowledge
- MEDLINE
- PsycINFO.

In addition to the systematic searches of the above databases, publicly available information on various genotyping tests was sought from the internet and advisory panel members and used to supplement the published literature as appropriate.

Selection of evidence

The records identified in the electronic searches were assessed for inclusion in two stages. Two reviewers (NF and RD for analytical validity, clinical validity and clinical utility) independently scanned all titles and abstracts identified in the search to identify reports that might be relevant to the review. Full text versions of all records selected during the initial screening process were obtained to permit more detailed assessment. These were assessed independently by two reviewers (NF and SP for analytical validity; NF and YD for clinical validity and clinical utility) using the inclusion and exclusion criteria shown in *Table 5*. The inclusion/exclusion assessment of each reviewer was recorded on a pretested, standardised form. Disagreements were resolved by discussion and, if necessary, another reviewer was consulted. A summary of the selection and inclusion of studies is provided in Appendix 2.

Data extraction

Data extraction was carried out by one reviewer (NF for analytical validity, clinical validity and clinical utility) and then checked for accuracy by a second reviewer (SP for analytical validity; YD for clinical validity and clinical utility).

Quality assessment

As no universally accepted quality assessment criteria exist for laboratory studies, no formal assessment was undertaken for analytical validity although general issues relating to genetic association studies[81] were considered

when reviewing the data. For clinical validity, the general study design and conduct of studies were considered based on accepted criteria,[82] and a tool, based on elements of a checklist developed to assess the methodological quality of pharmacogenetic studies,[83] was also used to assess specific issues considered important in terms of the reliability of such studies. As only one study was found for clinical utility and this was only presented as a poster, no formal quality assessment was undertaken for this component of the review.

Data synthesis

Information on study characteristics is summarised in structured tables and as a narrative description.

When more than one study presented the results of investigating the association between the same allele or combination of alleles and the same outcome they were combined in a meta-analysis using Review Manager (REVMAN) 4.2 software.

Forest plots were prepared with binary outcomes compared in terms of odds ratios and continuous outcomes compared in terms of difference in means. An assessment of heterogeneity between studies was made both by visually inspecting the forest plots and by calculating the I^2 statistic,[84] which measures the proportion of variation across studies that is due to genuine differences rather than random error. If heterogeneity was detected summary effects were estimated using a random-effects approach; otherwise a fixed-effects approach was taken.

When studies differed in terms of the ethnicity of included patients, separate effect estimates were calculated for each ethnic group. If the separate estimates appeared similar they were subsequently pooled to provide a single effect estimate. This was in view of the controversy surrounding possible confounding from population stratification and is the approach suggested in the HuGENet HuGE Review Handbook.[81] When studies differed in terms of their study design, when possible sensitivity analyses were conducted including only studies of the same study design.

For each allele–outcome combination two approaches to the analysis were undertaken. The first approach made no assumption regarding the underlying genetic model and comprised two separate meta-analyses, one comparing heterozygotes with wild-type homozygotes and the other comparing mutant-type homozygotes with wild-type homozygotes. The second approach assumed that the mutant allele had a dominant effect on outcome and compared both mutant-type homozygotes and heterozygotes combined with wild-type homozygotes. Because this meant grouping patients into any one of the genotype groups *wt/wt*, *wt/mut* or *mut/mut*, this required making the following assumptions for *CYP2D6*: that patients with the **1/*2* genotype can be classified as *wt/wt* (as the **2* allele may be associated with normal function), as can patients with the UM phenotype [as such patients have at least two *wt* alleles and not all studies will have used tests that are able to identify multiple copies (> two) of alleles]. Although there is currently a lack of evidence to support either of these assumptions, a similar approach was taken in a previous meta-analysis of *CYP2D6* polymorphisms and the risk of TD.[77]

To try and minimise the risk of publication bias, members of the advisory panel were consulted in an attempt to identify unpublished studies, as detailed in the search strategy.

Cost-effectiveness

Search strategy

Two separate search strategies were conducted: (1) to identify any full economic evaluations of *CYP* testing for prescribing antipsychotics; (2) to identify the available economic models for schizophrenia. Details of the search strategies and the number of records retrieved for each search are provided in Appendix 3. All references were exported to an EndNote bibliographic database.

Identification of full economic evaluations of CYP *testing for prescribing antipsychotics*

The search strategies undertaken for the clinical component of the review did not identify any full economic evaluations of *CYP* testing for prescribing antipsychotics. Therefore a separate, specifically economic search was undertaken. Because of the anticipated lack of published economic data available, the search strategy was expanded (solely for the purposes of the economic literature review) to include cost-effectiveness studies of *CYP* testing in the field of psychiatry (antidepressants, antipsychotics, etc.).

TABLE 5 *Inclusion and exclusion criteria*

Study design	**Analytical validity:** Any study design comparing one test with another except for single case studies **Clinical validity:** Any study design except for single case studies **Clinical utility:** Any study design
Population	**Analytical validity:** Healthy or unhealthy human subjects genotyped for any *CYP* polymorphisms **Clinical validity:** Adults with schizophrenia receiving treatment with antipsychotics and genotyped for CYP polymorphisms **Clinical utility:** Adults treated with antipsychotics undertaking genotyping tests for *CYP* polymorphisms
Outcomes	**Analytical validity:** Reports on accuracy of test (e.g. sensitivity) **Clinical validity:** Pharmacokinetic outcomes – bioavailability (AUC), half-life ($t_{1/2}$) or oral clearance Outcomes measuring efficacy Outcomes measuring adverse drug reactions **Clinical utility:** Use of *CYP* genotyping to prospectively predict clinical outcomes (outcomes include those addressed by clinical validity) Use of *CYP* genotyping to modify clinical management (e.g. changing doses based on genotype tests) Examples of the use of *CYP* genotyping in medical, personal and public health decision-making Harms associated with *CYP* genotyping
Exclusion criteria	Non-English language papers Narrative reviews, editorials, opinions Subjects not genotyped for *CYP* polymorphisms For clinical validity and clinical utility, patients not being treated with antipsychotics

AUC, area under the curve; $t_{1/2}$, elimination half-life.

For all searches the following electronic databases were searched (YD) for relevant published literature for the period up to April Week 3 2008:

- EMBASE
- Cochrane Library
- ISI Web of Knowledge
- MEDLINE
- PsycINFO.

Identification of the available economic models for schizophrenia

Searches were carried out to identify economic models that could be modified or used directly to investigate the cost-effectiveness of *CYP* testing for patients with schizophrenia. The following databases were searched up to January 2008 (apart from the HTA database, which was searched up to May 2008):

- MEDLINE
- NHS EED (NHS Economic Evaluation Database)
- HEED (Health Economic Evaluation Database)
- EMBASE
- Cost-effectiveness Analysis (CEA) Registry
- Centre for Health Economics website
- HTA database.

Search strategies for the large bibliographic databases MEDLINE and EMBASE were structured to capture the concepts of economic modelling combined with subject terms for schizophrenia. Searches were limited to English language studies.

Selection of evidence

Identification of full economic evaluations of CYP *testing for prescribing antipsychotics*

Two reviewers (CM and ABol) independently scanned all titles and abstracts identified in the search to identify reports that might be relevant to the review. Disagreements were resolved by discussion and if necessary another reviewer was consulted.

Inclusion criteria limited studies to those that considered both the costs and benefits of *CYP* testing for prescribing any drug in the field of psychiatry. Studies were excluded if they did not include a *CYP* test.

Identification of the available economic models for schizophrenia

The records identified in the electronic search were assessed for inclusion in two stages. Two reviewers (CM and SB) independently scanned all titles and abstracts identified in the search to identify reports of models that might be relevant to the review. Full text versions of all records selected during the initial screening process were obtained to permit more detailed assessment. These were assessed independently by two reviewers (CM and SB). Disagreements were resolved by discussion and if necessary another reviewer was consulted.

Inclusion criteria limited studies to those that included:

- independent models (publications of the same model were counted as one model)
- schizophrenia patients
- any antipsychotic medication.

Studies were excluded if they were reviews of models or 'thought pieces'.

Data extraction

Identification of full economic evaluations of CYP *testing for prescribing antipsychotics*

Data extraction was carried out by one reviewer (CM) and then checked for accuracy by a second reviewer (ABol).

Identification of the available economic models for schizophrenia

Data extraction was carried out by two reviewers (CM and SB) and then checked for accuracy by a third reviewer (ABol).

Quality assessment

Identification of full economic evaluations of CYP *testing for prescribing antipsychotics*

Detailed cost-effectiveness criteria, such as the Drummond and Jefferson economic evaluation checklist,[85] were not applied as the nature of the included economic evaluation was exploratory in nature. Applying a checklist would only serve to unfairly judge the study and would not be of any practical value.

Identification of the available economic models for schizophrenia

Formal quality assessment was not undertaken for this component of the review. However, a model criteria checklist was applied (see Chapter 7 for more details).

Data synthesis

Data are presented in structured tables and narratively discussed in the economics section of this report.

Chapter 4
Analytical validity

In total, 41 out of 2844 papers met the inclusion criteria for the review of analytical validity (Appendix 2). Three of these considered analytical validity for more than one *CYP* polymorphism, resulting in a total of 46 studies covering 11 different SNPs; almost half of the studies were concerned with genotyping *CYP2D6* polymorphisms (*Table 6*).

All but four of the studies were reported as full papers in academic journals; two studies[88,90] were reported as abstracts only and two others[5,100] were drug company submissions reported on the FDA website.

Study characteristics, participant characteristics and findings from each of the studies are presented in Appendix 4 and briefly summarised below.

Study characteristics

For all *CYP* polymorphisms, real-time PCR (such as LightCycler® or TaqMan) was the most frequent genotype method studied in 13 instances (14 if triplex real-time is included). However, for *CYP2D6*, the most common methods were microarrays (particularly the Roche AmpliChip) in six studies followed by multiplex methods in five instances and Pyrosequencing in four. Usually single methods were used to test for a number of different alleles for each *CYP* although, in some instances, multiple methods were utilised (e.g. tetra-primer PCR for testing for the *CYP2D6*3*, **4* and **6* polymorphisms and multiplex long PCR for **5* in Hersberger *et al.*[92]).

The most frequent methods used as a reference method for any *CYP* were PCR and restriction fragment length polymorphism (PCR-RFLP) analysis in 19 studies followed by sequencing in 14 studies. However, in the vast majority of these studies, only a very small number of the original samples were compared with sequencing, often as a second reference method to verify discordant cases. Allele-specific PCR (AS-PCR) was also commonly used as a reference method for *CYP2D6*.

The majority of studies were conducted in Europe, most often in Germany. This was particularly the case for *CYP2D6*, although five of the six US studies also investigated polymorphisms of

TABLE 6 *Summary of included studies: analytical validity*

Gene	Studies
CYP2D6 (*n* = 20)	Chou 2003,[86] Crescenti 2007,[87] Dukek 2006,[88b] Eriksson 2002,[89c] Heller 2005,[90] Heller 2006,[91] Hersberger 2000,[92] James 2004,[93] Lee 2007,[94] Melis 2006,[95c] Muller 2003,[96] Neville 2002,[97] Nielsen 2007,[98] Roberts 2000,[99] Roche 2004,[100] Schaeffeler 2003,[101] Soderback 2005,[102] Stamer 2007,[103] Stuven 1996,[104] Zackrisson 2003[105]
CYP1A2 (*n* = 2)	Casley 2006,[106] Popp 2003[107]
CYP2C9 (*n* = 7)	Burian 2002,[108] Eriksson 2002,[89c] Melis 2006,[95c] Pickering 2004,[109] Toriello 2006,[110] Wen 2003,[111] Zainuddin 2003[112]
CYP2C19 (*n* = 5)	Dukek 2006,[88b] Eriksson 2002,[89c] Melis 2006,[95c] Mizugaki 2000,[113] Roche 2005[5]
Other (*n* = 12)[a]	Bruning 1999,[114d] Fredericks 2005,[115] Harth 2001,[116d] Innocenti 2006,[117] Labuda 1999,[118] Muthiah 2004,[119] Oyama 1995,[120] Rohrbacher 2006,[121] Weise 2004,[122] Weise 2006,[123] Wen 2004,[124] Wu 2002[125]

a The other *CYP* polymorphisms are *CYP1A1* (*n* = 4), *CYP1B1* (*n* = 1), *CYP2B6* (*n* = 1), *CYP2C8* (*n* = 3), *CYP2E1* (*n* = 1), *CYP3A4* (*n* = 1), *CYP3A5* (*n* = 1).
b Tested for *CYP2D6* and *CYP2C19*.
c Tested for *CYP2D6*, *CYP2C9* and *CYP2C19*.
d Bruning 1997[114] and Harth 2001[116] report on the same patients but on different polymorphisms and are therefore classified as separate studies.

this gene. This represents a higher number of American studies than for all of the other *CYP* polymorphisms combined.

Studies varied in size from 40 subjects being genotyped in the smallest study[112] to 428 in the largest,[118] although the number of samples being compared by the reference method varied from just six samples tested by AS-PCR in Oyama *et al.*[120] to 1400 samples in Lee *et al.*[94]

Participant characteristics

Given that there are racial differences in function-altering polymorphisms, the most important participant characteristic to consider is ethnicity. Unfortunately, very few studies reported the ethnic origin of their subjects. However, given the high proportion of studies carried out in Europe (and in the USA for *CYP2D6*), it may be reasonable to assume that the majority of subjects studied were likely to have been of Caucasian origin (although given the high number of African Americans in the USA this assumption may not be correct).

Study findings

Although not all of the studies provided detailed genotype data, all those presenting any findings reported high concordance between methods (of 95% or more). This was the case no matter which *CYP* was genotyped or which methods were compared. No studies used exactly the same method as both method under test and reference method. In addition, given the overwhelming positive nature of all of the results regarding the analytical validity of each of the tests, it was not considered necessary to attempt to meta-analyse these findings.

A note of caution is, however, required when interpreting these findings. As noted in Chapter 2, analytical validity should include the reporting of sensitivity, specificity, quality control and robustness of the assessment process. Very few studies reported on all four aspects of analytical validity, quality control and assay robustness most usually being neglected. Similarly, very few studies actually presented results for sensitivity and specificity. It was, however, possible to calculate the sensitivity and specificity from 20 studies that presented relevant genotype data. In the vast majority of these instances, both sensitivity and specificity were 100% and, with the exception of Eriksson *et al.*,[89] in which specificity between Pyrosequencing™ and PCR-RFLP for *CYP2D6* was only 30.8%, it was always at least 99%.

The most comprehensive detailed data were provided in studies examining the AmpliChip for *CYP2D6* and *CYP2C19*. Compared with PCR-RFLP, for *CYP2D6* there was 95.6% concordance in Heller *et al.*[91] (sensitivity 95%, specificity 100%), which rose to 100% when the discordant cases were compared with more sensitive methods (SNaPshot and sequencing). Similar results had also been reported for both *CYP2D6* and *CYP2C19* by Roche.[5,100] Melis *et al.*[95] used the AmpliChip as a reference method for Tag-It™ (a bead-based array). Again, concordance was high between methods (100% sensitivity and specificity for both *CYP2D6* and *CYP2C9*) although it was stated by the authors that the Tag-It *CYP2D6* assays were less robust than the *CYP2C19* assays.

The findings for each *CYP* are summarised in *Tables 7–11* and, as already noted, more detailed findings can be found in Appendix 4.

Analytical validity summary

Based on the findings presented in this review, tests for determining genotypes are highly accurate, with concordance being 100%. However, not all aspects of analytical validity have been reported in the studies (quality control and assay robustness being commonly neglected). In studies in which data were presented to calculate sensitivity and specificity, this was typically between 99% and 100% for both.

TABLE 7 *Summary of analytical validity findings:* CYP2D6

Study	Alleles tested	Method under study and number tested	Reference method(s) and number tested	Summary of findings
Chou 2003[86]	**3*, **4*, **5*, **6*, **7*, **9*, **17*, **41*, **1XN*, **2XN/*35XN*, **4XN*	GeneChip; *n* = 232	AS-PCR; *n* = 232	Allele frequencies provided by each method For all alleles, concordance ≥ 99.8%
Crescenti 2007[87]	**3*, **4*, **5*, **6*	Multiplex long PCR + SBE; *n* = 290	Allelic discrimination (TaqMan) for **4* and **6*; *n* = 100 PCR-RFLP for **3*; *n* = 100	Genotype frequencies presented for each allele Results show 100% sensitivity and specificity of genotypes with both reference methods
Dukek 2006[88] (abstract only)	NS	AmpliChip; *n* = 207	Tag-It; *n* = 207 Sequencing for *CYP2D6*41*; *n* = NS	Limited relevant genotype data presented Stated perfect correlation in 207/207 samples for alleles for *CYP2D6* Stated AmpliChip improved discrimination between similar alleles (i.e. *41 vs *2 and *35 vs *2)
Eriksson 2002[89]	**2*, **3*, **4*, **6*, **7*, **8*, **14*	Pyrosequencing; *n* = 117	PCR-RFLP; *n* = 117	Stated the two methods were in complete agreement Genotype frequencies presented for each allele Genotype frequencies show sensitivity to be 100% but specificity appears to be only 30.8%
Heller 2005[90]	NS	AmpliChip; *n* = 47	PCR-RFLP; *n* = 47	No relevant genotype data presented Stated genotype frequencies identical in 45/47 samples In other 2/47 samples, allele assignment also consistent
Heller 2006[91]	29 SNPs tested	AmpliChip; *n* = 159	PCR-RFLP; *n* = 159 SNaPshot for duplications; *n* = 43 Sequencing; *n* = 1 (discordant cases)	Genotype frequencies presented for AmpliChip and corresponding readings by PCR-RFLP, SNaPshot and sequencing Stated concordance between AmpliChip and PCR-RFLP is 95.6% Overall concordance with RFLP is 152/159 (95.6%) Genotype frequencies show 100% sensitivity and 95.6% specificity with RFLP Of discordant cases, 6/7 agreed with SNaPshot with remaining 1/7 agreeing with sequencing Findings are also presented by phenotype and genotype – in the samples in which genotyping by AmpliChip and PCR-RFLP differed, the different genotypes did not affect the classification into one of the phenotypic groups (PM, IM, EM or UM). However, the SGD was different in 6/7 samples when PCR-RFLP overestimated these in comparison with AmpliChip

continued

TABLE 7 *Summary of analytical validity findings:* CYP2D6 *(continued)*

Study	Alleles tested	Method under study and number tested	Reference method(s) and number tested	Summary of findings
Hersberger 2000[92]	**3*, **4*, **5*, **6*	Tetra-primer PCR for **3*, **4* and **6*; *n* = 57 Multiplex long PCR for **5*; *n* = 57	PCR-RFLP; *n* = 57 Sequencing; *n* = 6	Genotype data only presented for that confirmed by sequencing Stated that reanalysis by reference methods confirmed allele frequencies by test Genotype frequencies show 100% sensitivity and specificity
James 2004[93]	**2*, **3*, **4*, **5*, **6*, **7*, **8*, **9*, **10*, **16*, **41*	Direct sequencing; *n* = 64	AS-PCR; *n* = 39	No relevant genotype data presented Stated that, with the exception of two samples for which the AS-PCR result was uncertain, there was agreement between methods
Labuda 1999[118]	**3*, **4*	Multiplex PCR + ASO; *n* = 428	PCR-RFLP; *n* = 428	No relevant genotype data presented Stated that there is 'good agreement' between methods
Lee 2007[94]	**3*, **4*, **5*, **6*, **7*, **8*	Pyrosequencing; *n* = 200	NanoChip Molecular Biology Workstation; *n* = 200 Sequencing; *n* = 8	Only data on genotype discrepancies presented (8/1400 samples) Stated that there was 99.4% concordance between methods
Melis 2006[95]	**2*, **3*, **4*, **5*, **6*, **7*, **8*, **9*, **10*, **11*, **12*, **17*, **Xn*	Tag-It; *n* = 150	AmpliChip; *n* = 150	Stated that no discrepancies found with AmpliChip, indicating > 99% analytical sensitivity and specificity Stated that *2D6* assays less robust than *2C9* and *2C19* assays Genotype frequencies show 100% sensitivity and specificity
Muller 2003[96]	**2*, **3*, **4*, **5*, **6*, **7*, **8*, **35*	Real-time PCR (LightCycler®); *n* = 105 (deletion and duplication), *n* = 116 (preamplification)	Multiplex PCR for **3*, **4*, **6*, **7 and **8*; *n* = NS PCR-RFLP for **2*; *n* = NS Real-time PCR for **5* and deletions/ duplications; *n* = NS Nearest neighbour model for **35*; *n* = 69	Limited relevant genotype data presented Stated that identical results were obtained between methods Genotype frequencies show 100% sensitivity
Neville 2002[97]	**2*, **3*, **4*, **6*, **10*, **11*, **18*, **33*, **35*, **37*	Invader® assay; *n* = 174/181	Long-range PCR; *n* = 171/181 (10 samples generated no visible product)	No relevant genotype data presented Stated 16/17 deletions and 11/17 duplications detected by Invader test confirmed by long-range PCR
Nielsen 2007[98]	**1*, **2*, **3*, **4*, **5*, **6*, **9*, **10*, **15*, **41*	One-step SimpleProbes™ analysis; *n* = 144	PCR-RFLP; *n* = 144	Genotype frequencies presented Stated the results of the test correspond completely with the PCR-RFLP results Genotype frequencies show 100% sensitivity and specificity
Roberts 2000[99]	**3*, **4*, **6*, **8*, **11*, **12*, **14*, **15*, **19*, **20*	Multiplex PCR; *n* = NS	PCR-RFLP; *n* = 100	Applicable genotype frequencies from controls (i.e. those possessing alleles detectable by test) presented for test (i.e. those genotypes that the test could ascertain) Stated that test found alleles in controls with 100% accuracy Genotype frequencies show 100% sensitivity and specificity

TABLE 7 *Summary of analytical validity findings:* CYP2D6 *(continued)*

Study	Alleles tested	Method under study and number tested	Reference method(s) and number tested	Summary of findings
Roche 2004[100]	**1*, **2*, **3*, **4*, **5*, **6*, **7*, **8*, **9*, **10*, **11*, **15*, **17*, **19*, **20*, **29*, **35*, **36*, **41*, **1XN*, **2XN*, **10XN*, **17XN*, **35XN*, **41XN*	AmpliChip; *n* = 403	Sequencing; *n* = 246 AS-PCR; *n* = 343 PCR-RFLP; *n* = 58 PCR size (**5* only); *n* = 2	Genotype frequencies presented For most genotypes percentage agreement was100% (overall 99.3%) Genotype frequencies show 99.2% sensitivity and 100% specificity
Schaeffeler 2003[101]	*1*, **2*, **3*, **4*, **5*, **6*, **7*, **8*, **9*, **10*, **16*, **17*, **35*, **41*, **2XN*	Real-time PCR (TaqMan); *n* = NS	Previously determined genotypes by method NS; *n* = 64	No relevant genotype data presented Stated test results in complete agreement with controls except in one instance in which an unclear result obtained
Soderback 2005[102]	**1*, **2*, **3*, **4*, **5*, **6*	Pyrosequencing; *n* = 470	Long-range PCR; *n* = 270	Limited relevant genotype data presented Stated reference method verified these findings
Stamer 2007[103]	**3*, **4*, **5*, **6*, **7*, **8*	Real-time PCR; *n* = 323	AS-PCR; *n* = 323	Allele frequencies presented Stated found 14 genotypes Limited relevant genotype data presented Stated test presented 100% reliable results as confirmed by sequencing (unlike AS-PCR, which was 89.9%) Genotype frequencies show 100% sensitivity and specificity for **5*
Stuven 1996[104]	**3*, **4*, **6*, **7*, **8*	Long-distance multiplex AS-PCR; *n* = NS	Multiplex PCR; *n* = 84	No relevant genotype data presented Stated 12 genotypes found and all were correctly identified by test Stated all 5 null alleles tested for were correctly identified
Zackrisson 2003[105]	**1*, **2*, **3*, **4*, **5*, **6*	Pyrosequencing for **1*, **2*, **3*, **4* and **6*; *n* = 282 Long multiplex PCR for *5; *n* = 282	AS-PCR; *n* = 20	Limited relevant genotype data presented Identical genotype in 19/20 samples Failure because of lack of visible control elements in AS amplifications

ASO, allele-specific oligonucleotide; AS-PCR, allele-specific polymerase chain reaction; EM, extensive metaboliser; IM, intermediate metaboliser; NS, not stated; PCR-RFLP, polymerase chain reaction–restriction fragment length polymorphism; PM, poor metaboliser; SBE, single base extension; SGD, semiquantitative gene dose; SNP, single-nucleotide polymorphism; UM, ultrarapid metaboliser.

TABLE 8 *Summary of analytical validity findings:* CYP1A2

Study	Alleles tested	Method under study and number tested	Reference method(s) and number tested	Summary of findings
Casley 2006[106]	**1C* **1F*	Real-time PCR (LightCycler); *n* = NS	PCR-RFLP; *n* = 62	No relevant genotype data presented Stated accuracy of allelic discrimination was confirmed by 100% concordance with PCR-RFLP methods in genotyping 62 individuals with genotypes represented
Popp 2003[107]	**1F*	Real-time PCR; *n* = 101	PCR-RFLP; *n* = 101	Genotype frequencies presented Stated genotypes determined by both methods in 100% concordance Genotype frequencies show 100% sensitivity and specificity

NS, not stated; PCR-RFLP, polymerase chain reaction–restriction fragment length polymorphism.

TABLE 9 *Summary of analytical validity findings:* CYP2C9

Study	Alleles tested	Method under study and number tested	Reference method(s) and number tested	Summary of findings
Burian 2002[108]	**1*, *2, **3*	Real-time PCR; *n* = 118	PCR-RFLP; *n* = 118	No relevant genotype data presented Stated that the concordance rate between methods was 100% for both polymorphic sites (*2 and **3*)
Eriksson 2002[89]	*2, **3*	Pyrosequencing; *n* = 28 (*2C9*)	PCR-RFLP; *n* = 28 (*2C9*)	Genotype frequencies presented for each allele Stated the two methods were in complete agreement Genotype frequencies show 100% sensitivity and specificity
Melis 2006[95]	*2, *3, **4*, **5*, **6*	Tag-It; *n* = 150	AmpliChipa; *n* = 150	Stated that no discrepancies found with AmpliChip indicating > 99% analytical sensitivity and specificity Genotype frequencies show 100% sensitivity and specificity
Pickering 2004[109]	*2, **3*	Multiplex PCR + Luminex® XMap System; *n* = 101	Microarray (eSensor®); *n* = 49	No relevant genotype data presented Stated that 100% agreement between the two methods for all 49 samples
Toriello 2006[110]	**1*, *2, **3*	Real-time PCR (TaqMan); *n* = 114	Real-time PCR (LightCycler); *n* = 114	No relevant genotype data presented Stated that there was 100% concordance in the genotyping results obtained with the two methods
Wen 2003[111]	*2, *3, **4*, **5*	Microarray; *n* = 62	Sequencing; *n* = 20	No relevant genotype data presented Stated the same genotype results were obtained with the 20 DNA samples typed with the two methods
Zainuddin 2003[112]	**1*, *2, **3*, **4*, **5*	Multiplex PCR; *n* = 40	Sequencing; *n* = 40	Genotype frequencies presented for samples tested by both methods Test found to be reproducible and specific when tested against controls Genotype frequencies show 100% sensitivity and specificity

PCR-RFLP, polymerase chain reaction–restriction fragment length polymorphism.
a The paper states that the test was compared with the AmpliChip but this does not test for *2C9* (Tag-It also tested for *CYP2D6* and *CYP2C19*, which can be tested for by AmpliChip).

TABLE 10 *Summary of analytical validity findings:* CYP2C19

Study	Alleles tested	Method under study and number tested	Reference method(s) and number tested	Summary of findings
Dukek 2006[88]	NS	AmpliChip; *n* = 207	Tag-It; *n* = 207	Limited relevant genotype data presented Stated that there was perfect correlation in 206/207 samples for alleles for *CYP2C19* (99.5% concordance)
Eriksson 2002[89]	*2, *3, *4	Pyrosequencing; *n* = 138 (*2C19*)	PCR-RFLP; *n* = 138	Genotype frequencies presented for each allele Stated that the two methods were in complete agreement Genotype frequencies show 100% sensitivity and specificity
Melis 2006[95]	*2, *3, *4, *5, *6, *7, *8	Tag-It; *n* = 150	AmpliChip; *n* = 150	Stated that no discrepancies found with AmpliChip, indicating > 99% analytical sensitivity and specificity Genotype frequencies show 100% sensitivity and specificity
Mizugaki 2000[113]	NS	Real-time PCR (AS TaqMan); *n* = 144	PCR-RFLP; *n* = 144	No relevant genotype data presented Stated that all of the genotypes determined by both methods were consistent
Roche 2005[5]	*1, *2, *3	AmpliChip; *n* = 399	Sequencing; *n* = 122 PCR-RFLP; *n* = 399	Genotype frequencies presented For most genotypes percentage agreement was 100% (overall 99.7%) Genotype frequencies show 99.6% sensitivity and 100% specificity

AS, allele specific; NS, not stated; PCR-RFLP, polymerase chain reaction–restriction fragment length polymorphism.

TABLE 11 *Summary of analytical validity findings: other* CYP *polymorphisms*

Study	CYP and alleles tested	Method under study and number tested	Reference method(s) and number tested	Summary of findings
Bruning 1997[114]	*1B1*, codon position 432	Real-time PCR; *n* = 300	Sequencing; *n* = NS	Genotype frequencies presented Stated 100% identification rate for test when compared with results of sequencing Genotype frequencies show 100% sensitivity and specificity
Fredericks 2005[115]	*3A5*, **1*, **3*	Real-time PCR (LightCycler); *n* = 263	Sequencing; *n* = 21	No relevant genotype data presented Stated 100% concordance between test and reference in subset of 21 samples compared
Harth 2001[116]	*1A1*, **1*, **2*, **3*	Real-time PCR (LightCycler); *n* = 300	PCR-RFLP; *n* = 300 Sequencing; *n* = 20	No relevant genotype data presented Stated that there was 5% discordancy rate between the methods
Innocenti 2006[117]	*2E1*, **1*, **5B*	SNuPE; *n* = 114	PCR-RFLP; *n* = 114	No relevant genotype data presented Stated results consistent (100% accuracy) with reference methods Genotype frequencies show 100% sensitivity and specificity
Labuda 1999[118]	*1A1*, **1*, **2A*, **2B*	Multiplex PCR + ASO; *n* = 428	PCR-RFLP; *n* = 428	No relevant genotype data presented Stated that there is 'good agreement' between methods
Muthiah 2004[119]	*2C8*, **1*, **2*, **3*, **4*	Multiplex PCR; *n* = NS	Sequencing; *n* = 57	Genotype frequencies presented for controls; stated that these confirmed test results Genotype frequencies show 100% sensitivity and specificity
Oyama 1995[120]	1A1	PCR-RFLP; *n* = 240	AS-PCR; *n* = 6	Genotype frequencies presented for controls; stated that these confirmed test results Genotype frequencies show 100% sensitivity and specificity
Rohrbacher 2006[121]	*2B6*, **1*, **4*, **5*, **6*, **7*	Pyrosequencing; *n* = 273	Sequencing; *n* = 31	No relevant genotype data presented Stated that results were in 'complete agreement' between methods
Weise 2004[122]	*2C8*, **2*, **3*, **4*	Real-time PCR; *n* = 122	PCR-RFLP; *n* = 122	Genotype and allele frequencies presented Stated that results of all analysed samples were identical for both methods except that some had to be repeated using classical PCR because of incomplete enzymatic digestion

continued

TABLE 11 *Summary of analytical validity findings: other* CYP *polymorphisms (continued)*

Study	CYP and alleles tested	Method under study and number tested	Reference method(s) and number tested	Summary of findings
Weise 2006[123]	*2C8*, **2*, **3*, **4*	Triplex real-time PCR; *n* = 200	Real-time PCR; *n* = 200	No relevant genotype data presented Stated that repeated runs by different investigators revealed the same results (presumably with 'older method' but this was unclear) Genotype frequencies show 100% sensitivity and specificity
Wen 2004[124]	*3A4*, **1B*, **1C*, **2*, **4*, **5*, **6*, **8*, **11*, **12*, **13*, **17*, **18*	Microarray; *n* = 387	Sequencing; *n* = 30	No relevant genotype data presented 'All samples were in concordance with the two genotyping methods'
Wu 2002[125]	*1A1*	Colorimetric hybridisation; *n* = NS	PCR-RFLP; *n* = NS	Presents effect of hybridisation temperature on ratios for wild-type and mutant samples in m1 and m2 sites and comparison of reference method (controls) with obtained ratios It is stated that the results demonstrate the feasibility of this assay to detect *CYP1A1* polymorphisms

ASO, allele-specific oligonucleotide; AS-PCR, allele-specific polymerase chain reaction; NS, not stated; PCR-RFLP, polymerase chain reaction–restriction fragment length polymorphism; SNuPE, single nucleotide primer extension.

Chapter 5
Clinical validity

In total, 47 out of 2161 papers were concerned with reporting on clinical validity. Some of these studied more than one *CYP* gene, resulting in a total of 51 studies covering six different genes. By far the most commonly studied gene was *CYP2D6* (*Table 12*).

All of the studies were reported as full papers in academic journals except for Iwahashi *et al.*,[141] Jeon *et al.*[143] and Yasar *et al.*,[171] which were presented as abstracts only.

The study characteristics, participant characteristics and findings from each of the studies are summarised below in relation to *CYP2D6*, *CYP1A2* and other *CYP* polymorphisms.

For ease of comparison across all *CYP* polymorphisms, and when possible, outcomes are expressed by genotype as 'standardised outcomes', i.e. *wt/wt* (EM homozygous), *wt/mut* (often classified as EM heterozygous but may also be considered IM depending on the alleles), *mut/mut* (PM) or a combination of these (*wt/wt* + *wt/mut* or *mut/mut* + *wt/mut*). In the few *CYP2D6* studies in which patients with duplicate alleles resulting in increased function (UMs) are reported, in accordance with the review by Patsopoulos *et al.*,[77] these are classified as *wt/wt* for the purpose of meta-analysis, as are patients possessing the **1/*2* genotype as **2* may not be associated with decreased enzyme activity.

Quality assessment of included studies

All studies reported sample size, ranging from nine to 309 with a mean size of 101 (median $n = 92$). Compared with the typical sample sizes required to provide sufficient power to detect a range of typical genetic effect sizes for various minor allele frequencies,[83] these sample sizes are all small. Further, none of the studies explained how the sample size had been chosen or stated the a priori power for detecting effect sizes of varying degrees. Therefore, it is unclear what range of effect sizes the studies were powered to detect.

TABLE 12 *Summary of included studies of patients with schizophrenia: clinical validit*

Gene	Study
CYP2D6 ($n = 37$)	Aitchison 1999,[126] Andreassen 1997,[127] Armstrong 1997,[128] Arranz 1995,[129] Arthur 1995,[130] Brockmoller 2002,[131] Culav-Sumic 2001,[132] de Leon 2004,[133b] Dettling 2000,[134] Ellingrod 2000,[135] Ellingrod 2002,[136] Ellingrod 2002,[137] Fu 2006,[138c] Hamelin 1999,[139] Inada 2003,[140] Iwahashi 2007,[141c] Jaanson 2002,[142] Jeon 2007,[143] Jerling 1996,[144] Kakihara 2005,[145] Kapitany 1998,[146] Lam 2001,[147] Lane 2006,[148] Liou 2004,[149] Lohmann 2003,[150] Mihara 2002,[151] Nikoloff 2002,[152] Ohmori 1998,[153d] Ohmori 1999,[154d] Panagiotidis 2007,[155] Plesnicar 2006,[156] Riedal 2005,[157] Scordo 2000,[158] Thanacoody 2007[159] and 2003,[160e,f] Tiwari 2005,[161g] Topic 2000,[162] Wang 2007[163]
CYP1A2 ($n = 10$)	Basile 2005,[164] Boke 2007,[165] Fu 2006,[138c] Iwahashi 2007,[141c] Matsumoto 2004,[166d] Schulze 2001,[167] Tay 2007,[168] Tiwari 2005,[169g] Tiwari 2007,[170g] Yasar 2007[171]
Other ($n = 4$)[a]	de Leon 2004,[133b] Segman 2002,[172] Thanacoody 2007[159] and 2003[160e,f] Tiwari 2005[161g]

a The other *CYP* polymorphisms are *CYP17* ($n = 1$), *CYP2C19* ($n = 1$), *CYP3A4* ($n = 1$), *CYP3A5* ($n = 1$).
b Tested for *CYP2D6* and *CYP3A5*.
c Tested for *CYP1A2* and *CYP2D6*.
d Matsumoto 2004[166] includes patients genotyped in Ohmori 1998[153] and Ohmori 1999[154] for *CYP2D6*; as these reported on the same patients but with different polymorphisms they are therefore classified as separate studies.
e These studies report on both *CYP2C19* and *CYP2D6*.
f Additional data not reported in Thanacoody 2007[159] is derived from the Thanacoody 2003[160] abstract.
g Tiwari 2005,[169] Tiwari 2005[161] and Tiwari 2007[170] all report on the same patients but with different *CYP1A2* and *CYP3A4* polymorphisms and are therefore classified as separate studies.

In terms of selecting the variants to genotype, although only three[141,143,145] did not give reasons why the gene being investigated was chosen, a minority ($n = 19$)[126,132,137,138,146,147,149–151,154,161,162,164,165,167–170,172] explained the process of choosing which specific variants to genotype within the gene. Given the large number of possible variants to choose from within each gene, this raised the question of whether any within-study selective reporting occurred whereby several variants may have been investigated but only those found to be most significant were reported.[173] However, when studies reporting significant outcomes were subsequently analysed, around half had adequately given reasons for the specific alleles tested.

Generally, studies presented adequate information about the genotyping procedures employed; however, only three studies[131,152,162] reported that genotype quality control procedures had been applied and thus it is unclear how reliable the allocated genotypes are in the remaining studies. Around half of the studies presented allele frequencies from previous studies, from which any significant problems with the genotyping procedures could have been identified.

Given that genotypes cannot always be called with sufficient confidence, some missing genotype data would not be unexpected in any study sample. In terms of the included studies, it was not always apparent from the manner in which data were reported whether any genotype data were missing. Some studies ($n = 9$)[127,139,145,146,148,152,153,162,164] clearly specified the number of missing genotypes and two-thirds of these[127,139,146,152,153,164] provided reasons for the missing data. All but two studies[142,171] gave the number of patients contributing to each analysis. However, none of the studies in which missing data were apparent reported on tests of whether the genotypes were missing at random or mentioned any attempts at imputing the missing genotypes.

No study mentioned conducting specific tests for population stratification even though six[128,133,139,144,164,169] were known to include patients with different ethnic backgrounds. These studies, in particular, are at risk from confounding because of population stratification. A minority ($n = 21$)[130,132,134,138–140,146,149,152–154,161,162,164–170,172] of studies reported on a test for Hardy–Weinberg equilibrium (HWE) that can highlight problems with the genotype data.[83] When a test had been conducted, all of the variants were said to be within HWE, although it was not always clear what significance level had been referred to.

Finally, only seven studies[132,135,141,143,151,162,171] failed to adequately define or justify their choice of outcomes. Four[135,141,143,171] of these were presented as abstracts in which space was limited. Another[162] was subsequently excluded from the analysis because on inspection of other data a number of inconsistencies were apparent (e.g. patients with the **6/*6* genotype were attributed with experiencing an EPS despite it earlier being stated that no patient in the study had this genotype). It should also be noted that, as several outcomes can be rationally chosen to assess the hypotheses of interest, it is not possible to ascertain if any studies conferred a risk of outcome reporting bias, in which several outcomes are investigated and only the most significant reported.

Study characteristics

CYP2D6

The study characteristics are summarised in *Table 13*.

There were 37 studies looking at aspects of the relationship between *CYP2D6* polymorphisms and metabolism, efficacy or ADRs. Three of these were retrospective case–control studies in which patients were assigned into a particular group according to their outcome status and their genotypes examined, 16 were cross-sectional studies in which data such as genotype were determined and outcome data collected retrospectively and 16 were prospective studies including one randomised trial.[133] The number of patients genotyped in each study varied from nine[151] to 308.[126] Tiwari *et al.*[161] stated that 335 patients were included in their study but only 91 appear to have been genotyped for *CYP2D6*. No explanation is given for this.

In most studies a number of different antipsychotics were taken by the patients – 10 studies stated that any antipsychotic was allowed whereas a further eight stated that any typical antipsychotic was allowed. In 15 studies a single drug was taken by patients, usually an atypical antipsychotic (risperidone,[145,148,157,163] olanzapine[136,141] or aripiprazole[143]), with haloperidol,[155] thioridazine,[159] zuclopenthixol,[142]

TABLE 13 *Summary of study characteristics: clinical validity studies in patients tested for* CYP2D6

Study	Type	*n*	Antipsychotic taken	Alleles genotyped	Outcome
Aitchison 1999[126]	Retrospective	308	Refractory group: clozapine Non-refractory group: any antipsychotic	**3*, **4*, **5*, duplications	Efficacy
Andreassen 1997[127]	Cross-sectional	100	Any antipsychotic	**3*, **4*, **5*, **6*, **7*	ADRs
Armstrong 1997[128]	Cross-sectional	76	Any antipsychotic	*wt*, *6A*, *6B*, *6D*, i.e. **1*, **3*, **4*, **5*	ADRs
Arranz 1995[129]	Prospective	123	Clozapine	**3*, **4*	Efficacy
Arthur 1995[130]	Cross-sectional	16	Any antipsychotic	**3*, **4*	ADRs
Brockmoller 2002[131]	Prospective	172	Haloperidol Other antipsychotics were prescribed in some patients In addition, 70% of patients received benzodiazepines, 58% anticholinergics and 34% other types of hypnotic drugs	**2*, **3*, **4*, **5*, **6*, **8*, **9*, **10*, **11*, **12*, **14*, **15*,**1XN*, **2XN*	Metabolism, efficacy, ADRs
Culav-Sumic 2001[132]	Cross-sectional	71	Any typical antipsychotic (daily equivalent dose calculated as mg of chlorpromazine equivalent)	**3*, **4*, **6*, **7*, **8*	ADRs
de Leon 2004[133]	Prospective randomised double-blind trial	40	Clozapine	**3*, **4*, **5*, **6*, **7*, **9*, **17*, **1XN*, **2XN*/**35XN*	Metabolism
Dettling 2000[134]	Cross-sectional	108	Clozapine	**3*, **4*, **5*, **6*, **8*, **14*, **1*×2, **2*×2	ADRs
Ellingrod 2000[135]	Cross-sectional	31	Any antipsychotic	**1*, **3*, **4*	ADRs
Ellingrod 2002[136]	Prospective	11	Olanzapine	**1*, **3*, **4*	ADRs
Ellingrod 2002[137]	Prospective	37	Any typical antipsychotic (primarily haloperidol)	**1*, **3*, **4*	ADRs
Fu 2006[138]	Cross-sectional	182	Any typical antipsychotic	*10	ADRs
Hamelin 1999[139]	Prospective	39	Any antipsychotic	**3*, **4*, **5*, **6*, **7*	Efficacy, ADRs
Inada 2003[140]	Cross-sectional	For **2*: 309; for **10*: 214	Any antipsychotic	**2*, **3*, **4*, **10*, **12*	ADRs
Iwahashi 2007[141]	NS	16	Olanzapine	NS	ADRs

continued

TABLE 13 *Summary of study characteristics: clinical validity studies in patients tested for CYP2D (continued)*

Study	Type	*n*	Antipsychotic taken	Alleles genotyped	Outcome
Jaanson 2002[142]	Prospective	52	Maintenance monotherapy with zuclopenthixol decanoate Concomitant treatment with benzodiazepines and the anticholinergic drug trihexyphenidyl was allowed	**3*, **4*	ADRs
Jeon 2007[143]	Prospective	80	Aripiprazole	**1*, **2*, **4*, **5*, **10*, **14*, **36*, **41*	Metabolism
Jerling 1996[144]	Prospective	36	Perphenazine (*n* = 16) or zuclopenthixol (*n* = 20)	**3*, **4*	Metabolism
Kakihara 2005[145]	Prospective	41	Risperidone Only benzodiazepines that are independent of *CYP2D6*, low-dose levomepromazine (≤ 75 mg/day), lithium and valproic acid, were permitted as comedication	**5*, **10*	Efficacy, ADRs
Kapitany 1998[146]	Prospective	45	Any typical antipsychotic	**3*, **4*, **5*	ADRs
Lam 2001[147]	Retrospective	76	Any antipsychotic	*10	ADRs
Lane 2006[148]	Prospective	116	Risperidone	*10	ADRs
Liou 2004[149]	Retrospective	216	Any typical antipsychotic	*10	ADRs
Lohmann 2003[150]	Cross-sectional	109	Any antipsychotic	NS but alleles detected were **1*, **3*, **4*, **5*, **6*	ADRs
Mihara 2002[151]	Cross-sectional	9	NS	**3*, **4*, **5*, **10*	ADRs
Nikoloff 2002[152]	Prospective	202	Any typical antipsychotic	**2*, **3*, **4*, **6*, **7*, **8*, **9*, **10*, **11*, **14*, **18*, **19*, **25*, **26*, **31*	ADRs
Ohmori 1998[153]	Cross-sectional	99/100	Any typical antipsychotic	**3*, **4*, **10*	ADRs
Ohmori 1999[154]	Cross-sectional	99	Any typical antipsychotic	*2	ADRs
Panagiotidis 2007[155]	Prospective	26	Haloperidol injections Concomitant use of anticholinergics was accepted	**3*, **4*, **5*	Metabolism, efficacy, ADRs
Plesnicar 2006[156]	Prospective	131	Long-term maintenance antipsychotic treatment	**2*, **3*, **4*, **5*, **6*, **8*, **9*, **10*, **12*, **14*	Efficacy, ADRs
Riedal 2005[157]	Prospective	59	Risperidone monotherapy	**4*, **6*, **14*	Efficacy
Scordo 2000[158]	Cross-sectional	119	Any antipsychotic	**3*, **4*, **5*, **6*	ADRs

TABLE 13 *Summary of study characteristics: clinical validity studies in patients tested for CYP2D (continued)*

Study	Type	*n*	Antipsychotic taken	Alleles genotyped	Outcome
Thanacoody 2007[159] and 2003[160]	Cross-sectional	97	Thioridazine	**3*, **4*, **5*, **6*	ADRs
Tiwari 2005[161]	Cross-sectional	91	Any antipsychotic	**4*	ADRs
Topic 2000[162]	Cross-sectional	86	Haloperidol, clozapine or thioridazine	**3*, **4*, **6*, **7*, **8*	ADRs
Wang 2007[163]	Prospective	105	Risperidone No other medication was given except for benzodiazepines	**3*, **4*, **5*, **10*	Efficacy

ADRs, adverse drug reactions; NS, not stated.

perphenazine or zuclopenthixol[144] or haloperidol or thioridazine[162] being the typical antipsychotics studied. Four studies[129,133,134,162] (including one[162] permitting haloperidol or thioridazine in other patients) were interested in clozapine. In five of these single-drug studies[142,144,145,155,163] it was stated that benzodiazepines and/or anticholinergics were also allowed. Of the remaining four studies, Brockmoller *et al.*[131] was interested in haloperidol but other antipsychotics were also permitted; Aitchison *et al.*[126] studied clozapine in the refractory group and any antipsychotic in the non-refractory group; Plesnicar *et al.*[156] was interested in 'long-term maintenance antipsychotic treatment'; and the remaining study[151] did not specify which antipsychotics were used.

The most common alleles for which patients were genotyped were **4* (30 studies) and **3* ($n = 27$). The other two most prevalent loss of function alleles (**5* and **6*) were studied in 17 and 12 studies respectively. The most commonly genotyped decreased function allele was **10* ($n = 13$). A third ($n = 12$) of the studies genotyped for two or three alleles (all 12 genotyped the **4* allele and 11 genotyped both **3* and **4*).The other studies genotyped for more than three alleles, apart from six studies in which only **2* ($n = 1$), **4* ($n = 1$) or **10* ($n = 4$) were genotyped.

The vast majority of studies were interested in the relationship between genotype/phenotype and ADRs ($n = 30$), most commonly TD or parkinsonism. Nine studies were interested in efficacy, usually using the Positive and Negative Syndrome Scale (PANSS), including five studies[131,139,145,155,156] that considered both ADRs and efficacy. Five[131,133,143,144,155] studies were interested in metabolism, the outcomes here being clearance or half-life.

CYP1A2

The study characteristics are summarised in *Table 14*.

There were 10 *CYP1A2* studies, eight cross-sectional and two[167,171] prospective. The number of patients genotyped in each study varied from 16[141] to 285.[170] In one study[166] genotyping 199 patients it was stated that 335 patients were included in the study but it appears that not all of them were genotyped for reasons not given.

The patients were taking any antipsychotic in half of the studies,[138,159,165,167–169] any typical antipsychotic in three studies[138,164,166] and only one specific atypical antipsychotic (olanzapine[141] or clozapine[171]) in the other two studies.

Nine of the studies were concerned with the relationship of outcomes to the **1F* allele. Two of these studies[166,169] also examined **1C* and a further study completely sequenced the exons/exon–intron boundaries of the *CYP1A2* gene (*1545C4T* region).[170]

All but one of the studies examined the relationship between ADRs and genotype/phenotype, usually TD but also QT interval (QTc)[168] and hyperglycaemia and body weight increase;[141] the other study[171] explored efficacy (number of patients responding to treatment as measured by PANSS).

TABLE 14 *Summary of study characteristics: clinical validity studies in patients tested for* CYP1A2

Study	Type	*n*	Antipsychotic taken	Alleles genotyped	Outcomes
Basile 2000[164]	Cross-sectional	85	Any typical antipsychotic in the preceding 5 years at a dose equivalent to or greater than 1000 mg/day of chlorpromazine for a period of at least 6 weeks	**1F*	ADRs
Boke 2007[165]	Cross-sectional	57	Any antipsychotic	**1F*	ADRs
Fu 2006[138]	Cross-sectional	73	Any typical antipsychotic	**1F*	ADRs
Iwahashi 2007[141]	Cross-sectional	16	Olanzapine	NS	ADRs
Matsumoto 2004[166]	Cross-sectional	199	Any typical antipsychotic	**1F*, **1C*	ADRs
Schulze 2001[167]	Prospective	119	Any antipsychotic	**1F*	ADRs
Tay 2007[168]	Cross-sectional	72	Any antipsychotic	**1C*, **1F*	ADRs
Tiwari 2005[169]	Cross-sectional	96	Any antipsychotic	**1F*, **1C*	ADRs
Tiwari 2007[170]	Cross-sectional	285	Any antipsychotic	*1545C4T* region	ADRs
Yasar 2007[171]	Prospective	97	Clozapine	**1F*	Efficacy

ADRs, adverse drug reactions; NS, not stated.

Other *CYP* polymorphisms

The study characteristics are summarised in *Table 15*.

There were four studies genotyping other *CYP* polymorphisms, three[133,159,161] of which tested for *CYP2D6* as well: Thanacoody *et al.*[159] genotyped *CYP2C19*, Tiwari *et al.*[161] *CYP3A4* (and also reported on *CYP1A2* in separate papers[169,170]) and de Leon *et al.*[133] *CYP3A5*. Thus, there was only one study that had no interest in *CYP2D6*, that of Segman *et al.*[172] who tested for *CYP17*.

Three of the four studies were cross-sectional[159,161,172] and one was a prospective randomised double-blind trial.[133] The number of patients genotyped varied from 40[133] to 113;[172] although it was stated in another study[161] that

TABLE 15 *Summary of study characteristics: clinical validity studies in patients tested for* CYP *polymorphisms other than* CYP2D6 *and* CYP1A2

Study	Type	*n*	Antipsychotic taken	*CYP* and alleles genotyped	Outcomes
de Leon 2004[133a]	Prospective randomised double-blind trial	40	Clozapine	*CYP3A5*; **3*, **6*	Metabolism
Segman 2002[172]	Cross-sectional	113	NS	*CYP17*; T>C transition	ADRs
Thanacoody 2007[159] and 2003[160b,c]	Cross-sectional	97	Thioridazine	*CYP2C19*; **2*	ADRs
Tiwari 2005[161d]	Cross-sectional	92	Any antipsychotic	*CYP3A4*; **1B*	ADRs

ADRs, adverse drug reactions; NS, not stated.
a *CYP2D6* and *CYP3A5*.
b *CYP2C19* and *CYP2D6*.
c Additional data not reported in Thanacoody 2007[159] is derived from the Thanacoody 2003[160] abstract.
d Tiwari 2005,[169] Tiwari 2005[161] and Tiwari 2007[170] all report on the same patients but for different *CYP1A2* and *CYP3A4* polymorphisms and are therefore classified as separate studies.

there were 335 patients, only 92 appear to have been genotyped for *CYP3A4*. Patients were taking any antipsychotic in one study,[161] thioridazine in another[159] and clozapine in a third.[133] It was not stated which drugs were being taken in the fourth study.[172] Three of the studies were interested in ADRs as an outcome (TD[161,172] or QTc prolongation[159]) and the other study was concerned with metabolism.[133]

Participant characteristics

CYP2D6

The participant characteristics are summarised in *Table 16*.

Fifteen of the studies were known ($n = 12$) or assumed ($n = 3$) to have genotyped only Asian patients, mostly of Japanese or Chinese origin. The remaining 22 studies were known ($n = 13$) or assumed ($n = 9$) to have genotyped Caucasian patients, including Armstrong *et al.*,[128] who included genotypes from 75 Caucasian subjects and one Asian subject; Hamelin *et al.*,[139] whose genotypes were derived not only from Caucasian (74%) but also from Hispanic (13%) and African American (13%) subjects; and Jerling *et al.*,[144] who genotyped 35 white subjects and one Arab subject.

Eleven studies were unbalanced in terms of the gender mix (i.e. there was 60% or more of one sex), with six[128,137,140,149,152,158] including more male genotypes and five[132,133,138,159,163] including more female genotypes.

Information about age was provided by 21 studies. However, comparisons are complicated by the fact that many studies gave age only by specific subgroups within their study, which often markedly differed. For example, in Ellingrod *et al.*,[137] mean±SD age is given by genotype and smoking status as follows: 32.3±11.1 and 28.0±9.0 for smokers and non-smokers, respectively, with the *wt/wt* genotype and 36.9±6.8 and 45.4±6.8 for smokers and non-smokers, respectively, with the *wt/mut* genotype.

CYP1A2

The participant characteristics are summarised in *Table 17*.

Most of the *CYP1A2* studies included patients of Asian origin. Although half of the studies seemed to have a fairly even mix of males and females, noticeably more males were reported by three studies[161,164,171] and more females by two.[138,165] Patients in the Chinese and Japanese studies[138,166,168] also appeared to be markedly older than the patients in the other studies.

Other *CYP* polymorphisms

The participant characteristics are summarised in *Table 18*.

All patients in the Thanacoody *et al.*[159] *CYP2C19* study were Caucasian, and all patients included in the Tiwari *et al.*[161] study of *CYP3A4* were of Indian origin. In the de Leon *et al.*[133] *CYP3A5* study there was a mix of predominantly Caucasian and African American patients, whereas in the Segman *et al.*[172] study of *CYP17*, ethnicity was not stated although the study was conducted in Israel. Two studies[133,159] that reported on gender included fewer males than females, and the mean age of patients genotyped for *CYP3A4*[161] was markedly younger than the mean age of patients genotyped for *CYP17*[172] or *CYP3A5*[133] or the median age of patients genotyped for *CYP2C19*.[159]

Data analysis

The detailed findings from all of the studies are summarised below. When appropriate the results from meta-analyses are also presented.

CYP2D6

Metabolism

The findings are summarised in *Table 19*.

It was apparent that, with the exception of the studies by de Leon *et al.*,[133] which reported on half-life (i.e. the amount of time required for the concentration of a drug to be halved), and Panagiotidis *et al.*,[155] which reported on maximum (peak) and minimum (trough) concentrations, there were no other studies that examined any of these pharmacokinetic outcomes ($t_{½}$, C_{max} and C_{min} respectively) or other parameters such as time to maximum concentration (t_{max}) or area under the curve (AUC). Although a number of studies used proxy measures for clearance (and were thus excluded), only three studies[131,143,144] mathematically derived this outcome.

Two studies[131,155] examined clearance in patients taking haloperidol, one after oral use and one after depot injection. In the earlier haloperidol

TABLE 16 *Summary of participant characteristics: clinical validity studies in patients tested for* CYP2D6

Study	Ethnicity	Sex	Age (years), mean±SD (range)
Aitchison 1999[126]	Caucasian	NS	NS
Andreassen 1997[127]	Caucasian (assumed – Scotland)	M: 56/100 (56.0%)	Male: 50 14; female: 57±16
Armstrong 1997[128]	Caucasian (European): 75 (98.7%); Asian: 1 (1.3%)	M: 56/76 (73.7%)	47±16
Arranz 1995[129]	Caucasian	NS	NS
Arthur 1995[130]	Caucasian	M: 9/16 (56.3%)	49±19 (24–79)[a]
Brockmoller 2002[131]	Caucasian (assumed – Germany)	NS	NS
Culav-Sumic 2001[132]	Caucasian (assumed – Croatia)	All women (*n*=71)	Patients with EPS: 39.8±11.8 (22–63); patients without EPS: 48.3±14.9(19–78)
de Leon 2004[133]	Caucasian: 27/31; African American: 4/31	M: 12/31 (38.7%)	47±9.3 (31–62)
Dettling 2000[134]	Caucasian	M: 53/108 (49.1%)	Patients with CA (*n*=31): 48±17.2 (22–85); patients without CA (*n*=77): 35±11 (19–82)
Ellingrod 2000[135]	Caucasian (assumed – USA)	M: 27/31 (87.1%)	NS
Ellingrod 2002[136]	Caucasian (assumed – USA)	NS	Homozygous **1/*1* (*n*=6): 32.8±4.4; heterozygous **1/*3*, **4* (*n*=5): 38.8±4.8
Ellingrod 2002[137]	Caucasian (assumed – USA)	M: 34/37 (91.9%)	Smokers: **1/*1* (*n*=14): 32.3±11.1; **1/*3* or **4* (*n*=23): 36.9±6.8 Non-smokers: **1/*1* (*n*=14): 28.0±9.0; **1/*3* or **4* (*n*=23): 45.4±6.8
Fu 2006[138]	Chinese	M: 68/182 (37.4%)	With TD: 63.19±11.71; without TD: 51.11±9.42
Hamelin 1999[139]	Caucasian: 74% (29); Hispanic: 13% (5); African American: 13% (5)	M: 51% (20)	40 ± 5
Inada 2003[140]	Japanese	**2*, **3* and **4*: M: 191/309 (61.8%); **10* and **12*: M: 139/214 (65.0%)	**2*, **3* and **4* (*n*=309): 53±14 (18–90); **10* and **12* (*n*=214): 53±13 (19–81)
Iwahashi 2007[141]	Japanese (assumed – Japan)	NS	NS
Jaanson 2002[142]	Caucasian (Estonian or Russian)	NS	NS
Jeon 2007[143]	Korean	M: 34/80 (42.5%)	NS
Jerling 1996[144]	White: 35/36; Arab: 1/36	NS	Perphenazine: 47±21 (20–87); zuclopenthixol: 44±16 (20–81)
Kakihara 2005[145]	Japanese (assumed – Japan)	NS	37±13 (27–80)
Kapitany 1998[146]	Caucasian	M: 26/45 (57.8%)	34.7±11.7
Lam 2001[147]	Chinese	M: 44/76 (57.9%)	Patients with TD: 49.7±9.3; patients without TD: 49.6±8.9
Lane 2006[148]	Han Chinese	M: 68/123 (55.3%)	34±9.7
Liou 2004[149]	Chinese	M: 133/216 (61/6%)	TD group (*n*=113): 46.93±9.72; non-TD group (*n*=103): 47.84±9.01
Lohmann 2003[150]	Caucasian (assumed – Germany)	M: 61/109 (56.0%)	Patients with TD: 44.3±9.1; patients without TD: 42.0±8.4
Mihara 2002[151]	Japanese	M: 4/9 (44.4%)	33.1±10.6
Nikoloff 2002[152]	Korean	With TD: M: 81/110 (73.7%); without TD: M: 62/92 (67.4%)	With TD: 45.4±9.1; without TD: 43±9.3

TABLE 16 *Summary of participant characteristics: clinical validity studies in patients tested for CYP2D6 (continued)*

Study	Ethnicity	Sex	Age (years), mean±SD (range)
Ohmori 1998[153]	Japanese	M: 58/100 (58.0%)	57.18±8.90
Ohmori 1999[154]	Japanese	As Ohmori 1998[153]	As Ohmori 1998[153]
Panagiotidis 2007[155]	Caucasian (assumed – Sweden)	M: 14/26 (53.8%)	Median age by genotype/functional alleles: EM/0 (*n* = 1): 39; EM/1 (*n* = 8): 49 (28–83); EM/2 (*n* = 16): 53 (29–75); EM/3 (*n* = 1): 45
Plesnicar 2006[156]	Caucasian	M: 55/131 (42.0%)	43.9±13.2 (18–70)
Riedal 2005[157]	Japanese (assumed – Japan)	All including patients not genotyped: M: 43/82 (52.4%)	All including patients not genotyped: 36.2±12.9
Scordo 2000[158]	Caucasian (European)	M: 99/119 (83.2%)	50±12 (25–75)
Thanacoody 2007[159] and 2003[160]	Caucasian	All including patients not genotyped: M: 31/97 (32.0%)	All including patients not genotyped: median: 58 (19–98)
Tiwari 2005[161]	Indian	M: 182/335 (54.3%)	With TD: 34.53±12.6; without TD: 31.42±10.2
Topic 2000[162]	Caucasian (assumed – Croatia)	NS	NS
Wang 2007[163]	Chinese	M: 40/118 (33.9%)	NS

CA, clozapine-induced agranulocytosis; EM, extensive metaboliser; EPS, extrapyramidal symptoms; M, male; NS, not stated; TD, tardive dyskinesia.
a Calculated from individual patient data.

TABLE 17 *Summary of participant characteristics: clinical validity studies in patients tested for* CYP1A2

Study	Ethnicity	Sex	Age (years), mean±SD (range)
Basile 2000[164]	Caucasian: 63/85 (74%); African American: 22/85 (26%)	M: 64/85 (75%)	34.3±9.5
Boke 2007[165]	Caucasian (Turkish)	M: 52/127 (40.9%)	Patients with TD: 46.62±9.98; patients without TD: 35.44±8.53
Fu 2006[138]	Chinese	M: 68/182 (37.4%)	Patients with TD: 63.19±11.71; patients without TD: 51.11±9.42
Iwahashi 2007[141]	NS	NS	NS
Matsumoto 2004[166]	Japanese	M: 97/199 (48.7%)	55.1±9.5
Schulze 2001[167]	NS	M: 63/119 (52.9%)	41±10
Tay 2007[168]	Indian	M: 182/335 (54.3%)	Patients with TD: 34.53±12.6; patients without TD: 31.42±10.2
Tiwari 2005[169]	Chinese: 61/72; Malay: 7/62; Indian: 3/72; other: 1/72	M: 60/72 (83.3%)	53.3±11.4
Tiwari 2007[170]	Indian	M: 182/335 (54.3%)	Patients with TD: 34.53±12.6; patients without TD: 31.42±10.2
Yasar 2007[171]	NS	M: 81/97 (83.5%)	Range 19–60

M, male; NS, not stated; TD, tardive dyskinesia.

TABLE 18 *Summary of participant characteristics: clinical validity studies in patients tested for* CYP *polymorphisms other than* CYP2D6 *and* CYP1A2

Study	Ethnicity	Sex	Age (years), mean ± SD (range)
de Leon 2004[133]	Caucasian: 27/31; African American: 4/31	M: 12/31 (38.7%)	47 ± 9.3 (31–62)
Segman 2002[172]	Jewish (assumed – Israel)	With TD: M: 29/55 (52.7%); without TD: M: 30/58 (51.7%)	With TD: 52.9 ± 12.2; without TD: 50.8 ± 10.3
Thanacoody 2007[159] and 2003[160]	Caucasian	All including patients not genotyped: M: 31/97 (32.0%)	All including patients not genotyped: median: 58 (19–98)
Tiwari 2005[161]	Indian	M: 182/335 (54.3%)	With TD: 34.53 ± 12.6; without TD: 31.42 ± 10.2

NS, not stated; M, male; TD, tardive dyskinesia.

study[131] of 172 patients it was found that there was a trend towards lower therapeutic efficacy with increasing number of functional alleles, with mean clearance steadily increasing with each additional functional allele. However, the numbers of patients with the PM (*mut/mut*) and UM phenotypes were small ($n = 5$ for both groups). In the later study of 26 patients,[155] clearance was measured at peak and trough and patients with the *wt/mut* genotype appeared to have a greater median concentration than those with the *wt/wt* genotype (of whom one patient was classified as UM, having an even lower median concentration than the EM). The authors state, however, that the association was not statistically significant. They acknowledge that the small number of included subjects may have limited the power of this study to detect differences.

For perphenazine, Jerling *et al.*[144] found the mean oral clearance (CL/F) to be similar amongst *wt/wt* and *wt/mut* patients and both to be higher than that in *mut/mut* patients whereas for zuclopenthixol the value decreased steadily by genotype although only two patients had the *mut/mut* genotype; the difference in clearance between *wt/wt* and *mut/mut* was thus threefold for perphenazine and twofold for zuclopenthixol. Regression analysis showed the effect to be statistically significant for both drugs. Similarly, for aripiprazole, Jeon *et al.*[143] found that for each functional allele the mean value of CL/F steadily decreased, being twice as high for *wt/wt* as for *wt/mut* patients.

Efficacy

Nine studies focused on the relationship between efficacy and genotype/phenotype but as all reported outcomes differed in how they were derived it was not possible to include the data from these studies in a meta-analysis. The findings are summarised in *Table 20*.

Three studies[126,129,157] concentrated on the number of responders to treatment. In patients taking clozapine, the response in the study by Arranz *et al.*,[129] as assessed by the Global Assessment Scale, was worse for those with the *mut/mut* genotype than for those with either the *wt/wt* or the *wt/mut* genotype. Riedal *et al.*[157] did not identify any patients with the *mut/mut* genotype but found that proportionately more patients with the *wt/mut* genotype than with the *wt/wt* genotype failed to respond, where response was defined by a difference of 30% or less in PANSS total scores between baseline and last observation. The findings from Aitchison *et al.*[126] must be treated with extreme caution in the context of this review because the aim of this study was to compare UMs with other phenotypes, whereas, as already described in the methods section, for the purposes of this review, UMs are considered as *wt/wt* and therefore no different to EMs. Furthermore, patients were also preselected into refractory and non-refractory groups and assessed retrospectively and the drug regimens in the two groups were not the same (clozapine in the refractory group versus any antipsychotic in the non-refractory group). Nevertheless, this study also found a greater proportion of patients with the *mut/mut* genotype to be refractory to treatment than those with the *wt/wt* + *wt/mut* genotype, although fewer patients with the UM phenotype were refractory than either EMs or PMs. However, the number of UMs and PMs combined in this study was significantly less than the number of EMs and it should be noted that response was not defined by validated criteria but by prescribing consultants.

TABLE 19 *Summary of metabolism findings: clinical validity studies in patients tested for* CYP2D6

Study	Outcomes as reported	'Standardised outcome'[a]
Brockmoller 2002[131]	Haloperidol clearance (litres/hour): UM (n = 5): 57.3 ± 31.7; EM (n = 106): 48.7 ± 20.9; IM (n = 56): 44.1 ± 25.4; PM (n = 5): 34.7 ± 13.7	NA
	Jonckheere–Terpstra test: p = 0.034 (n = 172)	
de Leon 2004[133]	Half-life < 3 days: PM (n = 6): 0	Half-life < 3 days: *mut/mut* (n = 6): 0
	Half-life ≥ 3 days: PM (n = 6): 2	Half-life ≥ 3 days: *mut/mut* (n = 6): 2
Jeon 2007[143]	CL/F (l/h):	NA
	Homozygous for functional alleles: 3.17	
	Heterozygous for one functional and one non-functional/ reduced function alleles: 2.55	
	Homozygous for reduced functional alleles: 1.85	
	Heterozygous for one reduced functional and one non-functional allele: 1.54	
Jerling 1996[144]	CL/F (l/h), mean ± SD (range):	CL/F (l/h), mean ± SD (range):
	Perphenazine: EM homozygote (n = 9): 454 ± 385 (213–1286); EM heterozygote (n = 5): 454 ± 279 (174–883); PM (n = 2): 250 ± 30 (229–271)	Perphenazine: *wt/wt* (n = 9): 454 ± 385 (213–1286); *wt/mut* (n = 5): 454 ± 279 (174–883); *mut/mut* (n = 2): 250 ± 30 (229–271)
	Zuclopenthixol: EM homozygote (n = 8): 95 ± 43 (38–165); EM heterozygote (n = 9): 65 ± 21 (38–95); PM (n = 3): 42±12 (31–54)	Zuclopenthixol: *wt/wt* (n = 8): 95 ± 43 (38–165); *wt/mut* (n = 9): 65 ± 21 (38–95); *mut/mut* (n = 3): 42 ± 12 (31–54)
Panagiotidis 2007[155]	Peak (Cmax), median (range) concentration (nmol/l): 0 functional alleles (n = 1): not available; 1 functional alleles (n = 8): 14.0 (3.3–67.0); 2 functional alleles (n = 16): 6.4 (1.6–19.0); 3 functional alleles (n = 1): 6	NA
	Trough (Cmin), median (range) concentration (nmol/l): 0 functional alleles (n = 1): 6; 1 functional alleles (n = 8): 10.5 (1–49); 2 functional alleles (n = 16): 4.0 (1.4–8.7); 3 functional alleles (n = 1): 3	
	p = 0.047	

CL/F, oral clearance; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; EM, extensive metaboliser; IM, intermediate metaboliser; NA, not applicable (cannot be calculated from data presented); PM, poor metaboliser; UM, ultrarapid metaboliser.

a For ease of comparison, outcomes have been summarised as *wt/wt* (wild type/wild type), *wt/mut* (wild type/mutant) or *mut/mut* (mutant type/mutant).

The remaining six studies all used PANSS or Brief Psychiatric Rating Scores (BPRS) to measure efficacy. Using total BPRS scores in patients using any antipsychotic, Hamelin *et al.*[139] found little difference between patients with the *wt/wt*, *wt/mut* or *mut/mut* genotypes, although only one patient possessed this last genotype. Brockmoller *et al.*[131] found that, for haloperidol, PMs (*mut/mut*) fared better than EMs, IMs or UMs (*wt/wt* or *wt/mut*) on median changes in general, positive and negative items on the PANSS. The score for UMs on the general items scale was notably different to the scores for EMs and IMs, in the other direction [+8 compared with between –9 (EMS) and –17 (IMs) for the other genotypes], but was similar to the scores for EMs and IMs for positive and negative items scale scores. Plesnicar *et al.*[156] found end of study PANSS scores for patients on long-term maintenance antipsychotic treatment to be similar between patients with the *mut/mut* genotype and those with the other two genotypes. In Panagiotidis *et al.*,[155] the median PANSS scores at both peak and trough for patients taking haloperidol injections were similar for UMs and PMs but higher for

TABLE 20 *Summary of efficacy findings: clinical validity studies in patients tested for* CYP2D6

Study	Outcomes as reported	'Standardised outcome'[a]
Aitchison 1999[126]	Total number of patients refractory to treatment: UM (*n* = 5): 2 (40.0%); EM (*n* = 287): 220 (76.7%); PM (*n* = 16): 13 (81.3%)	Number of patients refractory to treatment: *wt/wt* + *wt/mut* (*n* = 292): 222 (76.0%); *mut/mut* (*n* = 16): 13 (81.3%)
Arranz 1995[129]	Total number of non-responders to treatment: EM (*n* = 115): 42 (36.8%); PM (*n* = 8): 4 (50.0%)	Total number of non-responders to treatment: *wt/wt* + *wt/mut* (*n* = 115): 42 (36.8%); *mut/mut* (*n* = 8): 4 (50.0%)
Brockmoller 2002[131]	PANSS (day 28–day 3), median (range):	NA
	General items: UM (*n* = 5): +8 (–31 to +1); EM (*n* = 106): –9.5 (–33 to +17); IM (*n* = 56): –9 (–41 to +25); PM (*n* = 5): –17 (–33 to -4)	
	Positive items: UM (*n* = 5): –10 (–15 to –8); EM (*n* = 106): –9 (–25 to +18); IM (*n* = 56): –7 (–29 to +13); PM (*n* = 5): –13 (–15 to –3)	
	Negative items: UM (*n* = 5): –2 (–8 to +5); EM (*n* = 106): –3 (–27 to +27); IM (*n* = 56): –5 (–18 to +27); PM (*n* = 5):9 (–11 to –4)	
Hamelin 1999[139]	End of study BPRS scores, mean ± SD:	End of study mean ± SD BPRS scores:
	BPRS (total): **1/*1* (*n* = 23): 31 ± 7; **1/*4* (*n* = 15): 34 ± 7; **4/*4* (*n* = 1): 31	BPRS (total): *wt/wt* (*n* = 23): 31 ± 7; *wt/mut* (*n* = 15): 34 ± 7; *mut/mut* (*n* = 1): 31
	BPRS (+): **1/*1* (*n* = 23): 8 ± 4; **1/*4* (*n* = 15): 10 ± 4; **4/*4* (*n* = 1): 11	BPRS (+): *wt/wt* (*n* = 23): 8 ± 4; *wt/mut* (*n* = 15): 10 ± 4; *mut/mut* (*n* = 1): 11
	BPRS (–): **1/*1* (*n* = 23): 7 ± 3; **1/*4* (*n* = 15): 9 ± 3; **4/*4* (*n* = 1): 3	BPRS (–): *wt/wt* (*n* = 23): 7 ± 3; *wt/mut* (*n* = 15): 9 ± 3; *mut/mut* (*n* = 1): 3
Kakihara 2005[145]	Percentage improvement in scores of PANSS: **1/*1* (*n* = 16): 37.7± 15.8; **1/*10* (*n* = 14): 31.9 ±24.4; **10/*10* (*n* = 9): 43.5 ± 20.5	Percentage improvement in scores of PANSS: *wt/wt* (*n* = 16): 37.7± 15.8; *wt/mut* (*n* = 14): 31.9 ±24.4; *mut/mut* (*n* = 9): 43.5 ± 20.5
Panagiotidis 2007[155]	PANSS total score, median (range):	NA
	Peak: 0 functional alleles (*n* = 1): NA; 1 functional alleles (*n* = 8): 53 (35–88); 2 functional alleles (*n* = 16): 54 (38–91); 3 functional alleles (*n* = 1): 38	
	Trough: 0 functional alleles (*n* = 1): 35; 1 functional alleles (*n* = 8): 60.5 (38–86); 2 functional alleles (*n* = 16): 59 (33–95); 3 functional alleles (*n* = 1): 38	
	PANSS-G score, median (range):	
	Peak: 0 functional alleles (*n* = 1): NA; 1 functional alleles (*n* = 8): 24 (18–38); 2 functional alleles (*n* = 16): 28 (18–42); 3 functional alleles (*n* = 1): 18	
	Trough: 0 functional alleles (*n* = 1): 16; 1 functional alleles (*n* = 8): 25.5 (19–41); 2 functional alleles (*n* = 16): 28 (17–43); 3 functional alleles (*n* = 1): 19	

TABLE 20 *Summary of efficacy findings: clinical validity studies in patients tested for* CYP2D6 *(continued)*

Study	Outcomes as reported	'Standardised outcome'[a]
	PANSS-P score, median (range):	
	Peak: 0 functional alleles ($n = 1$): NA; 1 functional alleles ($n = 8$): 7.5 (7–24); 2 functional alleles ($n = 16$): 8 (7–16); 3 functional alleles ($n = 1$): 7	
	Trough: 0 functional alleles ($n = 1$): 7; 1 functional alleles ($n = 8$): 8 (7–20); 2 functional alleles ($n = 16$): 8 (7–16); 3 functional alleles ($n = 1$): 7	
	PANSS-N score, median (range):	
	Peak: 0 functional alleles($n = 1$): NA; 1 functional alleles($n = 8$): 23.5 (7–32); 2 functional alleles($n = 16$): 27 (12–36); 3 functional alleles($n = 1$): 13	
	Trough: 0 functional alleles ($n = 1$): 12; 1 functional alleles ($n = 8$): 24 (11–36); 2 functional alleles ($n = 16$): 24.5 (7–36); 3 functional alleles ($n = 1$): 13	
Plesnicar 2006[156]	PANSS – general subscale total score:	NA
	EM/IM/UM ($n = 125$): 23.02 ± 5.31; PM ($n = 6$): 23.50 ± 3.83; $p > 0.05$	
	PANSS – positive subscale total score:	
	EM/IM/UM ($n = 125$): 9.35 ± 3.22; PM ($n = 6$): 8.83 ± 3.06; $p > 0.05$	
	PANSS – negative subscale total score:	
	EM/IM/UM ($n = 125$): 13.77 ± 4.09; PM ($n = 6$): 17.83 ± 2.48; $p = 0.017$	
Riedal 2005[157]	Total number of non-responders to treatment: wild type ($n = 45$): 26/45 (57.8%); heterozygous ($n = 6$): 4 (66.7%)	Total number of non-responders to treatment: *wt/wt* ($n = 45$): 26 (57.8%); *wt/mut* ($n = 6$): 4 (66.7%); *mut/mut* ($n = 0$): 0
Wang 2007[163]	BPRS (% improvement): **1/*1* ($n = 22$): 37.49 ± 15.47; **1/*10* ($n = 39$): 45.32 ± 16.29; **10/*10* ($n = 41$): 41.31 ± 17.10	BPRS (% improvement): *wt/wt* ($n = 22$): 37.49 ± 15.47; *wt/mut* ($n = 39$): 45.32 ± 16.29; *mut/mut* ($n = 41$): 41.31 ± 17.10

BPRS, Brief Psychiatric Rating Score; EM, extensive metaboliser; IM, intermediate metaboliser; NA, not applicable (cannot be calculated from data presented); PANSS, positive and negative symptoms scale; PM, poor metaboliser; UM, ultrarapid metaboliser.

a For ease of comparison, outcomes have been summarised as *wt/wt* (wild type/wild type), *wt/mut* (wild type/mutant) or *mut/mut* (mutant/mutant).

EMs and IMs, suggesting lower efficacy in these phenotypes, although extreme caution is required in interpreting this finding as only one patient was reported as having either the PM or UM phenotype. For risperidone, the mean percentage improvement in PANSS scores was lowest in the *wt/mut* group and highest in the *mut/mut* group in Kakihara *et al.*;[145] however, using BPRS, Wang *et al.*[163] found little difference between the groups.

Adverse drug reactions

In total, 30 studies were found examining the relationship between ADRs and genotype. Results

for each type of ADR are presented in the following sections.

Tardive dyskinesia

A total of 14 studies quantified the number of patients with TD by genotype, with data from up to 13 included in the meta-analysis (but only between nine and 11 for any given comparison because of the manner in which these studies grouped their genotypes) (*Table 21*). Most of the studies measured the occurrence of TD using the validated Abnormal Involuntary Movement Scale (AIMS) and stipulated that patients were taking any typical or any antipsychotic.

In the meta-analyses no significant differences were found between genotypes for either Caucasian or Asian populations (Appendix 5, *Figure 6*). However, there was a significant amount of heterogeneity among the Asian studies. It should be noted that the meta-analyses included data from Lohmann *et al.*,[150] in which seven UMs were classified with EMs (of whom three developed persistent TD), and an unknown number of UMs (and thus an unknown number with TD) from Plesnicar *et al.*[156]

Sensitivity analysis was conducted to include only the studies that tested for **10* and no other *CYP*.[138,147,149] This increased heterogeneity and the effect was again non-significant for all comparisons (data not presented).

Sensitivity analysis was also carried out excluding one study[150] that did not use AIMS to define/measure TD but rather the Tardive Dyskinesia Rating Scale (TDRS). This produced almost identical findings to the original analysis (data not presented).

Further sensitivity analyses were also carried out for study type. When only cross-sectional studies were included,[127,138,140,150,154,158] heterogeneity was again increased while the odds ratios (ORs) varied slightly from those in the original analysis but remained non-significant (data not presented). However, the inclusion of only prospective studies[137,142,146,152] decreased heterogeneity to 0% and, for two comparisons (*wt/mut* versus *wt/wt* and *mut/mut* + *wt/mut* versus *wt/wt*), significant findings were found [OR 2.08 (95% CI 1.21 to 3.57) and OR 1.83 (95% CI 1.09 to 3.08) respectively; *Figure 2*].

The only study not included in the meta-analysis was that by Ohmori *et al*.[154] This was because it only genotyped **1* and **2*, both of which are being considered as *wt* alleles for the purposes of this review for reasons explained in the methods section. Here the proportion of patients with TD was highest amongst those with the **1/*1* genotype and lowest among those with the **2/*2* genotype, although there was only one patient with this genotype. Following regression analysis the authors concluded that there was no association of the *CYP2D6*2* genotype with the occurrence of TD.

Seven studies also assessed TD severity, which was usually measured using AIMS with only one study using the TDRS. Data from five of these studies could be included in the meta-analysis (but only between two and four for any given comparison because of the manner in which these studies grouped their genotypes, comprising between 136 and 264 patients). Significantly, the weighted mean difference (WMD) AIMS score was in favour of the *wt/wt* genotype compared with the *mut/mut* genotype [WMD 1.80 (95% CI 0.40 to 3.19)] (*Figure 3*). In the sole study that measured TD severity using the TDRS,[146] comprising 45 patients, the mean scores favoured patients with the *wt/wt* genotype compared with the *wt/mut* genotype.

It was not possible to include data from Plesnicar *et al.*[156] in the meta-analysis because this study of 131 patients only compared patients with the PM phenotype with non-PMs (including seven UMs). No significant difference in AIMS score was found between these groups in this study. Data from Ohmori *et al.*[154] were also excluded because this study only genotyped **1* and **2* and no significant differences were found across groups and the authors concluded that there was no association between the *CYP2D6*2* genotype and the AIMS score.

A further two studies measured AIMS only in patients who had TD and data from these were also included in the meta-analysis (an overall patient population of between 118 and 153 depending on the genotypes being compared). Although no significant differences were found, the WMD AIMS score was in the direction of favouring *wt/mut* compared with *mut/mut* (Appendix 5, *Figure 7*).

Finally, Ellingrod *et al.*[137] compared AIMS scores by genotype (*wt/wt* and *wt/mut*) in 14 smokers and 23 non-smokers – differences were only significant in smokers, in whom the mean AIMS score was much higher in the *wt/mut* group.

TABLE 21 *Summary of findings for tardive dyskinesia: clinical validity studies in patients tested for* CYP2D6

Study	Outcomes as reported	'Standardised outcome'[a]
Andreassen 1997[127]	Total number of patients with TD: EM homozygote (*n* = 61): 30 (49.2%); EM heterozygote (*n* = 29): 16 (55.2%); PM (*n* = 10): 5 (50.0%)	Total number of patients with TD: *wt/wt* (*n* = 61): 30 (49.2%); *wt/mut* (*n* = 29): 16 (55.2%); *mut/mut* (*n* = 10): 5 (50.0%)
	AIMS score – all patients, mean ± SD: EM homozygote (*n* = 61): 5.1 ± 4.0; EM heterozygote (*n* = 29): 5.8 ± 5.3; PM (*n* = 10): 6.8 ± 6.3	AIMS score – all patients, mean ± SD: *wt/wt* (*n* = 61): 5.1 ± 4.0; *wt/mut* (*n* = 29): 5.8 ± 5.3; *mut/mut* (*n* = 10): 6.8 ± 6.3
Arthur 1995[130]	Individual patient data presented	AIMS score – patients with TD, mean ± SD: *wt/wt* (*n* = 8): 5.7 ± 1.9; *wt/mut* (*n* = 7): 8 ± 5.2; *wt/wt* + *wt/mut* (*n* = 15): 7 ± 4.1; *mut/mut* (*n* = 1): 13
Ellingrod 2002[137]	Total number of patients with TD: **1/*1* (*n* = 11): 3 (27.3%); **1/*3* + **1/*4* (*n* = 26): 12 (46.2%); **3/*3* + **4/*4* (*n* = 0): 0	Total number of patients with TD: *wt/wt* (*n* = 11): 3 (27.3%); *wt/mut* (*n* = 26): 12 (46.2%); *mut/mut* (*n* = 0): 0
	Smokers with TD: **1/*1* (*n* = 5): 1 (20.0%); **1/*3* + **1/*4* (*n* = 9): 7 (77.8%); **3/*3* + **4/*4* (*n* = 0): 0	Smokers with TD: *wt/wt* (*n* = 5): 1 (20.0%); *wt/mut* (*n* = 9): 7 (77.8%); *mut/mut* (*n* = 0): 0
	Non-smokers with TD: **1/*1* (*n* = 6): 2 (33.3%); **1/*3* + **1/*4* (*n* = 17): 5 (29.4%); **3/*3* + **4/*4* (*n* = 0): 0	Non-smokers with TD: *wt/wt* (*n* = 6): 2 (33.3%); *wt/mut* (*n* = 17): 5 (29.4%); *mut/mut* (*n* = 0): 0
	AIMS score in smokers, mean ± SD: **1/*1* (*n* = 5): 1.23 ± 1.56; **1/*3* + **1/*4* (*n* = 9): 5.8 ± 4.3; **3/*3* + **4/*4* (*n* = 0): NA	AIMS score in smokers, mean ± SD: *wt/wt* (*n* = 5): 1.23 ± 1.56; *wt/mut* (*n* = 9): 5.8 ± 4.3; *mut/mut* (*n* = 0): NA
	AIMS score in non-smokers, mean ± SD: **1/*1* (*n* = 6): 1.7 ± 2.25; **1/*3* + **1/*4* (*n* = 17): 1.2 ± 2.17; **3/*3* + **4/*4* (*n* = 0): NA	AIMS score in non-smokers, mean ± SD: *wt/wt* (*n* = 6): 1.7 ± 2.25; *wt/mut* (*n* = 17): 1.2 ± 2.17; *mut/mut* (n = 0): NA
Fu 2006[138]	Total number of patients with TD: TT (*n* = 50): 37 (74.0%); CT (*n* = 64): 30 (46.9%); CC (*n* = 35): 15 (42.9%)	Total number of patients with TD: *wt/wt* (*n* = 50): 37 (74.0%); *wt/mut* (*n* = 64): 30 (46.9%); *mut/mut* (*n* = 35): 15 (42.9%)
	AIMS score – patients with TD, mean ± SD: TT (*n* = 37): 6.32 ± 2.62; CT (*n* = 30): 6.90 ± 2.83; CC (*n* = 15): 7.87 ± 3.60	AIMS score – patients with TD, mean ± SD: *wt/wt* (*n* = 37): 6.32 ± 2.62; *wt/mut* (*n* = 30): 6.90 ± 2.83; *mut/mut* (*n* = 15): 7.87 ± 3.60
Inada 2003[140]	Total number of patients vulnerable to TD with *2: WW (*n* = 234): 30 (12.8%); WM (*n* = 68): 11 (16.2%); MM (*n* = 7): 0	Total number of patients vulnerable to TD with *2: NA
	Total number of patients vulnerable to TD with **10*: WW (*n* = 78): 10 (12.8%); WM (*n* = 97): 13 (13.4%); MM (*n* = 39): 4 (10.3%)	Total number of patients vulnerable to TD with **10*: *wt/wt* (*n* = 78): 10 (12.8%); *wt/mut* (*n* = 97): 13 (13.4%); *mut/mut* (*n* = 39): 4 (10.3%)
Jaanson 2002[142]	Total number of patients with TD: EM homozygote (*n* = 35): 6 (17.1%); EM heterozygote (*n* = 13): 4 (30.8%); PM (*n* = 4): 1 (25.0%)	Total number of patients with TD: *wt/wt* (*n* = 35): 6 (17.1%); *wt/mut* (*n* = 13): 4 (30.8%); *mut/mut* (*n* = 4): 1 (25.0%)
Kapitany 1998[146]	Total number of patients with TD: EM homozygote (*n* = 28): 13 (46.4%); EM heterozygote (*n* = 16): 13 (81.3%); PM (*n* = 1): NAb	Total number of patients with TD: *wt/wt* (*n* = 28): 13 (46.4%); *wt/mut* (*n* = 16): 13 (81.3%); *mut/mut* (*n* = 1): NA[b]
	TDRS score – all patients, mean ± SD: EM homozygote (*n* = 28): 7.6 ± 5.94; EM heterozygote (*n* = 16): 11.6 ± 6; PM (*n* = 1): NAb	TDRS score – all patients, mean ± SD: *wt/wt* (*n* = 28): 7.6 ± 5.94; *wt/mut* (*n* = 16): 11.6 ± 6; *mut/mut* (*n* = 1): NA[b]

continued

TABLE 21 *Summary of findings for tardive dyskinesia: clinical validity studies in patients tested for* CYP2D6 *(continued)*

Study	Outcomes as reported	'Standardised outcome'[a]
Lam 2001[147]	Total number of patients with TD: *wt* and heterozygous (*n* = 40): 19 (47.5%); *mut* homozygote (*n* = 36): 19 (52.8%)	Total number of patients with TD: *wt/wt* + *wt/mut* (*n* = 40): 19 (47.5%); *mut/mut* (*n* = 36): 19 (52.8%)
	Male patients with TD: *wt* and heterozygous (*n* = 26): 16 (61.5%); *mut* homozygote (*n* = 18): 6 (33.3%)	Male patients with TD: *wt/wt* + *wt/mut* (*n* = 26): 16 (61.5%); *mut/mut* (*n* = 18): 6 (33.3%)
	Female patients with TD: *wt* and heterozygous (*n* = 14): 3 (21.4%); *mut* homozygote (*n* = 18): 13 (72.2%)	Female patients with TD: *wt/wt* + *wt/mut* (*n* = 14): 3 (21.4%); *mut/mut* (*n* = 18): 13 (72.2%)
Liou 2004[149]	Total number of patients with TD: TT (*n* = 87): 39 (44.8%); CT (*n* = 81): 47 (58.0%); CC (*n* = 48): 27 (56.3%)	Total number of patients with TD: *wt/wt* (*n* = 87): 39 (44.8%); *wt/mut* (*n* = 81): 47 (58.0%); *mut/mut* (*n* = 48): 27 (56.3%)
	Male patients with TD: TT (*n* = 54): 20 (37.0%); CT (*n* = 47): 29 (61.7%); CC (*n* = 32): 21 (65.6%)	Male patients with TD: *wt/wt* (*n* = 54): 20 (37.0%); *wt/mut* (*n* = 47): 29 (61.7%); *mut/mut* (*n* = 32): 21 (65.6%)
	AIMS score – patients with TD, mean ± SD: TT (*n* = 39): 12.0 ± 6.0; CT (*n* = 47): 8.8 ± 4.1; CC (*n* = 27): 11.3 ± 6.1	AIMS score – patients with TD, mean ± SD: *wt/wt* (*n* = 39): 12.0 ± 6.0; *wt/mut* (*n* = 47): 8.8 ± 4.1; *mut/mut* (*n* = 27): 11.3 ± 6.1
Lohmann 2003[150]	Total number of patients with TD: ≥ 2 functional alleles (*n* = 68): 31 (45.6%); 1 functional alleles (*n* = 34): 15 (44.1%); 0 functional alleles (*n* = 7): 4 (57.1%)	Total number of patients with TD: *wt/wt* (*n* = 68): 31 (45.6%); *wt/mut* (*n* = 34): 15 (44.1%); *mut/mut* (*n* = 7): 4 (57.1%)
Nikoloff 2002[152]	Total number of patients with TD: **1/*1* (*n* = 24): 11 (45.8%); **1/*2* (*n* = 15): 8 (53.3%); **1/*2* (*n* = 4): 1 (25.0%); all wild/wild (*n* = 43): 20 (46.5%) **1/*10B* (*n* = 82): 46 (56.1%); **1/*41* (*n* = 3): 1 (33.3%); **2/*10B* (*n* = 16): 10 (62.5%); **2/*41* (*n* = 1): 0; all wild/decreased (*n* = 102): 57 (55.9%) **2/*14* (*n* = 1): 1 (100%); **1/*5* (*n* = 7): 6 (85.7%); all wild/loss (*n* = 8): 7 (87.5%) **10B/*10B* (*n* = 42): 22 (52.4%); **10B/*41* (*n* = 3): 2 (66.7%); all decreased/decreased (*n* = 45): 24 (53.3%) **10B/*5* (*n* = 4): 2 (50.0%); all decreased/loss (*n* = 4): 2 (50.0%)	Total number of patients with TD: *wt/wt* (*n* = 43): 20 (46.5%); *wt/mut* (*n* = 110): 64 (58.2%); *mut/mut* (*n* = 49): 26 (53.1%)
Ohmori 1998[153]	Total number of patients with TD: **1/*1* (*n* = 26): 4 (15.4%); **1/*10* (*n* = 43): 9 (20.9%); **10/*10* (*n* = 30): 11 (36.7%)	Total number of patients with TD: *wt/wt* (*n* = 26): 4 (15.4%); *wt*/dec (*n* = 43): 9 (20.9%); dec/dec (*n* = 30): 11 (36.7%)
	AIMS score – all patients, mean ± SD: **1/*1* (*n* = 26): 1.54 ± 1.78; **1/*10* (*n* = 43): 2.00 ± 2.01; **10/*10* (*n* = 30): 3.31 ± 3.69	AIMS score – all patients, mean ± SD: *wt/wt* (*n* = 26): 1.54 ± 1.78; *wt*/dec (*n* = 43): 2.00 ± 2.01; dec/dec (*n* = 30): 3.31 ± 3.69
Ohmori 1999[154]	Total number of patients with TD: *wt/wt* (*n* = 67): 18 (26.9%); *wt/m* (*n* = 26): 5 (19.2%); *m/m* (*n* = 6): 1 (16.7%)	Total number of patients with TD: *wt/wt* (*n* = 67): 18 (26.9%); *wt/mut* (*n* = 26): 5 (19.2%); *mut/mut* (*n* = 6): 1 (16.7%)
	AIMS score – all patients, mean ± SD: *wt/wt* (*n* = 67): 2.46 ± 2.88; *wt/m* (*n* = 26): 2.00 ± 2.27; *m/m* (*n* = 6): 2.17 ± 2.41	AIMS score – all patients, mean ± SD: *wt/wt* (*n* = 67): 2.46 ± 2.88; *wt/mut* (*n* = 26): 2.00 ± 2.27; *mut/mut* (*n* = 6): 2.17 ± 2.41

TABLE 21 *Summary of findings for tardive dyskinesia: clinical validity studies in patients tested for* CYP2D6 *(continued)*

Study	Outcomes as reported	'Standardised outcome'[a]
Plesnicar 2006[156]	Total number of patients with TD: non-PM (*n* = 125): 22 (17.6%); PM (*n* = 6): 1 (16.7%)	Total number of patients with TD: *wt/wt* + *wt/mut* (*n* = 125): 22 (17.6%); *mut/mut* (*n* = 6): 1 (16.7%)
	AIMS score – all patients, mean ± SD: non-PM (*n* = 125): 5.44 ± 3.9; PM (*n* = 6): 5.16 ± 3.4	AIMS score – all patients, mean ± SD: *wt/wt* + *wt/mut* (*n* = 125): 5.44 ± 3.9; *mut/mut* (*n* = 6): 5.16 ± 3.4

AIMS, Abnormal Involuntary Movement Scale; EM, extensive metaboliser; IPD, individual patient data; NA, not applicable; PM, poor metaboliser; TDRS, Tardive Dyskinesia Rating Scale.
a For ease of comparison, outcomes have been summarised as *wt/wt* (wild type/wild type), *wt/mut* (wild type/mutant) or *mut/mut* (mutant/mutant).
b Patient excluded from analysis.

Parkinsonism

Seven studies examined the relationship between parkinsonism and genotype. Five of these reported the total number of patients with parkinsonism and four of these reported mean Simpson–Angus Scale (SAS) scores. Patients were taking at least one typical antipsychotic in all of the studies. The findings are summarised in *Table 22*.

For the total number of patients with parkinsonism, it was possible to include data from between four and five studies of between 233 and 470 patients in the meta-analyses depending on the genotypes being compared. Nevertheless, the number of patients with the *mut/mut* genotype included in the meta-analyses was still small ($n < 30$).

Patients with the *mut/mut* or *wt/mut* genotype were significantly more likely to develop parkinsonism than patients with *wt/wt* (OR 1.64, 95% CI 1.04 to 2.58) (*Figure 4*). It should be noted that this meta-analysis includes in the *wt/wt* group six patients from Scordo *et al.*[158] who were classified as UMs (none of whom had developed parkinsonism) and an unknown number of patients (and thus those with parkinsonism) from Plesnicar *et al.*[156]

In two studies the criteria for measuring parkinsonism were either unknown[132] or known to be different from those in the other studies[142] and so sensitivity analyses were carried out removing these studies. In these sensitivity analyses none of the effect sizes was statistically significant and the new OR comparing *mut/mut* or *wt/mut* with *wt/wt* was now 1.21 (95% CI 0.69 to 2.14) (data not presented). A further sensitivity analysis was carried out that included only the three cross-sectional studies.[127,132,158] Again, none of the effects was statistically significant and the heterogeneity increased for all.

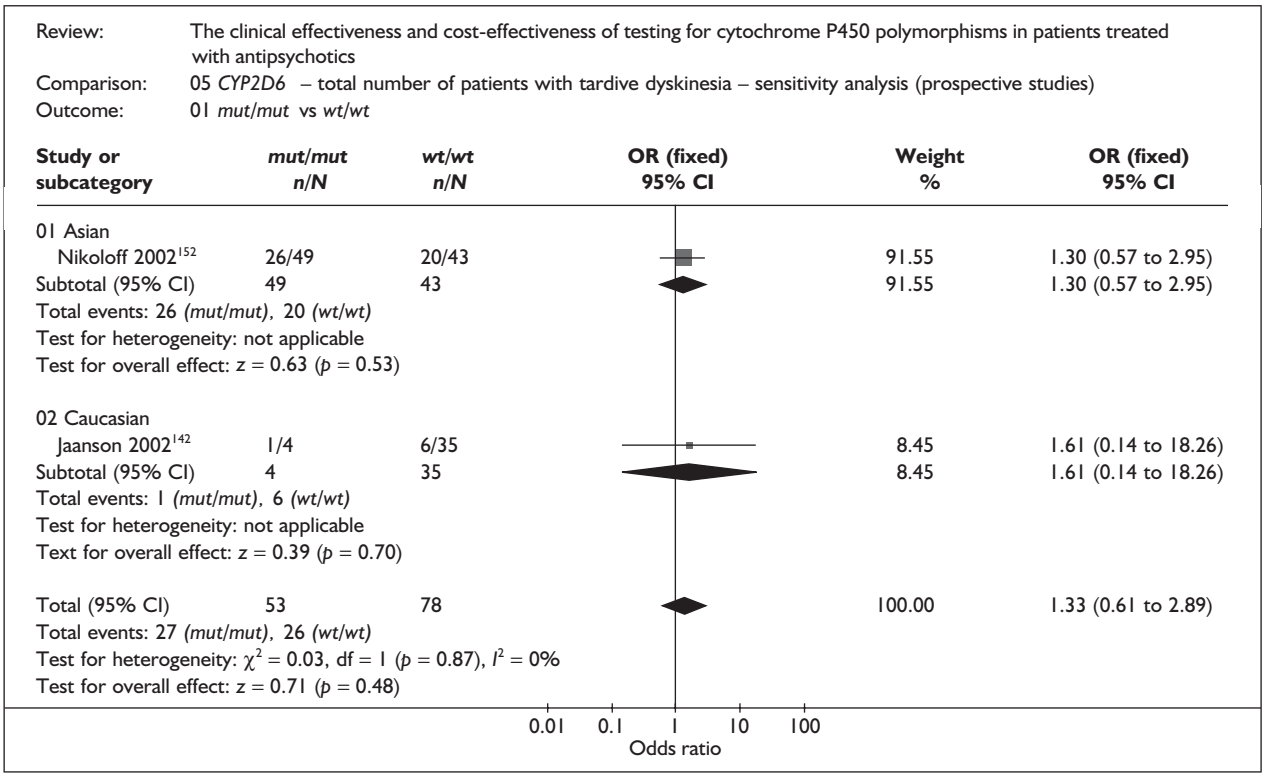
Regarding mean SAS score, no consistency in the results was found, with some studies reporting higher scores for *wt/wt* and others for *mut/mut* or *wt/mut* + *mut/mut*.

Acute dystonia

Data from both studies[128,158] that examined dystonia in 195 patients taking any antipsychotic in relation to genotype were included in the meta-analysis and the findings are summarised in *Table 23*. No significant effect was found for any of the genotypes (Appendix 5, *Figure 9*) although the numbers of patients with the *mut/mut* genotype was small ($n = 9$). Furthermore, it should be noted that Scordo *et al.*[158] also included six UMs (two of whom had acute dystonia) who have been included here with the *wt/wt* patients and so the results should be treated with caution.

Akathisia

Two studies[127,156] in which a total of 231 patients were taking any typical antipsychotic quantified the number of patients with akathisia. As Plesnicar *et al.*[156] combined all patients who did not have the *mut/mut* genotype (including an unknown number of patients with the UM phenotype) then the study findings were also pooled in this manner (Appendix 5, *Figure 10*). Based on this meta-analysis, the number of patients with akathisia did not significantly differ between those having the *mut/mut* genotype and those who did although heterogeneity between the studies was large and effect sizes were in opposite directions. Plesnicar *et al.*[156] was the only study to measure severity and found no significant difference between the patients with the *mut/mut* genotype and those without. Heterogeneity may have been explained by either differences in study design or differences in the gender mix of these two studies. The findings are summarised in *Table 24*.



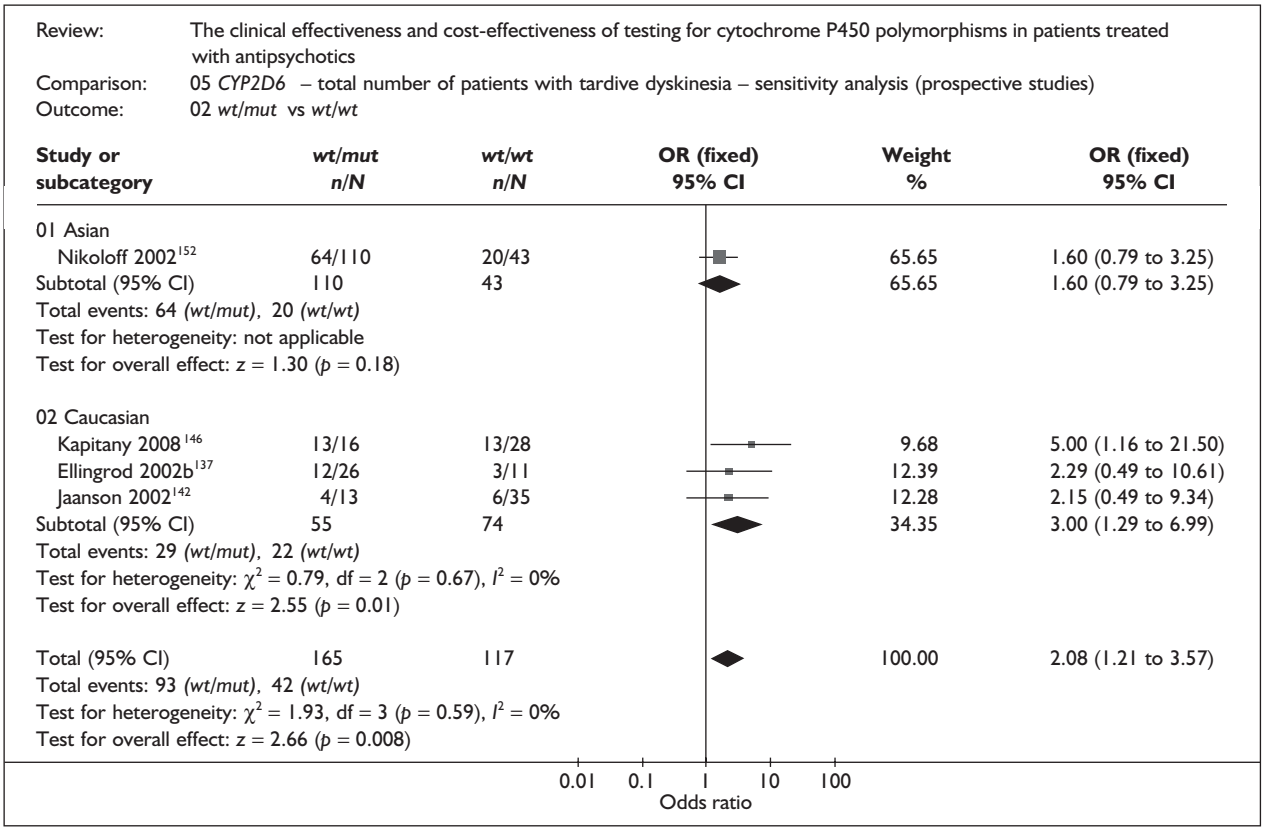
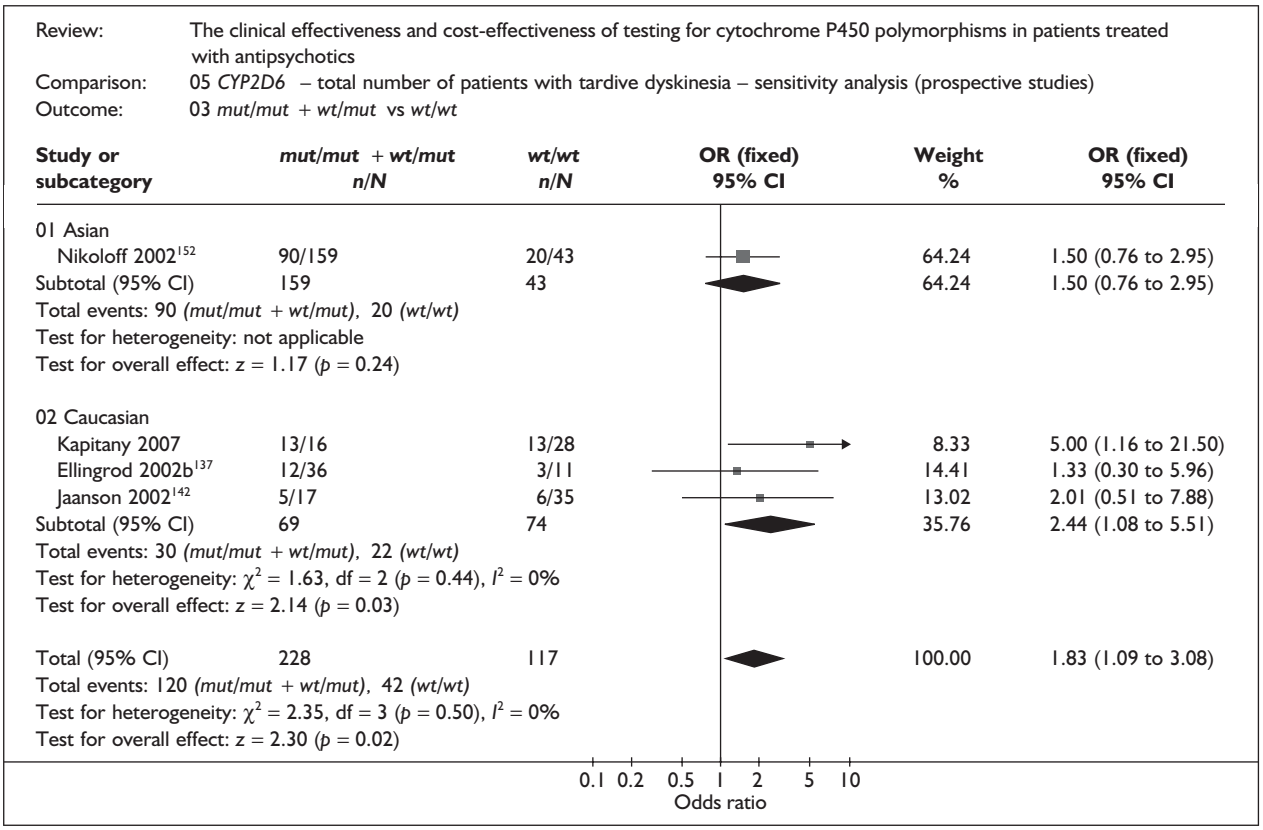


FIGURE 2 *Meta-analysis for patients tested for the* CYP2D6 *genotype – total number of patients with tardive dyskinesia: (a)* wt/wt *vs* mut/mut*; (b)* wt/wt *vs* wt/mut.



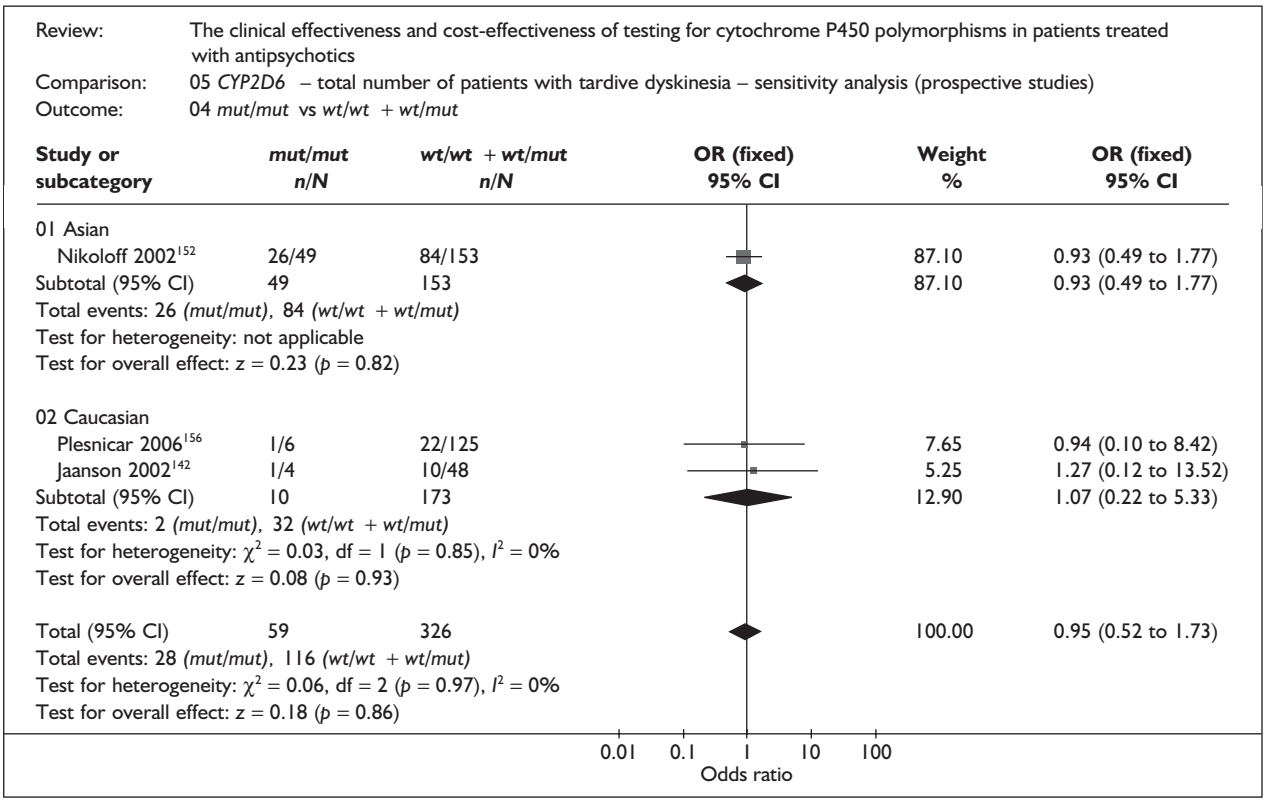
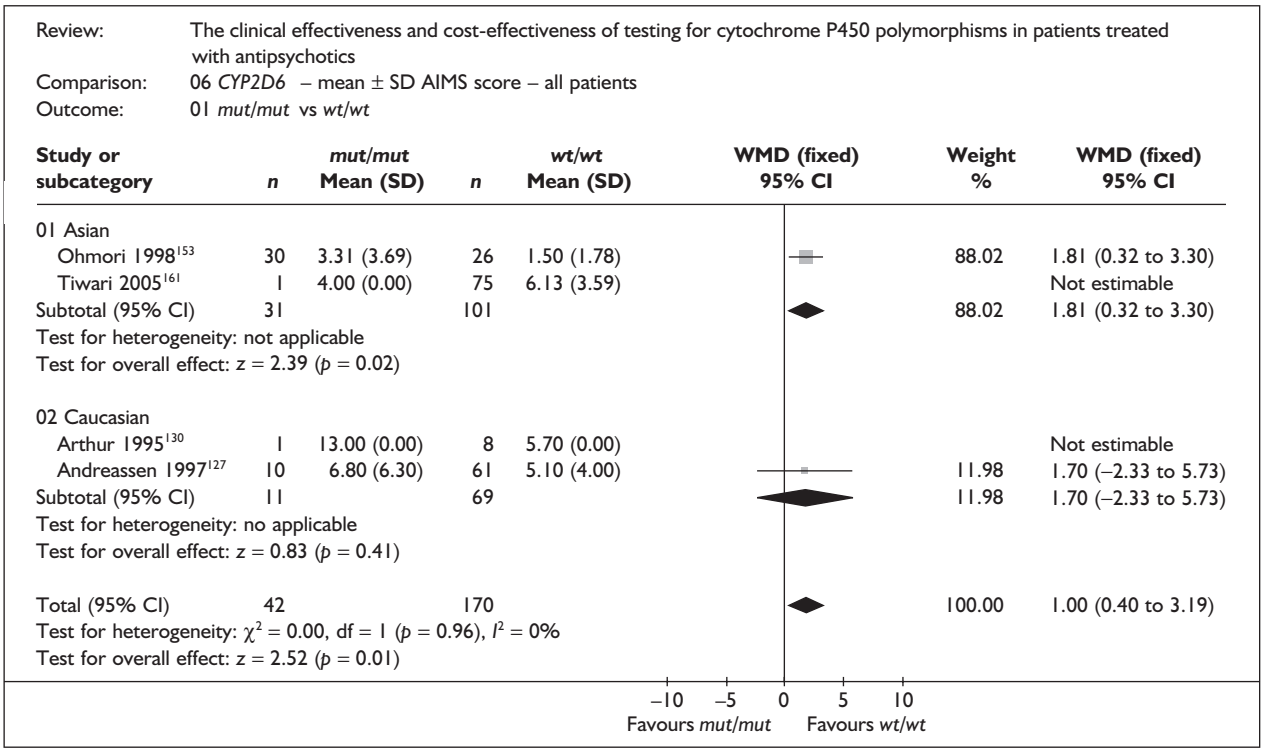


FIGURE 2 *Meta-analysis for patients tested for the* CYP2D6 *genotype – total number of patients with tardive dyskinesia: (c)* wt/wt *vs* mut/mut + wt/mut; *(d)* wt/wt + wt/mut *vs* mut/mut. *Sensitivity analysis by study type (only prospective studies included).*



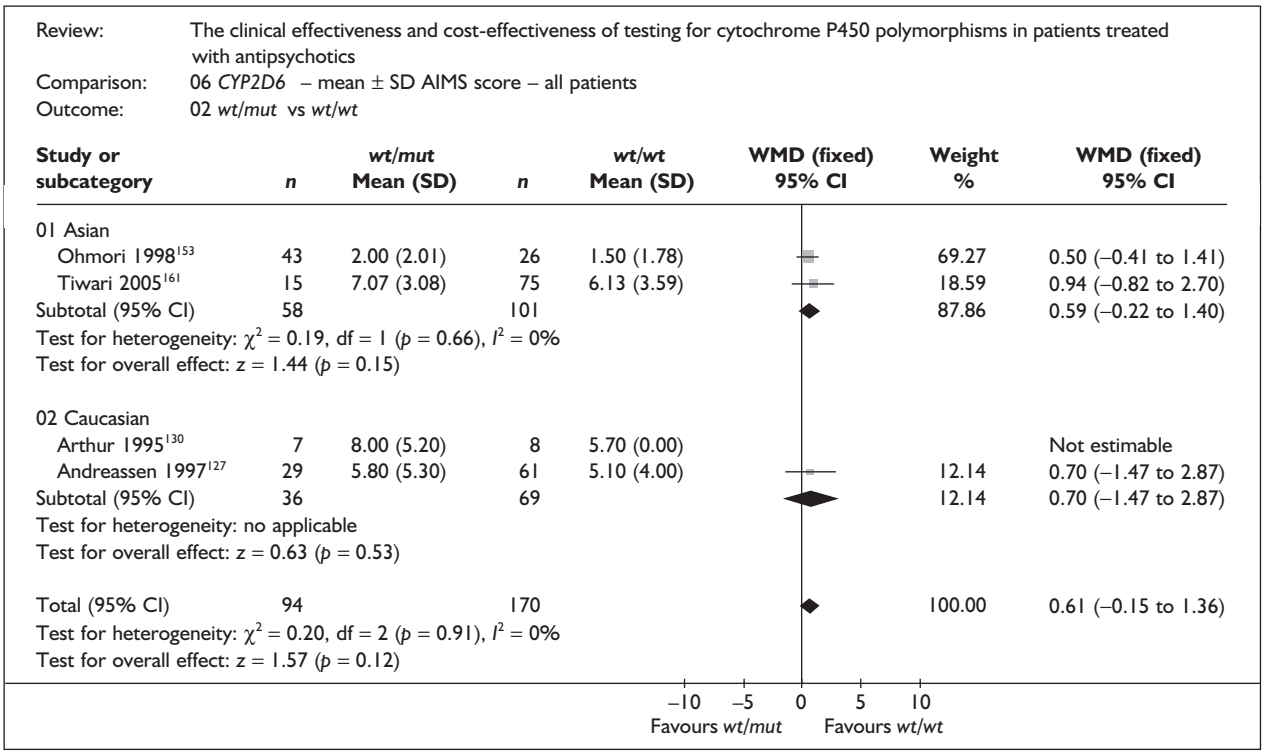


FIGURE 3 *Meta-analysis for patients tested for the* CYP2D6 *genotype – mean ± SD AIMS score for all patients: (a)* wt/wt *vs* mut/mut*; (b)* wt/wt *vs* wt/mut*.*

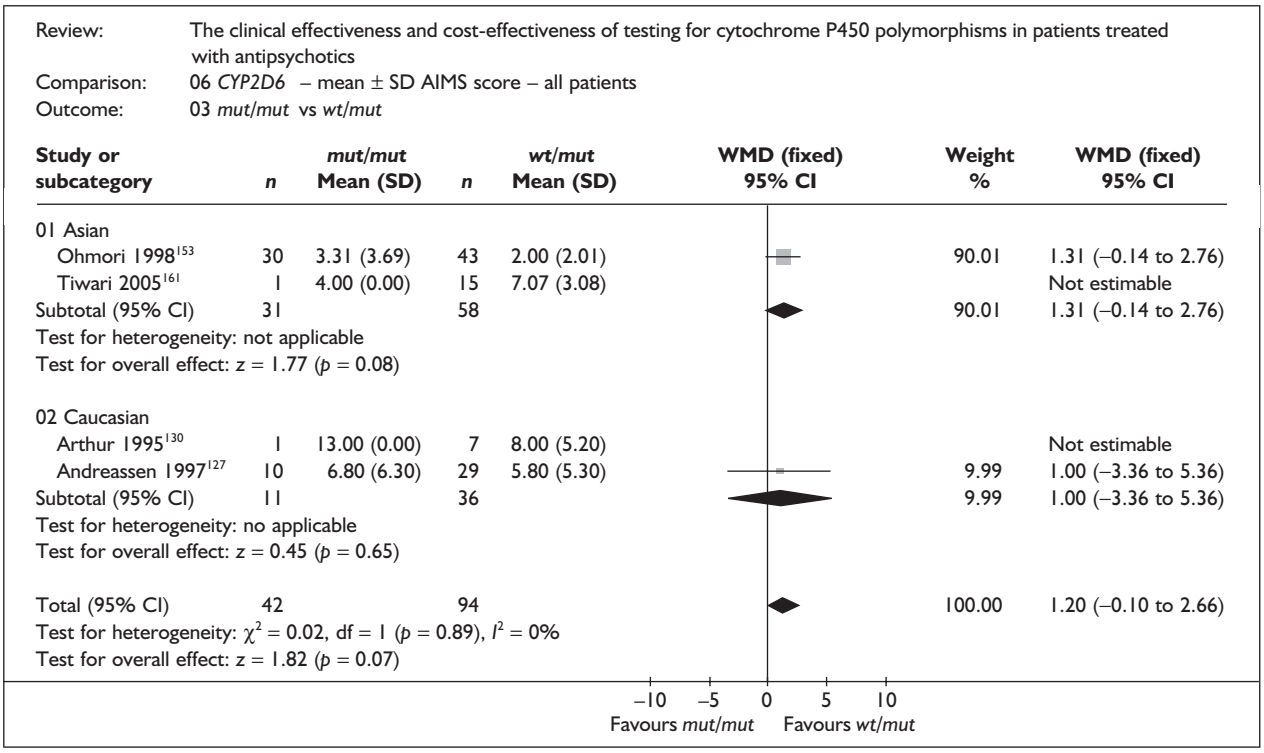


FIGURE 3 *Meta-analysis for patients tested for the* CYP2D6 *genotype – mean ± SD AIMS score for all patients: (c)* wt/wt *vs* mut/mut + wt/mut.

General chronic movement disorder

One study[128] in which 76 patients were taking any antipsychotic examined the association between genotype and chronic movement disorders, which were defined as experiencing either parkinsonism or TD, or both. A much higher proportion of patients with the *mut/mut* genotype than with either the *wt/wt* or the *wt/mut* genotype experienced such disorders but the number of *mut/mut* patients was small ($n = 5$). The findings are summarised in *Table 25*.

Extrapyramidal symptoms in general

Six studies focused on the relationship between EPS and genotype/phenotype. It was not possible to include data from any of these in a meta-analysis because each study measured or reported the data differently. The findings are summarised in *Table 26*.

Haloperidol was taken by patients in at least three of the studies[131,155,162] and possibly also in the other three,[130,140,158] which stipulated that patients were taking any antipsychotic. Three studies[140,158,162] quantified patients with this ADR and three[130,131,155] assessed the severity. However, one[162] of the studies quantifying EPS has been excluded from the analysis in this review for reasons discussed earlier in this chapter (see Quality assessment of included studies).

One study[158] reported that around half of the patients carrying the *wt/wt* (including UMs) or *wt/mut* genotype developed EPS (defined as having any one of acute dystonia, TD or parkinsonism) but that all *mut/mut* patients had EPS, albeit the number of patients with this last genotype was only four. The other study also found that significantly more patients with the *mut/mut* genotype were vulnerable to EPS than patients with the *wt/wt* or *wt/mut* genotype.[140]

The mean SAS scores for patients with EPS were found to be lowest in the *wt/wt* group and highest in the *mut/mut* group in one study,[130] a finding echoed by median EPS sum scores in a later study,[131] although, here, when the EPS sum score was not stratified for comedication with biperiden (which is taken to alleviate ADRs associated with some antipsychotics such as stiffness, tremors, spasms and poor muscle control) the score for UMs was similar to that for PMs. The most recent study[155] reported the median Extrapyramidal Symptoms Rating Scale (ESRS) scores at peak and trough; however, there was only one *mut/mut* patient in this study and data were only available at trough for this patient making comparisons problematic.

TABLE 22 *Summary of findings for parkinsonism: clinical validity studies in patients tested for* CYP2D6

Study	Outcomes as reported	'Standardised outcome'[a]
Andreassen 1997[127]	Total number of patients with parkinsonism: EM homozygote (*n* = 61): 23 (37.1%); EM heterozygote (*n* = 29): 13 (44.8%); PM (*n* = 10): 2 (20.0%)	Total number of patients with parkinsonism: *wt/wt* (*n* = 61): 23 (37.1%); *wt/mut* (*n* = 29): 13 (44.8%); *mut/mut* (*n* = 10): 2 (20.0%)
	SAS score – all patients, mean ± SD: EM homozygote (*n* = 61): 0.37 ± 0.35; EM heterozygote (*n* = 21): 0.40 ± 0.36; PM (*n* = 10): 0.56 ± 0.74	SAS score – all patients, mean ± SD: *wt/wt* (*n* = 61): 0.37 ± 0.35; *wt/mut* (*n* = 21): 0.40 ± 0.36; *mut/mut* (*n* = 10): 0.56 ± 0.74
Culav-Sumic 2001[132]	Total number of patients with parkinsonism: EM (*n* = 43): **1/*1* (*n* = 43): 13 (30.2%) IM (*n* = 23): **4/*1* (*n* = 20): 11 (52.6%); **6/*1* (*n* = 3): 1 (33.3%) PM (*n* = 5): **4/*4* (*n* = 5): 4 (80.0%)	Total number of patients with parkinsonism: *wt/wt* (*n* = 43): 13 (30.2%); *wt/mut* (*n* = 20): 12 (52.2%); *mut/mut* (*n* = 5): 4 (80.0%)
Jaanson 2002[142]	Total number of patients with parkinsonism: EM homozygote (*n* = 35): 20 (57.2%); EM heterozygote (*n* = 13): 8 (61.5%); PM (*n* = 4): 4 (100.0%)	Total number of patients with parkinsonism: *wt/wt* (*n* = 35):20 (57.2%); *wt/mut* (*n* = 13): 8 (61.5%); *mut/mut* (*n* = 4): 4 (100.0%)
Kakihara 2005[145]	SAS score – all patients, mean ± SD: **1/*1* (*n* = 16): 2.6 ± 2.0; **1/*10* (*n* = 14): 2.0 ± 1.7; **10/*10* (*n* = 9): 1.3 ± 1.5	SAS score – all patients, mean ± SD: *wt/wt* (*n* = 16): 2.6 ± 2.0; *wt/mut* (*n* = 14): 2.0 ± 1.7; *mut/mut* (*n* = 9): 1.3 ± 1.5
Panagiotidis 2007[155]	Median (range) ESRS parkinsonism score – peak: 3 functional alleles (*n* = 1): 5; 2 functional alleles (*n* = 16): 7 (0–13); 1 functional alleles (*n* = 8): 3 (0–12); 0 functional alleles (*n* = 1): NA	NA
	Median (range) ESRS parkinsonism score – trough: 3 functional alleles (*n* = 1): 3; 2 functional alleles (*n* = 16): 5 (1–19); 1 functional alleles (*n* = 8): 3 (0–12); 0 functional alleles (*n* = 1): 2	
Plesnicar 2006[156]	Total number of patients with parkinsonism: non-PM (*n* = 125): 18 (14.4%); PM (*n* = 6): 0	Total number of patients with parkinsonism: *wt/wt* + *wt/mut* (*n* = 125): 18 (14.4%); *mut/mut* (*n* = 6): 0
	SAS score, mean ± SD: non-PM (*n* = 125): 1.35 ± 3.1; PM (*n* = 6): 0.16 ± 0.41	SAS score, mean ± SD: *wt/wt* + *wt/mut* (*n* = 125): 1.35 ± 3.1; *mut/mut* (*n* = 6): 0.16 ± 0.41
Scordo 2000[158]	Total number of patients with parkinsonism: UM (*n* = 6): 0; EM homozygote (*n* = 65): 20 (30.8%); EM heterozygote (*n* = 44): 14 (31.8%); PM (*n* = 4): 3 (75.0%)	Total number of patients with parkinsonism: *wt/wt* (*n* = 71: 20 (28.2%); *wt/mut* (*n* = 44): 14 (31.8%); *mut/mut* (*n* = 4): 3 (75.0%)
	SAS score – all patients, mean ± SD: hom (*n* = 65): 4.8 ± 1.9; *mut* (*n* = 48): 5.1 ± 1.7	SAS score – all patients, mean ± SD: *wt/wt* (*n* = 65): 4.8 ± 1.9; *wt/mut* + *mut/mut* (*n* = 48): 5.1 ± 1.7

EM, extensive metaboliser; ESRS, Extrapyramidal Symptoms Rating Scale; NA, not applicable; PM, poor metaboliser; SAS, Simpson–Angus Scale; TDRS, Tardive Dyskinesia Rating Scale.

a For ease of comparison, outcomes have been summarised as *wt/wt* (wild type/wild type), *wt/mut* (wild type/mutant) or *mut/mut* (mutant/mutant).

Adverse drug reactions in general

Among patients taking any antipsychotic, one study[139] of 39 patients focused on the association between genotype and mean number of ADRs as assessed by the SAFTEE (Systematic Assessment For Treatment Emergent Effects), which is a technique for the systematic assessment of side effects. This study found that neither the *wt/mut* or *mut/mut* genotype differed statistically from the *wt/wt* genotype in relation to disease severity or number or severity of ADRs. The findings are summarised in *Table 27*.

Agranulocytosis

Dettling *et al.*[134] quantified the number of subjects with clozapine-induced agranulocytosis by genotype (*wt/wt*, *wt/mut* and *mut/mut*) in a sample of 108 patients. This study found that the occurrence of clozapine-induced agranulocytosis was similar in each group. The findings are summarised in *Table 28*.

QTc prolongation

Thioridazine-induced QTc prolongation was assessed in relation to genotype in one study of

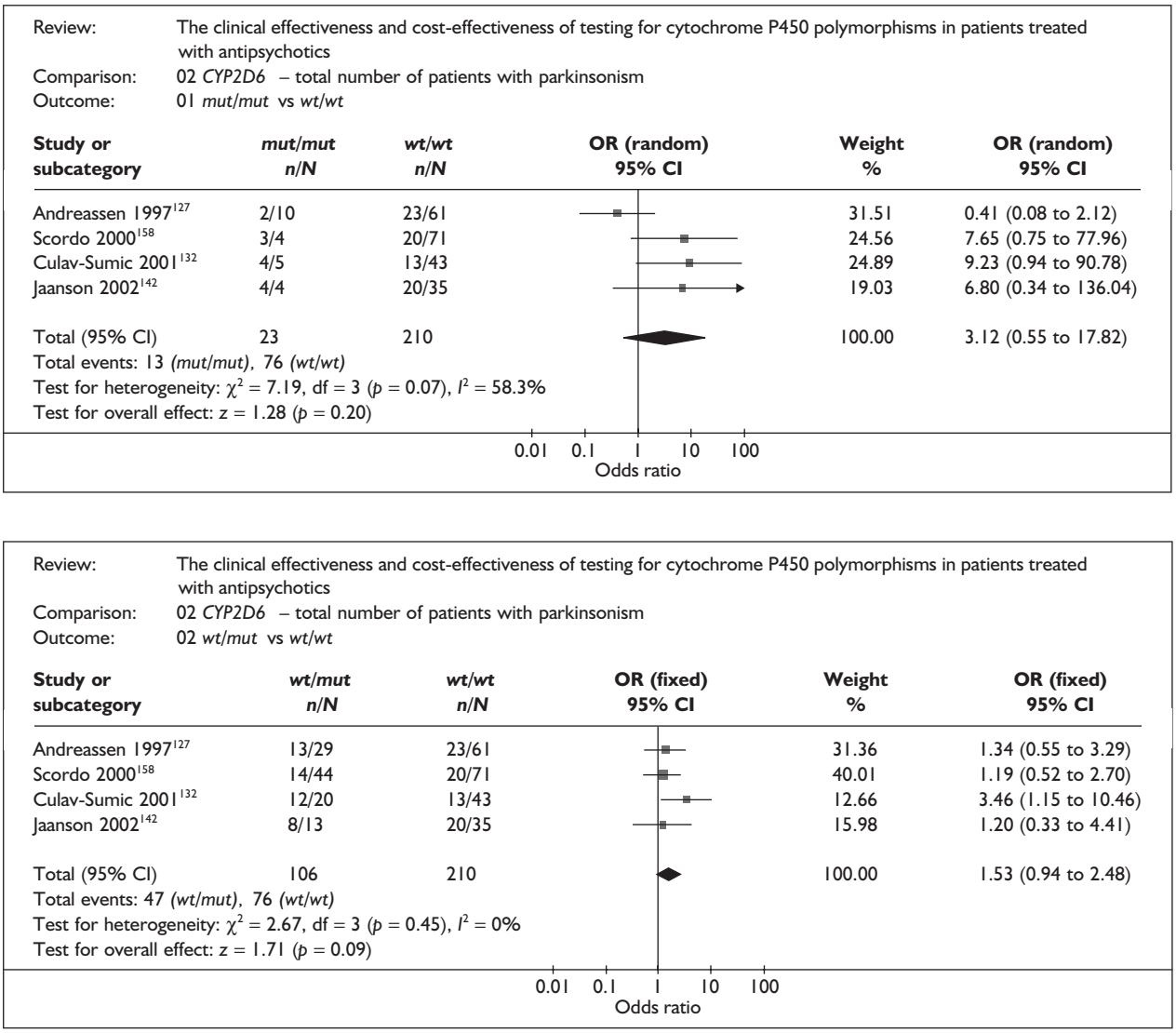


FIGURE 4 *Meta-analysis for patients tested for the* CYP2D6 *genotype – total number of patients with parkinsonism: (a)* wt/wt *vs* mut/mut*; (b)* wt/wt *vs* wt/mut.

91 patients.[159] This study provided no evidence that patients with any particular genotype are at increased risk of QTc prolongation. The findings are summarised in *Table 29*.

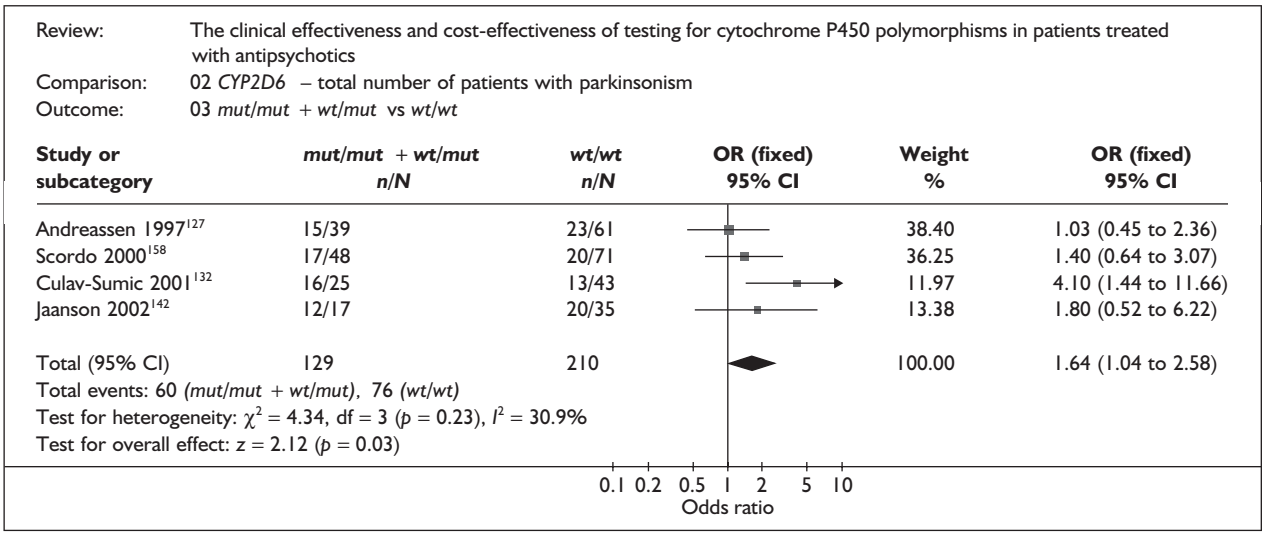
Weight gain

Two prospective studies examined the association between genotype and weight gain in patients taking olanzapine[136] and risperidone.[148] Differences in the outcomes measured made it impossible to include these data in a meta-analysis. In a small study[136] of only 11 patients it was found that those with a *wt/mut* genotype taking olanzapine experienced a statistically significantly larger percentage change in body mass index than the *wt/wt* group. Derived from multiple linear regression analysis, the other study[148] of 29 patients estimated the difference in body weight to be greater in the patients with a *wt/wt* genotype compared with a *wt/mut* genotype than in those with a *wt/wt* genotype compared with a *mut/mut* genotype. The findings are summarised in *Table 30*.

CYP1A2

Metabolism

No studies of patients were found measuring metabolism outcomes by genotype or phenotype.



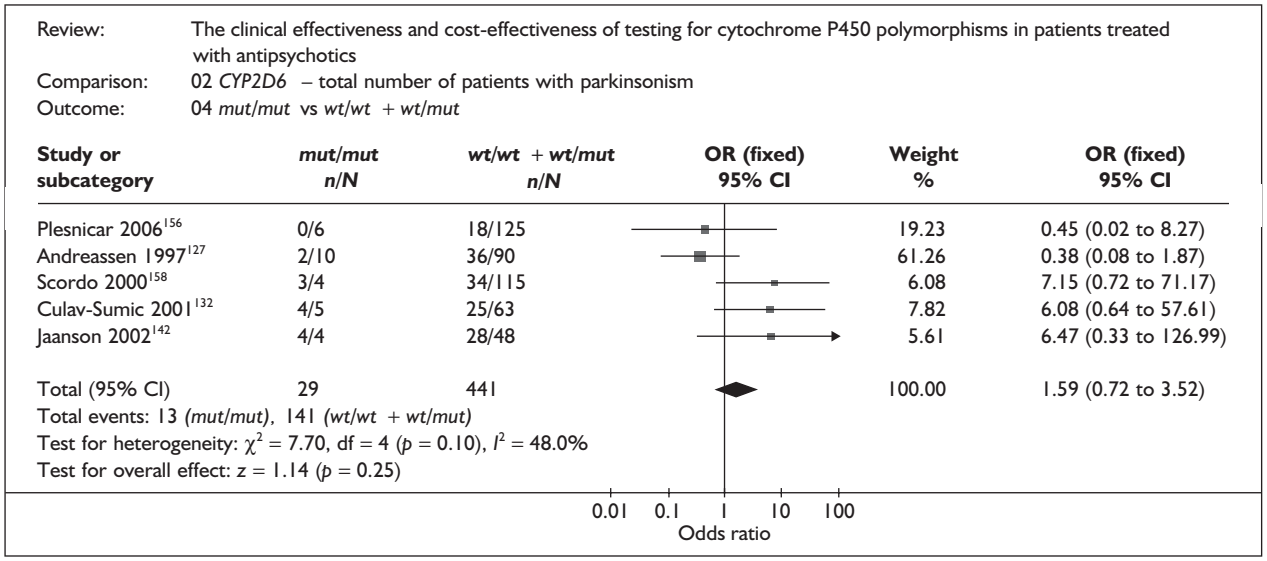


FIGURE 4 *Meta-analysis for patients tested for the* CYP2D6 *genotype – total number of patients with parkinsonism: (c)* wt/wt *vs* mut/mut + wt/mut*; (d)* wt/wt + wt/mut *vs* mut/mut.

TABLE 23 *Summary of findings for acute dystonia: clinical validity studies in patients tested for* CYP2D6

Study	Outcomes as reported	'Standardised outcome'[a]
Armstrong 1997[128]	Total number of patients with acute dystonia: *wt* homozygote (*n* = 43): 4 (9.3%); *wt* heterozygote (*n* = 28): 5 (17.9%); *mut* homozygote (*n* = 5): 0	Total number of patients with acute dystonia: *wt/wt* (*n* = 43): 4 (9.3%); *wt/mut* (*n* = 28): 5 (17.9%); *mut/mut* (*n* = 5): 0
Scordo 2000[158]	Total number of patients with acute dystonia: UM (*n* = 6): 2 (33.3%); EM homozygote (*n* = 65): 14 (21.5%); EM heterozygote (*n* = 44): 6 (13.6%); PM (*n* = 4): 1 (25.0%)	Total number of patients with acute dystonia: *wt/wt* (*n* = 71): 16 (22.5%); *wt/mut* (*n* = 44): 6 (13.6%); *mut/mut* (*n* = 4): 1 (25.0%)

EM, extensive metaboliser; PM, poor metaboliser; UM, ultra rapid metaboliser.
a For ease of comparison, outcomes have been summarised as *wt/wt* (wild type/wild type), *wt/mut* (wild type/mutant) or *mut/mut* (mutant/mutant).

TABLE 24 *Summary of findings for akathisia: clinical validity studies in patients tested for* CYP2D

Study	Outcomes as reported	'Standardised outcome'[a]
Andreassen 1997[127]	Total number of patients with akathisia: EM homozygote (*n* = 61): 10 (16.4%); EM heterozygote (*n* = 29): 5 (17.2%); PM (*n* = 10): 0	Total number of patients with akathisia: *wt*/*wt* (*n* = 61): 10 (16.4%); *wt*/*mut* (*n* = 29): 5 (17.2%); *mut*/*mut* (*n* = 10): 0
Plesnicar 2006[156]	Total number of patients with akathisia: non-PM (*n* = 125): 6 (4.8%); PM (*n* = 6): 1 (16.7%) Barnes Scale score – all patients, mean ± SD: non-PM (*n* = 125): 0.27 ± 1.3; PM (*n* = 6): 0.0	Total number of patients with akathisia: *wt*/*wt* + *wt*/*mut* (*n* = 125): 6 (4.8%); *mut*/*mut* (*n* = 6): 1 (16.7%) Barnes Scale score – all patients, mean ± SD: *wt*/*wt* + *wt*/*mut* (*n* = 125): 0.27 ± 1.3; *mut*/*mut* (*n* = 6): 0.0

EM, extensive metaboliser; PM, poor metaboliser.
a For ease of comparison, outcomes have been summarised as *wt*/*wt* (wild type/wild type), *wt*/*mut* (wild type/mutant) or *mut*/*mut* (mutant/mutant).

TABLE 25 *Summary of findings for general chronic movement disorders: clinical validity studies in patients tested for* CYP2D6

Study	Outcomes as reported	'Standardised outcome'[a]
Armstrong 1997[128]	Total number of patients with chronic movement disorders: homozygous *wt* (*n* = 43): 18 (41.9%); heterozygous *wt* (*n* = 28): 13 (46.4%); homozygous *mut* (*n* = 5): 4 (80.0%)	Total number of patients with chronic movement disorders: *wt*/*wt* (*n* = 43): 18 (41.9%); *wt*/*mut* (*n* = 28): 13 (46.4%); *mut*/*mut* (*n* = 5): 4 (80.0%)

a For ease of comparison, outcomes have been summarised as *wt*/*wt* (wild type/wild type), *wt*/*mut* (wild type/mutant) or *mut*/*mut* (mutant/mutant).

Efficacy

The only study[171] measuring efficacy reported that patients homozygous for the **1F* allele had significantly lower rates of treatment response to clozapine than patients homozygous or heterozygous for the wild-type **1A* allele. The findings are summarised in *Table 31*.

Adverse drug reactions

Nine studies were found that examined the relationship between ADRs and *CYP1A2* genotypes. The findings for each type of ADR are presented below.

Tardive dyskinesia

Seven studies considered TD in relation to genotype or phenotype, with six quantifying patients with TD and five reporting average AIMS scores. In all of these studies patients were taking any typical antipsychotic, whereas in four others[165,167,169,170] atypicals were also permitted. The findings are summarised in *Table 32*.

Four of the studies reporting the total number of patients with TD did so in relation to the **1F* allele and the findings from these were meta-analysed (comprising between 243 and 443 patients depending on the comparison). No significant differences were found (Appendix 5, *Figure 11*).

For the **1C* allele, results were available by genotype for 101 patients taking any antipsychotic, any typical antipsychotic and any atypical antipsychotic in Tiwari *et al.*,[169] which found no significant differences between groups. In the only study in which the exons/exon–intron boundaries of the *CYP1A2* gene were completely sequenced there were also no notable differences across genotypes.[170]

It was not possible to meta-analyse average AIMS scores because these were not presented in the same manner across studies. The only study reporting mean scores,[164] in 85 Caucasian patients, found the mean score to be threefold higher in those with the *mut*/*mut* genotype than in those with the *wt*/*wt* or *wt*/*mut* genotype. Another study[167] of 119 German patients found no such differences in terms of median score. In the other studies, similar means by genotype were found in 73 Asian patients

TABLE 26 *Summary of findings for extrapyramidal symptoms in general: clinical validity studies in patients tested for* CYP2D6

Study	Outcomes as reported	'Standardised outcome'[a]
Arthur 1995[130]	Individual patient data presented	SAS score – patients with EPS, mean ± SD: *wt/wt* (*n* = 8): 2.5 ± 2.6; *wt/mut* (*n* = 7): 3.9 ± 4.6; *wt/wt* + *wt/mut* (*n* = 15): 3.4 ± 3.9; *mut/mut* (*n* = 1): 20
Brockmoller 2002[131]	Median EPS sum score: UM (*n* = 5): 9; EM (*n* = 106): 4; IM (*n* = 56): 5; PM (*n* = 5): 8 Median EPS sum score stratified for comedication with biperiden: UM (*n* = 5): 7; EM (*n* = 106): 6; IM (*n* = 56): 5; PM (*n* = 5): 12	NA
Inada 2003[140]	Total number of patients vulnerable to EPS with *2: *wt/wt* (*n* = 234): 20 (8.5%); *wt/mut* (*n* = 68): 13 (19.1%); *mut/mut* (*n* = 7): 5 (71.4%)	Total number of patients vulnerable to EPS with *2: NA
	Total number of patients vulnerable to EPS with **10*: *wt/wt* (*n* = 78): 10 (12.8%); *wt/mut* (*n* = 97): 16 (16.5%); *mut/mut* (*n* = 39): 6 (15.4%)	Total number of patients vulnerable to EPS with **10*: *wt/wt* (*n* = 78): 10 (12.8%); *wt/mut* (*n* = 97): 16 (16.5%); *mut/mut* (*n* = 39): 6 (15.4%)
Panagiotidis 2007[155]	Peak ESRS parkinsonism score, median (range): 3 functional alleles (*n* = 1): 8; 2 functional alleles (*n* = 16): 7.5 (0–18); 1 functional allele (*n* = 8): 3.5 (0–17); 0 functional alleles (*n* = 1): NA Trough ESRS parkinsonism score, median (range): 3 functional alleles (*n* = 1): 2; 2 functional alleles (*n* = 16): 4.5 (1–18); 1 functional allele (*n* = 8): 3.5 (0–20); 0 functional alleles (*n* = 1): 2	NA
Scordo 2000[158]	Total number of patients with EPS: UM (*n* = 6): 3 (50.0%); EM homozygote (*n* = 65): 33 (50.8%); EM heterozygote (*n* = 44): 23 (52.3%); PM (*n* = 4): 4 (100.0%)	Total number of patients with EPS: *wt/wt* (*n* = 71): 36 (50.7%); *wt/mut* (*n* = 44): 23 (52.3%); *mut/mut* (*n* = 4): 4 (100.0%)
Topic 2000[162]	Inconsistent data[b]	NA

EM, extensive metaboliser; EPS, extrapyramidal symptoms; ESRS, Extrapyramidal Symptoms Rating Scale; NA, not applicable; PM, poor metaboliser; SAS, Simpson–Angus Scale; UM, ultra-rapid metaboliser.

a For ease of comparison, outcomes have been summarised as wt/wt (wild type/wild type), wt/mut (wild type/mutant) or mut/mut (mutant/mutant).

b In one table there are *3/wt and *6/*6 genotypes in patients with EPS but there are no schizophrenic patients with these genotypes in an earlier table of patient demographics (or indeed, any patients with *6/*6 at all).

TABLE 27 *Summary of findings for ADRs in general: clinical validity studies in patients tested for* CYP2D6

Study	Outcomes as reported	'Standardised outcome'[a]
Hamelin 1999[139]	Number of ADRs, mean ± SD: **1/*1* (*n* = 23): 2 ± 2; **1/*4* (*n* = 15): 4 ± 5; **4/*4* (*n* = 1): 1	Number of ADRs, mean ± SD: *wt/wt* (*n* = 23): 2 ± 2; *wt/mut* (*n* = 15): 4 ± 5; *mut/mut* (*n* = 1): 1
	Number of ADRs and severity scores (ADR × severity), mean ± SD: **1/*1* (*n* = 23): 3 ± 3; **1/*4* (*n* = 15): 6 ± 7; **4/*4* (*n* = 1): 1	Number of ADRs and severity scores (ADR × severity), mean ± SD: *wt/wt* (*n* = 23): 3 ± 3; *wt/mut* (*n* = 15): 6 ± 7; *mut/mut* (*n* = 1): 1

ADR, adverse drug reaction.

a For ease of comparison, outcomes have been summarised as *wt/wt* (wild type/wild type), *wt/mut* (wild type/mutant) or *mut/mut* (mutant/mutant).

TABLE 28 *Summary of findings for agranulocytosis: clinical validity studies in patients tested for* CYP2D6

Study	Outcomes as reported	'Standardised outcome'[a]
Dettling 2000[134]	Total number of patients with clozapine-induced agranulocytosis: 3 active genes ($n=4$): 1 (25.0%); 2 active genes ($n=69$): 21 (30.4%); 1 active gene ($n=30$): 8 (26.7%); 0 active genes ($n=5$): 1 (20.0%)	Total number of patients with clozapine-induced agranulocytosis: *wt/wt* ($n=73$): 22 (30.1%); *wt/mut* ($n=30$): 8 (26.7%); *mut/mut* ($n=5$): 1 (20.0%)

a For ease of comparison, outcomes have been summarised as *wt/wt* (wild type/wild type), *wt/mut* (wild type/mutant) or *mut/mut* (mutant/mutant).

TABLE 29 *Summary of findings for QTc prolongation: clinical validity studies in patients tested for* CYP2D6

Study	Outcomes as reported	'Standardised outcome'[a]
Thanacoody 2007[159] and 2003[160]	QTc prolongation (ms), mean ± SD: EM (n=51): 425 ± 29; IM ($n=31$): 427 ± 22; PM ($n=9$): 411 ± 41	QTc prolongation (ms), mean ± SD: *wt/wt* ($n=51$): 425 ± 29; *wt/mut* ($n=31$): 427 ± 22; *mut/mut* ($n=9$): 411 ± 41

EM, extensive metaboliser; IM, intermediate metaboliser; PM, poor metaboliser.
a For ease of comparison, outcomes have been summarised as *wt/wt* (wild type/wild type), *wt/mut* (wild type/mutant) or *mut/mut* (mutant/mutant).

TABLE 30 *Summary of findings for weight gain: clinical validity studies in patients tested for* CYP2D6

Study	Outcomes as reported	'Standardised outcome'[a]
Ellingrod 2002[136]	Baseline BMI (kg/m2), mean ± SD: **1/*1* (n=6): 28 ± 4.2; **1/*3* or **1/*4* ($n=5$): 24 ± 4.0; **3/*3* or **4/*4* ($n=0$): NA	Baseline BMI (kg/m2), mean ± SD: *wt/wt* ($n=6$): 28 ± 4.2; *wt/mut* ($n=5$): 24 ± 4.0; *mut/mut* ($n=0$): NA
	End-point BMI (kg/m2), mean ± SD: **1/*1* ($n=6$): 31.8 ± 4.1; **1/*3* or **1/*4* ($n=5$): 31.4 ± 6.9; **3/*3* or **4/*4* ($n=0$):NA	End-point BMI (kg/m2), mean ± SD: *wt/wt* ($n=6$): 31.8 ± 4.1; *wt/mut* ($n=5$): 31.4 ± 6.9; *mut/mut* ($n=0$): NA
Lane 2000[148]	Difference in body weight (kg): C/C ($n=29$) vs C/T ($n=37$): –1.138; C/C ($n=29$) vs T/T ($n=50$): –0.799	Difference in body weight (kg): *wt/wt* ($n=29$) vs *wt/mut* ($n=37$): –1.138; *wt/wt* ($n=29$) vs *mut/mut* ($n=50$): –0.799

BMI, body mass index; EM, extensive metaboliser; IM, intermediate metaboliser; NA, not available; UM, ultra rapid metaboliser.
a For ease of comparison, outcomes have been summarised as *wt/wt* (wild type/wild type), *wt/mut* (wild type/mutant) or *mut/mut* (mutant/mutant).

TABLE 31 *Summary of findings for efficacy: clinical validity studies in patients tested for* CYP1A2

Study	Outcomes as reported	'Standardised outcome'[a]
Yasar 2007[171]	Number of patients responding to treatment: FF: 18/30 (60.0%); AF: 48/53 (90.6%); AA: 13/14 (92.9%)	Number of patients responding to treatment: *wt/wt*: 18/30 (60.0%); *wt/mut*: 48/53 (90.6%); *mut/mut*: 13/14 (92.9%)

a For ease of comparison, outcomes have been summarised as *wt/wt* (wild type/wild type), *wt/mut* (wild type/mutant) or *mut/mut* (mutant/mutant).

TABLE 32 *Summary of findings for tardive dyskinesia: clinical validity studies in patients tested for* CYP1A2

Study	Outcomes as reported	'Standardised outcome'[a]
Basile 2000[164]	AIMS score – all patients with **1F* allele, mean ± SD: *A/A* (*n* = 37): 5.2 ± 7.9; *A/C* (*n* = 32): 6.6 ± 8.6; *C/C* (*n* = 16): 17.8 ± 9.8	AIMS score – all patients with **1F* allele, mean ± SD: *wt/wt* (*n* = 37): 5.2 ± 7.9; *wt/mut* (*n* = 32): 6.6 ± 8.6; *mut/mut* (*n* = 16): 17.8 ± 9.8
	AIMS score – Caucasian patients with **1F* allele, mean ± SD: *A/A* (*n* = 29): 3.9 ± 6.3; *A/C* (*n* = 25): 4.9 ± 6.1; *C/C* (*n* = 9): 15.9 ± 9.7	AIMS score – Caucasian patients with **1F* allele, mean ± SD: *wt/wt* (*n* = 29): 3.9 ± 6.3; *wt/mut* (*n* = 25): 4.9 ± 6.1; *mut/mut* (*n* = 9): 15.9 ± 9.7
	AIMS score – African American patients with **1F* allele, mean ± SD: *A/A* (*n* = 6): 9.7 ± 11.7; *A/C* (*n* = 7): 12.4 ± 13.4; *C/C* (*n* = 7): 20.3 ± 10.1	AIMS score – African American patients with **1F* allele, mean ± SD: *wt/wt* (*n* = 6): 9.7 ± 11.7; *wt/mut* (*n* = 7): 12.4 ± 13.4; *mut/mut* (*n* = 7): 20.3 ± 10.1
Boke 2007[165]	Total number of patients with TD with **1F* allele: *A/A* (*n* = 21): 12 (57.1%); *A/C* (*n* = 50): 28 (56.0%); *C/C* (*n* = 17): 7 (41.2%)	Total number of patients with TD with **1F* allele: *wt/wt* (*n* = 21): 12 (57.1%); *wt/mut* (*n* = 50): 28 (56.0%); *mut/mut* (*n* = 17): 7 (41.2%)
Fu 2006[138]	Total number of patients with TD with **1F* allele: *A/A* (*n* = 67): 27 (40.3%); *C/A* (*n* = 56): 36 (64.3%); *C/C* (*n* = 16): 10 (62.5%)	Total number of patients with TD with **1F* allele: *wt/wt* (*n* = 67): 27 (40.3%); *wt/mut* (*n* = 56): 36 (64.3%); *mut/mut* (*n* = 16): 10 (62.5%)
	AIMS score – patients with TD with **1F* allele, mean ± SD: *A/A* (*n* = 27): 6.81 ± 3.38; *C/A* (*n* = 36): 7.22 ± 2.97; *C/C* (*n* = 10): 6.30 ± 2.05	AIMS score – patients with TD with **1F* allele, mean ± SD: *wt/wt* (*n* = 27): 6.81 ± 3.38; *wt/mut* (*n* = 36): 7.22 ± 2.97; *mut/mut* (*n* = 10): 6.30 ± 2.05
Matsumoto 2004[166]	Total number of patients with TD with 734 allele: *A/A* (*n* = 98): 20 (20.4%); *A/C* (*n* = 81): 17 (21.0%); *C/C* (*n* = 20): 5 (25.0%)	Total number of patients with TD with 734 allele: *wt/wt* (*n* = 98): 20 (20.4%); *wt/mut* (*n* = 81): 17 (21.0%); *mut/mut* (*n* = 20): 5 (25.0%)
	Total number of patients with TD with –2964 allele: G/G (*n* = 111): 23 (20.7%); G/*A* (*n* = 74): 16 (21.6%); *A/A* (*n* = 14): 3 (21.4%)	Total number of patients with TD with –2964 allele: *wt/wt* (*n* = 111): 23 (20.7%); *wt/mut* (*n* = 74): 16 (21.6%); *mut/mut* (*n* = 14): 3 (21.4%)
	Number of smokers with TD with 734 allele: *A/A* (*n* = 47): 10 (21.3%); *A/C* (*n* = 47): 12 (25.5%); *C/C* (*n* = 9): 2 (22.2%)	Number of smokers with TD with 734 allele: *wt/wt* (*n* = 47): 10 (21.3%); *wt/mut* (*n* = 47): 12 (25.5%); *mut/mut* (*n* = 9): 2 (22.2%)
	Number of smokers with TD with –2964 allele: G/G (*n* = 60): 13 (21.7%); G/*A* (*n* = 35): 10 (28.6%); A/A (n = 8): 1 (12.5%)	Number of smokers with TD with –2964 allele: *wt/wt* (*n* = 60): 13 (21.7%); *wt/mut* (*n* = 35): 10 (28.6%); *mut/mut* (*n* = 8): 1 (12.5%)
Schulze 2001[167]	Total number of patients with TD with **1F* allele: *A/A* (*n* = 62): 30 (48.4%); *A/C* (*n* = 48): 21 (43.8%); *C/C* (*n* = 9): 5 (55.6%)	Total number of patients with TD with **1F* allele: *wt/wt* (n=62): 30 (48.4%); *wt/mut* (*n* = 48): 21 (43.8%); *mut/mut* (*n* = 9): 5 (55.6%)
	Number of smokers with TD with **1F* allele: *A/A* (*n* = 39): 21 (53.8%); *A/C* (*n* = 38): 16 (42.1%); *C/C* (*n* = 5): 3 (60.0%)	Number of smokers with TD with **1F* allele: *wt/wt* (*n* = 39): 21 (53.8%); *wt/mut* (*n* = 38): 16 (42.1%); *mut/mut* (*n* = 5): 3 (60.0%)
	Median AIMS score – all patients with **1F* allele: *A/A* (*n* = 62): 4; *A/C* (*n* = 48): 5; *C/C* (*n* = 9): 7	Median AIMS score – all patients with **1F* allele: *wt/wt* (*n* = 62): 4; *wt/mut* (*n* = 48): 5; *mut/mut* (*n* = 9): 7
	Median AIMS score – smokers with **1F* allele: *A/A* (*n* = 39): 8; *A/C* (*n* = 38): 5; *C/C* (*n* = 5): 7	Median AIMS score – smokers with **1F* allele: *wt/wt* (*n* = 39): 8; *wt/mut* (*n* = 38): 5; *mut/mut* (*n* = 5): 7

with TD,[138] and in up to 25 Asian patients taking either typical or atypical antipsychotics.[169,170]

For *CYP1A2* genotypes, two studies[166,167] of between 57 and 199 patients also compared the proportion of known smokers with TD with the proportion of all patients with TD but for different alleles. No significant differences were found by genotype in either study.

QTc prolongation

In one study,[168] of 66 patients, QTc prolongation varied little across genotypes for patients with the **1F* allele taking any antipsychotic. However, subgroup analysis of patients receiving a drug dose of > 300 mg suggested that patients homozygous for the wild-type **1A* allele had a lower mean interval (ms). The findings are summarised in *Table 33*.

TABLE 32 *Summary of findings for tardive dyskinesia: clinical validity studies in patients tested for* CYP1A2 *(continued)*

Study	Outcomes as reported	'Standardised outcome'[a]
Tiwari 2005[169]	Total number of patients with TD with **1F* allele:	Total number of patients with TD with **1F* allele:
	Typical antipsychotics: *A/A* (*n* = 36): 12 (33.3%); *A/C* (*n* = 46): 9 (19.6%); *C/C* (*n* = 15): 3 (20.0%)	Typical antipsychotics: *wt/wt* (*n* = 36): 12 (33.3%); *wt/mut* (*n* = 46): 9 (19.6%); *mut/mut* (*n* = 15): 3 (20.0%)
	Atypical antipsychotics: *A/A* (*n* = 19): 6 (31.6%); *A/C* (*n* = 36): 12 (33.3%); *C/C* (*n* = 13): 4 (30.8%)	Atypical antipsychotics: *wt/wt* (*n* = 19): 6 (31.6%); *wt/mut* (*n* = 36): 12 (33.3%); *mut/mut* (*n* = 13): 4 (30.8%)
	Both antipsychotics: *A/A* (*n* = 86): 24 (27.9%); *A/C* (*n* = 111): 27 (24.3%); *C/C* (*n* = 42): 12 (28.6%)	Both antipsychotics: *wt/wt* (*n* = 86): 24 (27.9%); *wt/mut* (*n* = 111): 27 (24.3%); *mut/mut* (*n* = 42): 12 (28.6%)
	AIMS score – patients with TD with **1F* allele, mean ± SD:	AIMS score – patients with TD with **1F* allele, mean ± SD:
	Typical antipsychotics: *A/A* (*n* = 12): 7.08 ± 4.19; *A/C* (*n* = 6): 5.67 ± 3.08; *C/C* (*n* = 3): 6.33 ± 3.1	Typical antipsychotics: *wt/wt* (*n* = 12): 7.08 ± 4.19; *wt/mut* (*n* = 6): 5.67 ± 3.08; *mut/mut* (*n* = 3): 6.33 ± 3.1
	Atypical antipsychotics: *A/A* (*n* = 9): 5.44 ± 2.60; *A/C* (*n* = 12): 5.50 ± 3.61; *C/C* (*n* = 4): 6.50 ± 3.51	Atypical antipsychotics: *wt/wt* (*n* = 9): 5.44 ± 2.60; *wt/mut* (*n* = 12): 5.50 ± 3.61; *mut/mut* (*n* = 4): 6.50 ± 3.51
	Both antipsychotics: *A/A* (*n* = 3): 6.33 ± 3.1; *A/C* (*n* = 27): 6.36 ± 2.80; *C/C* (*n* = 12): 5.75 ± 3.14	Both antipsychotics: *wt/wt* (*n* = 3): 6.33 ± 3.1; *wt/mut* (*n* = 27): 6.36 ± 2.80; *mut/mut* (*n* = 12): 5.75 ± 3.14
	Total number of patients with TD with **1C* allele:	Total number of patients with TD with **1C* allele:
	Typical antipsychotics: G/G (*n* = 84): 24 (28.6%); G/A (*n* = 16): 4 (25.0%); *A/A* (*n* = 1): 0	Typical antipsychotics: *wt/wt* (*n* = 84): 24 (28.6%); *wt/mut* (*n* = 16): 4 (25.0%); *mut/mut* (*n* = 1): 0
	Atypical antipsychotics: G/G (*n* = 66): 21 (31.8%); G/A (*n* = 4): 2 (50.0%); *A/A* (*n* = 0): 0	Atypical antipsychotics: *wt/wt* (*n* = 66): 21 (31.8%); *wt/mut* (*n* = 4): 2 (50.0%); *mut/mut* (*n* = 0): 0
	Both antipsychotics: G/G (*n* = 211): 64 (30.3%); G/A (*n* = 35): 7 (20.0%); *A/A* (*n* = 1): 0	Both antipsychotics: *wt/wt* (*n* = 211): 64 (30.3%); *wt/mut* (*n* = 35): 7 (20.0%); *mut/mut* (*n* = 1): 0
Tiwari 2007[170]	Total number of patients with TD in which the exons/exon–intron boundaries of the *CYP1A2* gene were completely sequenced: *C/C* (*n* = 164): 43 (26.2%); *C*/T (*n* = 111): 40 (36.0%); T/T (*n* = 10): 3 (30.0%)	Total number of patients with TD in which the exons/exon–intron boundaries of the *CYP1A2* gene were completely sequenced: *wt/wt* (*n* = 164): 43 (26.2%); *wt/mut* (*n* = 111): 40 (36.0%); *mut/mut* (*n* = 10): 3 (30.0%)
	AIMS score in patients in which the exons/exon–intron boundaries of the *CYP1A2* gene were completely sequenced, mean ± SD:	AIMS score in patients in which the exons/exon–intron boundaries of the *CYP1A2* gene were completely sequenced, mean ± SD:
	Typical antipsychotics: *C/C* (*n* = 9): 6.33 ± 3.87; *C*/T (*n* = 15): 7.25 ± 3.92; T/T (*n* = 1): NS	Typical antipsychotics: *wt/wt* (*n* = 9): 6.33 ± 3.87; *wt/mut* (*n* = 15): 7.25 ± 3.92; *mut/mut* (*n* = 1): NS
	Atypical antipsychotics: *C/C* (*n* = 13): 6.0 ± 3.91; *C*/T (*n* = 6): 5.83 ± 2.64; T/T (*n* = 0): NA	Atypical antipsychotics: *wt/wt* (*n* = 13): 6.0 ± 3.91; *wt/mut* (*n* = 6): 5.83 ± 2.64; *mut/mut* (*n* = 0): NA

AIMS, Abnormal Involuntary Movement Scale; NA, not available; NS, not stated.
a For ease of comparison, outcomes have been summarised as *wt/wt* (wild type/wild type), *wt/mut* (wild type/mutant) or *mut/mut* (mutant/mutant).

Hyperglycaemia and body weight increase

The data from the study[141] considering hyperglycaemia are not presented as this study of 16 patients has so far been published only as an abstract. Here it was simply stated that there were no relationships between side effects and the gene polymorphisms.

Other *CYP* polymorphisms

Metabolism

One study[133] of patients was found measuring metabolism by genotype. Although *CYP3A5* was not expressed in all patients, *CYP3A5* genotyping did not appear to be a major factor able to explain the large differences in haloperidol half-life. The results are summarised in *Table 34*.

TABLE 33 *Summary of findings for QTc prolongation: clinical validity studies in patients tested for* CYP1A2

Study	Outcomes as reported	'Standardised outcome'[a]
Tay 2007[168]	QTc interval (ms) – all patients with **1F* allele, mean ± SD: *A/A* (*n* = 31): 406 ± 24.4; *A/C* (*n* = 27): 412 ± 30.4; *C/C* (*n* = 8): 412 ± 28.0	QTc interval (ms) – all patients with **1F* allele, mean ± SD: *wt/wt* (*n* = 31): 406 ± 24.4; *wt/mut* (*n* = 27): 412 ± 30.4; *mut/mut* (*n* = 8): 412 ± 28.0
	QTc interval (ms) – patients with **1F* allele with drug dose > 300mg, mean ± SD: *A/A* (*n* = NS): 395.5 ± 15.1; *A/C* (*n* = NS): 425.7 ± 25.1; *C/C* (*n* = NS): 427.8 ± 25.2	QTc interval (ms) – patients with **1F* allele with drug dose > 300mg, mean ± SD: *wt/wt* (*n* = NS): 395.5 ± 15.1; *A/C* (*n* = NS): 425.7 ± 25.1; *C/C* (*n* = NS): 427.8 ± 25.2
	QTc interval (ms) – patients with **1F* allele with drug dose > 300 mg on antipsychotics that are substrates for *CYP1A2*, mean ± SD: *A/A* (*n* = NS): 399.5 ± 19.6; *A/C* (*n* = NS): 425.7 ± 25.1; *C/C* (*n* = NS): 427.3 ± 25.3	QTc interval (ms) – patients with **1F* allele with drug dose > 300 mg on antipsychotics that are substrates for *CYP1A2*, mean ± SD: *wt/wt* (*n* = NS): 399.5 ± 19.6; *wt/mut* (*n* = NS): 425.7 ± 25.1; *mut/mut* (*n* = NS): 427.3 ± 25.3

NS, not stated.
a For ease of comparison, outcomes have been summarised as *wt/wt* (wild type/wild type), *wt/mut* (wild type/mutant) or *mut/mut* (mutant/mutant).

TABLE 34 *Summary of metabolism findings: clinical validity studies in patients tested for* CYP3A5

Study	Outcomes as reported	'Standardised outcome'[a]
de Leon 2004[133]	Half-life < 3 days: PM (*n* = 6): 5	Half-life < 3 days: *mut/mut* (*n* = 6): 5
	Half-life ≥ 3 days: PM (*n* = 6): 2	Half-life ≥ 3 days: *mut/mut* (*n* = 6): 2

PM, poor metaboliser.
a For ease of comparison, outcomes have been summarised as *wt/wt* (wild type/wild type), *wt/mut* (wild type/mutant) or *mut/mut* (mutant/mutant).

Efficacy

No studies were found measuring efficacy.

Adverse drug reactions

Two studies were found examining ADRs in patients genotyped for other *CYP* polymorphisms.

Tardive dyskinesia

In 92 patients genotyped for *CYP3A4* it was found that those with the *A/A* genotype taking any antipsychotic had a higher mean AIMS score than those with the *wt/mut* genotype.[161] Regarding *CYP17*, a study[172] of 113 patients aimed to investigate the interactive effects with the dopamine D3 *Ser9Gly* polymorphism and thus AIMS scores for each genotype were presented by dopamine receptor. AIMS scores were higher for patients with the *DRD gly* allele and significantly so in the patients who also had the *A2-A2* genotype. The results are summarised in *Table 35*.

QTc prolongation

There was no increased risk of QTc prolongation in 97 patients taking thioridazine by *CYP2C19* genotype.[159] The findings are summarised in *Table 36*.

Clinical validity summary

Half of the studies included in this review genotyped for *CYP2D6*, a quarter for *CYP1A2* and the rest for other *CYP* polymorphisms. Around half of the studies were prospective and around half were cross-sectional. This can make combining data into a meta-analysis problematic. When possible, sensitivity analyses were carried out to include studies of the same study type. In the majority of studies, patients were taking any antipsychotic, most often typical antipsychotics. Therefore, not all

TABLE 35 *Summary of findings for tardive dyskinesia: clinical validity studies in patients tested for* CYP3A4

Study	Outcomes as reported	'Standardised outcome'[a]
Tiwari 2005[161]	AIMS score – patients with TD, mean ± SD: *A/A* (*n* = 88): 6.39 ± 3.475; *A/G* (*n* = 4): 3.50 ± 2.517; *G/G* (*n* = 0): NA	NA

AIMS, Abnormal Involuntary Movement Scale; NA, not applicable.
a For ease of comparison, outcomes have been summarised as *wt/wt* (wild type/wild type), *wt/mut* (wild type/mutant) or *mut/mut* (mutant/mutant).

TABLE 36 *Summary of findings for QTc prolongation: clinical validity studies in patients tested for* CYP2C19

Study	Outcomes as reported	'Standardised outcome'[a]
Thanacoody 2007[159] and 2003[160]	Rapid metabolisers (*wt/wt*) (*n* = 79): 422 ± 25	*wt/wt* (*n* = 79): 422 ± 25
	Heterozygotes (*wt/*2*) (*n* = 26): 421 ± 38	*wt/mut* (*n* = 26): 421 ± 38
	Homozygotes (*2/*2) (*n* = 4): 425 ± 13	*mut/mut* (*n* = 4): 425 ± 13

a For ease of comparison, outcomes have been summarised as *wt/wt* (wild type/wild type), *wt/mut* (wild type/mutant) or *mut/mut* (mutant/mutant).

of the drugs included in any given study may have been metabolised by the CYP being investigated.

ADR outcomes were most commonly investigated with only a handful of studies measuring efficacy or metabolism using pharmacokinetic parameters. Given the multiple CYP enzymes involved in metabolism of the antipsychotics, there was variation in the *CYP* alleles investigated between studies, with no study undertaking a comprehensive assessment of the variants in all CYP isoforms. It is difficult to generalise the efficacy findings because of the small number of studies and a lack of any consistent effect being evident across the studies. ADR findings were also generally contradictory. Outcomes that could be included in the meta-analysis by genotype were the number of patients with TD and the mean AIMS scores, the number of patients with parkinsonism, the number of patients with acute dystonia and the number of patients with akathisia. The only significant findings were that, for *CYP2D6*, patients included in prospective studies were at increased risk of TD if they had the *wt/mut* and *mut/mut* + *wt/mut* genotypes compared with those with the *wt/wt* genotype; the WMD AIMS score was significantly in favour of the *wt/wt* genotype compared with the *mut/mut* genotype; and patients with the *wt/wt* genotype were significantly less likely to develop parkinsonism than patients with the *mut/mut* + *wt/mut* genotypes. Most, if not all, of the patients in these two TD meta-analyses were taking typical antipsychotics.

Chapter 6
Clinical utility

Out of 1236 papers, no completed published studies were found that met the inclusion criteria for clinical utility. However, one study outlining the contents of an oral presentation to the 42nd Congress of the Royal Australian and New Zealand College of Psychiatrists (RANZCP),[174] and one Danish study in progress[175] were found, both of which appeared to meet the inclusion criteria. The authors were therefore contacted for further information.

The ongoing Danish study is a three-armed prospective randomised clinical trial including 300 patients with schizophrenia in which prospectively testing for *CYP2D6* and *CYP2C19* is being compared with the effect of intense clinical monitoring and a control group. The study has the working title *Effect of CYP genotyping vs intense clinical monitoring on antipsychotic drug treatment*. The outcome measures are time to discontinuation of all antipsychotic medications, number of changes in medication dose, number of changes in medication, compliance, clinical symptoms and adverse effects. Alongside the clinical analysis in this trial will be an economic analysis. Parts of the study (genotyping versus control) will be included in the Danish Health Technology Assessment *Does genotyping for CYP polymorphisms improve individual antipsychotic drug treatment?* Data collection in this trial has only just begun and the trial is expected to end in 2010 and the HTA in 2011 (Louise Herbild and Gesche Jürgens, April, May and June 2008, personal communication).

In the conference abstract for the RANZCP, Miles *et al.*[174] hypothesised that, if clinicians have CYP2D6 phenotype data for patients at the initial point of decision-making regarding risperidone dose, and at each subsequent prescription review, they will adopt differing dosing strategies in an attempt to achieve similar blood levels across the range of metabolisers. Although data analysis has only recently been completed, the author was able to provide a poster presented at the 26th Collegium Internationale Neuro-Psychopharmacologicum Congress in Munich in July 2008 (Wayne Miles, 14 August 2008, personal communication). Thus information on study characteristics, participant characteristics and outcomes is limited (*Tables 37–39*).

In this observational study, AmpliChip testing was made available to clinicians in New Zealand prescribing risperidone, with the results fed back in a similar manner to other laboratory tests. From a retrospective review of case notes, and semistructured interviews with doctors who had ordered the tests, data on prescribing behaviour (change in drug dose) and knowledge about and satisfaction with the test were obtained. In total, 42 doctors ordered tests for 93 patients, of which only 88 test results yielded a phenotype (94.6%). It is reported that doctors felt well informed about the test and its purpose, although a potential harm of the test highlighted in this study was associated with nomenclature – a doctor misinterpreted the status label of 'extensive' (for EMs) to imply 'rapid' as opposed to 'normal' metabolism. Quotes derived from semistructured interviews are provided, in which the test was reported to assist with various aspects of dosage, including doctor confidence and changes in dose levels. However, analysis of risperidone dose in patients at 12 weeks post baseline produced apparently contradictory results: no differences between patients with *wt/wt* genotypes (EMs) and those with *mut/mut* + *wt/mut* genotypes (PMs + IMs) were reported.

The authors conclude that, because of the small sample size, extreme caution must be taken when interpreting these study findings.

Although two completed studies[155,176] that were considered initially for inclusion in this section (based on title/abstract) did not fulfil the inclusion criteria once the full papers were obtained, they are worth mentioning briefly as they have implications for clinical utility. The first of these was a retrospective follow-up study of 62 hospitalised psychiatric patients in the Netherlands genotyped for *CYP2D6*.[176] Patients were taking either antidepressants or antipsychotics. For antidepressants it was found that the phenotype PM (*mut/mut*) or IM (*wt/mut*) was associated with increased plasma concentrations compared with the phenotype EM (*wt/wt*). However, this study

TABLE 37 *Summary of study characteristics: clinical utility study in patients tested for* CYP2D6

Study	Type	*n*	Antipsychotic taken	Test used/alleles genotyped	Outcome
Miles 2007[174a]	Prospective and retrospective	Doctors: *n* = 42 Patients: *n* = 93	Risperidone	AmpliChip used, which tests for 29 SNPs	Doctors: knowledge about test, satisfaction with test Patients: metabolic status; drug dose at 12 weeks

SNP, single-nucleotide polymorphism.
a Data obtained from personal communication with author (14 August 2008).

TABLE 38 *Summary of patient characteristics: clinical utility study in patients tested for* CYP2D6

Study	Ethnicity	Sex	Age (years), mean ± SD (range)
Miles 2007[174a]	NS	NS	NS

NS, not stated.
a Data obtained from personal communication with author (14 August 2008).

TABLE 39 *Summary of findings: clinical utility study in patients tested for* CYP2D6

Study	Outcomes as reported	'Standardised outcome'[a]
Miles 2007[174b]	Doctors: Knowledge about test: assessed qualitatively – see text Satisfaction with test: assessed qualitatively – see text Perceived benefits of test: assessed qualitatively – see text	Doctors: NA
	Patients: Metabolic status: UM = 0; EM = 68; IM = 10; PM = 10; No call = 5 Risperidone dose (mg/day) at 12 weeks post baseline, mean ± SD: EM (*n* = 68): 2.30 ± 0.78; PM/IM (*n* = 20): 1.89 ± 1.49	Patients: Metabolic status: *wt*/*wt* = 68; *wt*/*mut* = 10; *mut*/*mut* = 10; NA = 5 Risperidone dose (mg/day) at 12 weeks post baseline, mean ± SD: *wt*/*wt* (*n* = 68): 2.30 ± 0.78; *mut*/*mut* + *wt*/*mut* (*n* = 20): 1.89 ± 1.49

EM, extensive metaboliser; IM, intermediate metaboliser; NA, not applicable; PM, poor metaboliser; UM, ultrarapid metaboliser.
a For ease of comparison, outcomes have been summarised as *wt*/*wt* (wild type/wild type), *wt*/*mut* (wild type/mutant) or *mut*/*mut* (mutant/mutant).
b Data obtained from personal communication with author (14 August 2008).

found no such association for antipsychotics. Thus, the study concludes that prospective trials are needed to establish the clinical utility of genotyping.

The other study from Sweden by Panagiotidis *et al.*,[155] including 26 patients who were prescribed haloperidol depot injections, has already been included in the clinical validity review. In this prospective follow-up study, some efficacy and ADR data were presented at peak and trough. As well as the main aim of assessing the importance of *CYP2D6* for treatment outcome, this study also aimed to establish a model for predicting

steady state plasma concentrations from dose and genotype. Although no significant correlation was found between *CYP2D6* and PANSS or ESRS scores (as reported in Chapter 5), trough haloperidol concentration was significantly correlated. Thus, the model developed was able to effectively predict trough plasma concentrations in subjects and was argued to have the potential to be a valuable tool for the individualisation of haloperidol depot medication in patients with known *CYP2D6* genotype.

Clinical utility summary

There is currently a lack of evidence for clinical utility. The only known study findings have yet to be published in a comprehensive or peer-reviewed manner, and, because of the small size of the study, extreme caution must be taken in interpreting these findings.

Chapter 7
Cost-effectiveness

This chapter is concerned with exploring the issues surrounding the cost-effectiveness of *CYP* testing for prescribing antipsychotics. The first section describes an economic review of the published cost-effectiveness evidence. We then go on to discuss the major challenges associated with modelling *CYP* testing for prescribing antipsychotics.

Economic review

Methods for the review are presented in Chapter 3. No evidence relating to the costs and benefits of *CYP* testing for prescribing antipsychotics was identified. Therefore, we expanded our search to identify published literature on the costs and benefits of *CYP* testing for prescribing in the field of psychiatry as a whole. The aim of broadening the search was to identify the key issues that may be relevant to our decision problem.

Identification of studies

A total of 199 records were identified from the economics search for evidence relating to the costs and benefits of *CYP* testing in the field of psychiatry. From this only one proved to be relevant to our objectives; this is an economic evaluation carried out by the Agency for Healthcare Research and Quality (AHRQ),[24] which considered the costs and benefits of selective serotonin reuptake inhibitors (SSRIs) for the treatment of depression.

Study characteristics and model overview

The AHRQ study[24] undertook a modelling analysis to determine the benefits, and to a lesser degree the costs, of *CYP* testing for prescribing SSRIs using decision-analytical techniques (Appendix 6, *Table 43*). The authors presented benefits in terms of response to therapy at 6 weeks and quality-adjusted survival at 6 weeks. The model considered both testing and non-testing options, as well as non-CYP2D6-metabolised SSRIs (sertraline used as an example) and CYP2D6-metabolised SSRIs (fluoxetine used as an example). A US health-care perspective was adopted and the study population was limited to treatment-naive adult patients who met DSM-IV (*Diagnostic and Statistical Manual of Mental Disorders*, 4th edn) criteria for major depression and were not taking any other medications that could interact with SSRIs. The time frame of 6 weeks was justified in terms of the time that best predicted ultimate success with, and adherence to, a medication (no reference source provided), although in the assessment of costs the time frame was extended for up to 9 months.

Four scenarios were considered within the model:

1. do not test and treat with sertraline
2. test and if PM or UM give sertraline, if EM/IM give fluoxetine
3. test and if PM or UM alter dose of fluoxetine
4. do not test and give fluoxetine.

Model inputs and data sources

A number of parameters were included in the AHRQ[24] model including prevalence of genotypes; probabilities required to link genotype to phenotype and clinical outcome; costs of SSRIs and testing; and utility of treated/untreated depression. These are discussed in more detail below.

Prevalence of genotypes

As discussed in Chapter 2 there are four main genotypes, ultrarapid metaboliser (UM), extensive metaboliser (EM), intermediate metaboliser (IM) and poor metaboliser (PM). In the AHRQ review[24] the prevalence rates of UMs (0.03), EM/IMs (0.86) and PMs (0.11) in the general depressed population were taken from the published literature.[177,178]

Probabilities

Probability of responding to sertraline

The response rate of sertraline (56%) was taken from a small trial ($n = 93$) of sertraline versus fluvoxamine.[179]

Probability that a genotype will predict phenotype

The probabilities that the various phenotypes will be predicted by a genotype were estimated using bootstrapping techniques. Scenarios for high

correlation (0.8) and low correlation (0.2) between phenotype and genotype were presented (see Appendix 6, *Table 44*).

Probability that a phenotype will predict a response to fluoxetine

The probability of responding to the CYP-metabolised SSRI fluoxetine (at low, medium and high doses) was predicted for the various phenotypes (UM, EM/IM, PM) using expert opinion. Once again scenarios for high correlation (0.8) and low correlation (0.2) were presented (see Appendix 6, *Table 44*).

Costing

The costs of the SSRI and the pharmacogenetic test were included (see Appendix 6, *Table 45*). Costs of adverse events or any capital or administration costs were not considered. All costs were from weak data sources (SSRI costs from Costco[180] and pharmacogenetic test costs from a bulletin[181]) and are not relevant to the UK. Furthermore, the currency units of the costs were not stated, although presumably the costs are in US$.

Neither the cost of fluoxetine (12) nor of sertraline (130) could be verified as neither agent could be found on the Costco website address provided in the AHRQ reference list. Furthermore, it was not possible to determine if this was a monthly cost or the cost for the 6-week time frame.

Conflicting costs are given for the AmpliChip test itself; the original reference[181] states that one test costs US$500, whereas in the AHRQ review[24] a cost of US$1000 is quoted. The reason for the discrepancy is uncertain.

Health state utility

The health-related utility estimates of untreated and treated depression were taken from the published literature and expert opinion respectively (see Appendix 6, *Table 45*). The utility value for untreated depression (0.32) appears to be based on the imputed utility score for moderate depression, as reported in the McSad study.[182] The McSad study also presented the utility of treated moderate depression (0.64) and treated mild depression (0.75). Thus it is unclear why the AHRQ reviewers chose to seek expert opinion to determine the utility of treated depression. Furthermore, their estimate (0.99) seems high in comparison to the McSad study as well as other published literature.[183–185]

Results and sensitivity analysis

The results are presented in terms of response rate and quality-adjusted life at 6 weeks split into the four scenarios (see Appendix 6, *Table 46*). They indicate that treating with sertraline (a non-CYP-metabolised SSRI) without testing is the most effective strategy. The least effective strategy was treating with fluoxetine (a CYP-metabolised SSRI) without testing.

In terms of costs, the results were not fully presented. However, in the discussion it was stated that at 6 weeks it was difficult to offset the high costs of testing. The cheapest strategy was to treat with fluoxetine without testing – the least effective strategy. Using pharmacogenetic testing to guide SSRI *choice* cost $909 more than not testing and treating with sertraline (a non-CYP-metabolised SSRI). Using pharmacogenetic testing to guide SSRI *dose* cost $882 more than not testing and treating with sertraline.

One-way sensitivity analyses were performed for the following variables: prevalence of each phenotype, utility of depression, probability of responding to sertraline, cost of fluoxetine, cost of sertraline and cost of pharmacogenetic testing. The results of these analyses were not presented, but the authors describe them as 'robust, with the relationship between the various options remaining similar at all levels of linkage between genotype and clinical response'.

Summary

There is currently no available evidence on the costs and benefits of *CYP* testing for prescribing antipsychotics. Expanding the search to include *CYP* testing for prescribing any drug in the field of psychiatry produced only one study,[24] which was a very limited exploratory analysis considering only immediate costs and benefits in separate analyses (some of which were not fully reported). This report did, however, highlight the difficulties in obtaining accurate parameter values to populate a model of *CYP* testing and provides a framework for future evaluations in this area.

To decide if *CYP* testing is cost-effective for prescribing antipsychotics we would need to identify the key economic issues associated with *CYP* testing in relation to schizophrenia, which is itself a complex disease. The next section of this report endeavours to identify and discuss these issues.

Modelling *CYP* testing for prescribing antipsychotics

Although the technology being considered is a relatively simple diagnostic test, the potential implications are large and the means of representing the various aspects of the decision to employ the pharmacogenetic test are not straightforward. *Figure 5* illustrates the high-level design structure for a mathematical model required to carry out the assessment, and indicates that four distinct modules are involved, each with its own assumptions and data needs.

In principle the first two modules ('pharmacogenetic test' and 'clinical effects') may be readily constructed but require the results of clinical trials relevant to the specific treatments and patient populations involved. The findings from Chapters 4 and 5 indicate that such data are currently very limited. The third ('translational') module depends on more empirical studies of clinician behaviour, and to date such information does not exist (see Chapter 6). Additionally, the NICE schizophrenia guidelines recommend the use of risperidone, olanzapine, quetiapine, amisulpride and zotepine for both initiation and acute episodes, but only risperidone and olanzapine are metabolised by CYP2D6, neither of which are that important, as the former has an active metabolite and the latter is primarily metabolised by other isoenzymes. This means that results from the test could, at best, only inform the choice of two out of the five currently recommended drugs. So, from a practical standpoint, there is only a slight incentive to carry out the test. As neither the evidence nor the guidelines support clinicians' use of *CYP* test results to determine the most appropriate treatment strategy for patients with schizophrenia it appears to be premature to attempt a full economic modelling and evaluation exercise for this technology at this time. There are clearly important knowledge gaps that should be remedied by primary research.

When these deficiencies in the evidence have been addressed it will be necessary to develop a suitable disease and economic 'schizophrenia module' that can encompass all relevant aspects of schizophrenia and its treatment in the UK. To assist in future economic evaluations of *CYP* testing and similar technologies for schizophrenia prescribing, in the following sections we consider the necessary features of such a schizophrenia model and then use these to assess the suitability of published models for this decision problem.

Requirements for an economic model

Population characteristics

It is envisaged that the pharmacogenetic test may be carried out for three distinct patient groups:

- those recently diagnosed with schizophrenia to inform treatment of the initial episode and/or the choice and sequencing of subsequent maintenance medications
- those whose maintenance medication either has failed or is not considered satisfactory

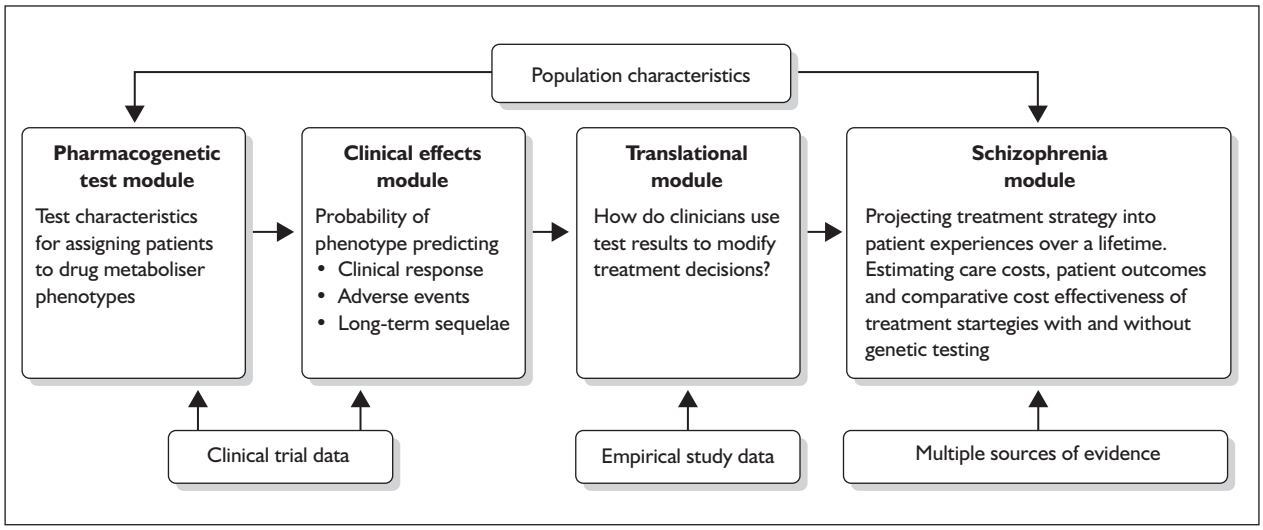


FIGURE 5 *Outline structure for an economic model to assess* CYP *pharmacogenetic testing for schizophrenia prescribing.*

for any reason (e.g. unacceptable ADRs or suboptimal response) to assist in adjusting the prescribed dose or in selecting an alternative medication
- those shown to be treatment resistant, to indicate which medications are most likely to offer potential benefits.

Ideally a model should be capable of assessing the role of the pharmacogenetic test for all three groups. Of course, as all three scenarios can occur at different times for a single patient (i.e. they represent different points on the treatment pathway for at least some patients) a single model structure could accommodate all three, the main difference being the timing of the pharmacogenetic test.

Additionally a schizophrenia model should be designed to allow projection and analysis for particular subgroups, such as second-generation Afro-Caribbean patients; cannabis users; populations from urban environments; and any other high-risk groups who may be identified by epidemiological studies. Such flexibility would maximise the model's usefulness to decision-makers.

Time horizon

An economic model should cover the period during which an intervention may result in differences in resource use and/or changes in patient outcomes. Schizophrenia is a long-term condition and, although patients may experience long periods when symptoms are controlled on medication, there is always the possibility of a relapse that may require a change of drug dosage, switch of medication and/or change in management to control symptoms. Thus the default position is that a schizophrenia model should encompass the remaining lifetime of all patients unless it can be shown that all relevant effects will be limited to a shorter period. In particular, if any difference in mortality rates as a direct or indirect consequence of the test is supported by reliable evidence then only a lifetime model can provide credible results.

Type of economic analysis

The combination of serious non-reversible ADRs associated with commonly used antipsychotics, and the possibility of changes in life expectancy, suggest that a model should be designed to accommodate a full cost–utility analysis using quality-adjusted life-years as the primary outcome measure. As a corollary, both costs and benefits should be discounted to reflect the value of investment foregone and the temporal pattern of costs and benefits.

Model architecture

The choice of model structure (and software platform) is often a matter of personal preference and familiarity on the part of the modeller. However, each approach involves specific features that render it more or less appropriate to the particular disease/intervention/decision problem combination being considered.

The traditional decision-analytical (or 'decision tree') structure is best suited to acute conditions or interventions with only short-term consequences, as in long-term projections the number of potential branches expands exponentially and creates demands for parameter values far exceeding the available evidence.

By contrast, Markov models are more naturally appropriate to longer-term projective modelling. The major limitation of a conventional Markov model is its lack of 'memory', which means that when the risk of future events is known to vary with a patient's previous history, more complex structures may be required. This highlights the shortcomings of any projective model that depends on either cross-sectional observational studies or prospective trials with short-term follow-up.

Patient-level discrete event simulation may also be used but is equally subject to future uncertainty. Furthermore it makes additional data demands in terms of distributional assumptions, parameters and covariances.

Mortality

Schizophrenia is associated with increased mortality compared with that of the general population, with individuals with schizophrenia having an 'all-cause' SMR of between 2 and 3.[30,31] Suicide has been shown to have a large impact on the all-cause SMR, with an SMR for suicide or unexplained violence being greater than 10. The prevalence of suicide amongst those with schizophrenia is currently estimated at around 4.9%.[30,32]

Any model of schizophrenia should incorporate cause-specific mortality rates (at least at the level of suicide/non-suicide) appropriate to the study population.

Relapse

The importance of relapses should not be overlooked in any model as they have been estimated to account for a significant proportion

of the total economic burden of schizophrenia. Tarrier *et al.*[186] reported that delaying relapse in patients with schizophrenia may result in cost savings of up to 37%. A schizophrenia model should be structured to allow the time to next relapse to be estimated, recognising that this is likely to vary over time (i.e. time-dependent transition rates in Markov models) and be influenced by a patient's previous clinical history. Several authors note that approximately 20–25% of patients do not experience a relapse following their initial acute episode.[50–52] This may be interpreted as 'cure', although it is possible that it merely reflects a much reduced (but non-zero) continuing risk. In addition, the generally higher mortality rates noted above may have the effect of prematurely censoring the life expectancy (and hence relapse experience) of some patients. It should be possible to test the impact of alternative interpretations of the evidence through sensitivity analysis within a model.

Other key aspects of modelling relapse are the duration of each relapse, the proportion of relapsing patients admitted for acute care/stabilisation and their expected length of inpatient stay, and the types and proportions of community-based care provided during a relapse episode.

A particular difficulty in modelling relapse is the lack of a uniform definition. Some UK studies define relapse as any deterioration that requires rehospitalisation, whereas others use a simpler definition, i.e. any deterioration of a psychotic symptom. In many cases studies use existing scales to measure the health state of the patient and define relapse in terms of changes in such measures. Various instruments exist including the PANSS and the BPRS. The use of multiple methods by researchers means that it is difficult to aggregate study results and modellers are obliged to adopt a definition but thereby to exclude a substantial proportion of the available evidence collected in relation to this issue. It would be helpful if researchers could agree on a definition for relapse and how it should be measured.

Ideally a model should take account of factors that influence the number of relapses, the relationship between number of relapses and future risk of relapse, and the length of time in relapse. There appear to be multiple factors that influence relapse. It has been reported that:

- TD increases the risk of relapse[187]
- older patients and female patients are less likely to be rehospitalised[188]
- being an alcoholic or substance abuser increases the chances of relapse[189]
- factors associated with increased rehospitalisation rates are previous suicide attempts, crisis intervention treatment strategies and previous hospitalisation.[188]

The effects of medications on relapse have also been studied.

Such a large number of potentially important contributing factors makes modelling relapse a challenge, especially as currently there does not appear to be any study that reports the relative, or combined, influence of any of these factors. It is likely that this aspect of modelling schizophrenia can only be partial and exploratory until large-scale multifactorial prospective studies are carried out to provide credible relative risks.

Adverse drug reactions and drug-related sequelae

The conventional antipsychotic drugs are associated with a wide range of unwanted effects. It is often helpful to separate these into short-term effects, which may or may not require remedial treatment and which may lead to early discontinuation of the prescribed medication, and long-term sequelae, which can result in cumulative irreversible disability and degradation of quality of life.

The most common unwanted effects of the atypical antipsychotics overlap with those expected with conventional antipsychotic drugs, such as sedation, dysphoria, sexual dysfunction, weight gain, adverse endocrine effects, autonomic and cardiovascular effects, anticholinergic effects and seizures.[190] Early research[38] suggested that atypical antipsychotics pose substantially less risk of neurological side effects, especially TD. However, Rosenheck *et al.*[41] report that recent studies have raised questions about this early optimism.

Practically, it is not possible to model all of these problems. However, it is felt that the major EPS should be modelled, the most common being parkinsonism. Also thought to be important are akathisia, dystonia and TD. EPS might be modelled as substates of main Markov states, whereas other ADRs could be incorporated as simple proportions of patients with these conditions.

The incorporation of short-term effects is only necessary when they can be shown to incur additional health-care costs and/or disutility, or when they have been shown to have a strong link to

response to treatment (i.e. high patient withdrawal from taking medication).

Comorbidities

The association between schizophrenia and poor physical health is well established.[191] It is estimated that life expectancy is reduced by 20%[192] and that 60% of the excess mortality is due to physical illness.[193] Identified factors that lead to increased levels of poor health include smoking, poor diet, little exercise and the negative health effects of psychiatric drugs.[194] This excess morbidity should not be overlooked in any long-term model, especially if it is likely that the model results will indicate differences in expected survival.

However, incorporating estimates of the impact of comorbidities may be difficult, primarily because relevant incidence and prevalence information relating to schizophrenia patients is not available from national surveys of psychiatric morbidity. Additionally, lifestyle factors that lead to suboptimal self-administration of medications for schizophrenia may also have a similar effect with regard to other medications, suggesting that correlated model variables may be required.

Incorporation of general comorbidities is desirable but may not currently be practical except perhaps at a crude aggregate level.

Patient performance in taking prescribed medication

The behaviour of schizophrenia patients in taking prescribed medication is an important issue in clinical management. A recent study[195] in schizophrenic patients found that only 67.5% of patients initiated with an atypical antipsychotic persisted with the medication at 1 year, and of those that did continue approximately 78.6% were classed as compliant (at least 80% of days with medication). Evidence suggests that poor adherence patterns lead to an increased likelihood of relapse, hospital admission and exhibiting persistent psychotic symptoms.[196] Reasons for non-adherence and non-persistence are varied, but in general it appears that factors such as comorbid drug abuse, initial antipsychotic treatment choice and patients' subjective responses are key.[197]

Unfortunately there is no uniformity in measuring self-medication behaviours that take several different forms (e.g. occasionally missing dose, deliberate 'drug holidays', periodic switching between full compliance and extended non-use, or systematic multiple dosing). Evidence suggests that measurement of adherence in schizophrenia is complex and lacks a gold standard.[66] Furthermore, adherence instruments in schizophrenia may not actually measure the same thing, which makes comparison of different adherence studies problematic.[66]

It is probably unnecessary and inappropriate to attempt detailed modelling of these issues in view of the lack of relevant information required to achieve a reliable structure, let alone to populate it with credible parameters. However, the model should allow for sensitivity analysis of the main effects that may be expected to flow from pharmacogenetic testing – improved response to adjusted dosing, and reduced incidence of short- and long-term unwanted effects. This can be achieved simply by applying adjustment multipliers to the drug effect parameters derived from clinical trials, and the failure risk for each medication.

Costs

The cost of care for individuals with schizophrenia is high. Davies[78] estimated that 1.6% of the total national health-care budget was attributable to schizophrenia treatment. On the basis of this figure and estimated government spending on health,[79] NHS expenditure on schizophrenia in 2008–9 is calculated to be in the region of £1.2 million. A patient with schizophrenia may need help not only from health services but also from social services and the benefits system. Informal carers also carry significant burdens in terms of not only time input but also additional private expenditure. Furthermore, costs may arise from loss of productivity because of unemployment or absence from work by patients and carers. These costs are very hard to measure, primarily because they are difficult to generalise, and it is therefore recommended that an economic model should initially be limited to consideration of costs to the NHS and personal social services.

The need for a long-term modelling horizon means that the model must also reflect all care costs related to the immediate treatment of schizophrenia, as well as those sequelae, unwanted effects and any comorbidities incorporated into the analysis.

Pharmacogenetic test costs

The cost of the test would need to be included in any model. TDL currently provides the Roche AmpliChip *CYP2D6/2C19* testing facility to the NHS at a cost of £300 per test, including platform costs and any administration fees (TDL, April

2008, personal communication). The turnaround time is stated as 1–2 weeks.[27]

It is also possible to carry out the same test in a standard NHS laboratory (although not currently accredited). It is not possible to estimate the cost of this, although it is likely to be less than that of the AmpliChip.

Patient utility and quality of life

Adoption of a cost–utility analytical framework requires that health states be assigned utility values using a general utility measurement instrument, and this should be incorporated in any schizophrenia model.

Gee *et al*.[198] report that the health-related quality of life literature for schizophrenia is dominated by research utilising lengthy questionnaires that require administration by trained interviewers. They found that measures had not always been developed specifically for schizophrenic populations or, alternatively, questionnaires that had been developed for schizophrenia had limited application. They concluded that the content of the questionnaires varied and that, although there were some similarities in the domains that were represented, there were numerous differences. The differences make comparison of findings across studies difficult and limit the evidence available to support model assumptions.

Estimation of the cost-effectiveness of interventions requires measurement of changes in utility over time. Following patients for an extended period can prove to be a logistical challenge; this is perhaps a particular issue when measuring the quality of life of patients with schizophrenia whose condition and lifestyles may impact on response patterns. Additionally, there appears to be some debate as to whether patients with cognitive impairment can reliably assess treatment outcomes. There is also uncertainty whether a clinician's objective assessment of a patient's quality of life generates the same results as a patient's subjective assessment. An alternative approach to measuring quality of life would be to seek the views of carers, but the validity of their views has yet to be determined for patients with schizophrenia and such an approach could present significant practical difficulties.

Data sources

Data generated by randomised controlled trials are widely regarded as the preferred resource to populate models. However, in the case of schizophrenia, a number of issues relating to the length of trials and the exclusion criteria used when selecting trial populations might limit the generalisability of results to normal clinical practice. The authors of the review of pharmacological interventions in the treatment and management of schizophrenia carried out to inform the development of NICE guidelines on core interventions in primary and secondary care commented that the conclusions that could be drawn from the majority of studies reviewed were limited because of the lack of long-term follow-up, high attrition rates and the inadequacy of collection and reporting of ADRs. The authors also felt that the generalisability of individual study results was limited by the exclusion of elderly people, as well as individuals with resistant schizophrenia, predominantly negative symptoms, learning disabilities, comorbid depression and substance misuse disorders.[199] Furthermore, this study found that few trials run for more than 6 months.

Although data collected over 6 months may be extrapolated to a longer time frame, this would involve a number of assumptions, which would add considerable uncertainty to model results. It is important that modellers are explicit about these assumptions and recognise that results from very short clinical trials are not necessarily more reliable than those from large long-term observational studies. Those involved in caring for patients with schizophrenia should be encouraged to collect longitudinal data to inform future decisions. At the moment there is very little long-term evidence available on issues such as self-medication behaviours, risk of relapse or the frequency of drug-related effects, or relating to comorbidities.

Overview of published schizophrenia models

To explore the possible approaches to modelling schizophrenia and its care, we undertook a literature review of the available published economic models of schizophrenia. The purpose of the review of schizophrenia models was to consider whether there is an existing published and validated model that could be readily adapted for assessing pharmacogenetic testing for the treatment of schizophrenia.

Details of the search strategy and the methods for selecting evidence are presented in Chapter 3. In total, 93 studies were identified by the search strategies. Of these, only 28 met our inclusion

TABLE 40 *Countries to which models relate*

Country	Number of models	Study
UK	8	Almond 2000[200] (and 1998[201]); Bagnall 2003;[47] Byrom 1998;[207] Davies 2000;[208] Duggan 2003;[237] Heeg 2005;[218] Mortimer 2003;[224] Tilden 2002[231]
USA	5	Bounthavong 2007;[206] Glazer 1996[211] (related to Edwards 2005,[212] Obradovic 2007[213] and Ganguly 2003[214]); Palmer 1998[227] (and 2002,[228] and Sacristan 1997[229]); Vera-Llonch 2004[232] (and 2005[233]); Wang 2004[234] (and Perlis 2005[230])
Canada	3	Glennie 1997;[215] Laurier 1997;[221] Oh 2001[225] (and 2001[226])
Spain	3	Bernardo 2006[203] (and 2007[204]); Bobes 2004;[205] Gutierrez-Recacha 2006[216]
Australia	2	Davies 1998;[209] Magnus 2005[223]
Belgium	2	De Graeve 2005;[210] Lecomte 2000[222]
France	2	Launois 1998;[220] Hansen 2002[217]
Germany	1	Beard 2006[202]
Taiwan	1	Yang 2005[235]
Thailand	1	Kongsakon 2005[219]

criteria and were subsequently data extracted (in terms of study characteristics, description of clinical outcomes and description of costs and resource use) (see Appendix 7).

The 28 reviewed studies presented models from a range of countries. Eight of the models considered schizophrenia in the UK and five modelled schizophrenia in the USA. There were three Canadian and three Spanish models, and two models each from Australia, Belgium and France. There were also models from Germany, Thailand and Taiwan. Further details are given in *Table 40*.

The time horizon of the reviewed models ranged from 16 weeks to lifetime (*Table 41*). Shorter models tended to be decision trees and longer models tended to be based on Markov processes.

To determine if any of the 28 models could be used or adapted to explore the cost-effectiveness of *CYP* testing for prescribing antipsychotics we developed a 10-point checklist of desirable features:

1. Patient population – does the model address all three patient types?
2. Timespan – does the model have a long-term (> 20 years) or whole-life horizon?
3. Analytical framework – is the model designed for a cost–utility analysis?
4. Model structure – is the model suitable/adaptable for the schizophrenia module?
5. Mortality – does the model include higher schizophrenia mortality risks and suicide risks?
6. Relapse – are all aspects of relapse modelled adequately?
7. Unwanted drug effects – are both short- and long-term effects properly modelled?
8. Comorbidities – are any comorbidities modelled?
9. Medication taking – can the effects of drug-taking behaviours be tested (e.g. via sensitivity analysis)?
10. Costs – are all relevant costs included?

As can be seen from *Table 42*, none of the models satisfies all of these criteria and, therefore, none appears to be suitable for incorporating into a model designed to assess the cost-effectiveness of *CYP* testing for prescribing antipsychotics.

Summary

As neither the evidence nor the published guidelines support clinicians' use of *CYP* status to determine the most appropriate treatment strategy for patients with schizophrenia, it is premature to attempt a meaningful economic modelling and evaluation exercise for this technology at this time. These important knowledge gaps should be remedied by primary research.

As a pharmacogenetic test is required only once for each patient, the maximum lifetime benefit from each test is likely to be gained if patients are tested when schizophrenia is first diagnosed. However, if treatments routinely used in the early stages of a clinical strategy are not related to the genetic anomalies detected by the test then early testing will incur unnecessary costs for patients, in whom test results will prove uninformative.

TABLE 41 *Summary details of reviewed models*

Model category	No models	Author	Time period
Very short (< 12 months)	2	Bounthavong 2007[206]	16 weeks
		Laurier 1997[221]	9 days
Short (1 year)	10	Bagnall 2003[47]	1 year
		Bernardo 2006[203] (and 2007[204])	1 year
		Bobes 2004[205]	1 year
		Byrom 1998[207]	1 year
		Glazer 1996[211]	1 year
		Kongsakon 2005[219]	1 year
		Lecomte 2000[222]	1 year
		Mortimer 2003[224]	1 year
		Oh 2001[225] (and Oh 2001[226])	1 year
		Vera-Llonch 2004[232] (and 2005[233])	1 year
Medium (2–5 years)	10	Almond 2000[200]	5 years
		Beard 2006[202]	1-year results but model appears to have capacity to run for longer
		Davies 1998[209]	2 years
		Davies 2000[208]	3 years
		De Graeve 2005[210]	2 years
		Hansen 2002[217]	5 years
		Heeg 2005[218]	5 years
		Palmer 1998[227] (and 2002,[228] and Sacristan 1997[229])	5 years
		Tilden 2002[231]	5 years
		Yang 2005[235]	2 years
Long (> 5 years)	6	Duggan 2003[237]	40 years
		Glennie 1997[215]	Lifetime
		Gutierrez-Recacha 2006[216]	Lifetime
		Launois 1998[220]	10 years
		Magnus 2005[223]	Lifetime
		Wang 2004[234] (and Perlis 2005[230])	Lifetime
Total	28		

Establishing economic benefit from the use of *CYP* testing in these patient populations is especially demanding as it requires modelling of the performance of the test itself and the impact of the test results on clinical decisions, as well as the effect on clinical outcomes and health costs in an under-researched chronic disease. The chain of logic and assumptions must be supported at each stage by credible evidence before any conclusions can be drawn with confidence.

However, it is worth noting that the prospects of such a full economic evaluation finding in favour of *CYP* testing are probably quite positive. On the basis of a single test per patient costing around £300, the expected lifetime benefit per patient need be only about 0.01 quality-adjusted life-years (QALYs) to achieve the current cost-effectiveness standard (≤ £30,000 per QALY gained). If any survival improvement can be shown to be supported by evidence then this level of gain appears to be modest, particularly if opportunities arise to target testing on those patients most likely to show improvements in their care and expected outcomes.

TABLE 42 *Suggested criteria for model suitability*

Model	Patient population – does it address all three patient types?	Timespan – does it have a long-term (>20 years) or whole-life horizon?	Analytical framework – is it a cost–utility model?	Model structure – is it suitable/ adaptable for the schizophrenia module?	Mortality – does it include higher schizophrenia mortality risks and suicide risks?
Almond 2000[200] (and 1998[201])	×	×	×	×	/ (suicide)
Bagnall 2003[47]	×	×	✓	×	×
Beard 2006[202]	✓	×	✓	?	/ (suicide)
Bernardo 2006[203] (and 2007[204])		×	×	?	
Bobes 2004[205]	×	×	×	?	×
Bounthavong 2007[206]	×	×	×	?	×
Byrom 1998[207]	×	×	×	×	×
Davies 2000[208]	×	×	✓	×	×
Davies 1998[209]	×	×	×	×	×
De Graeve 2005[210]	×		×	×	×
Duggan 2003[237]	×	✓	×	?	/ (suicide)
Glazer 1996[211] (related to Edwards 2005,[212] Obradovic 2007[213] and Ganguly 2003[214])	×		×	×	×
Glennie 1997[215]	×	✓	✓	×	×
Gutierrez-Recacha 2006[216]	?	✓	✓ (DALY)	?	✓
Hansen 2002[217]	×	×	×	?	/ (suicide)
Heeg 2005[218]	×	×	×	×	×
Kongsakon 2005[219]	×	×	×	×	×
Launois 1998[220]	×	×	×	×	×
Laurier 1997[221]	×	×	×	x	×
Lecomte 2000[222]	×	×	×	?	/ (suicide)
Magnus 2005[223]	?	✓	✓	?	?
Mortimer 2003[224]	×	✓	✓	✓	/ (suicide)
Oh 2001[225]	×	×	✓	×	×
Oh 2001[226]	×	×	✓	×	×
Palmer 1998[227] (and 2002,[228] and Sacristan 1997[229])	×	×	✓	?	/ (suicide)
Perlis 2005[230]	×	✓	✓	×	/ (suicide)
Tilden 2002[231]	×	×	×	✓	/ (suicide)
Vera-Llonch, 2004[232] (and 2005[233])	×	×	×	?	/ (suicide)
Wang 2004[234]	×	✓	✓	✓	/ (suicide)
Yang 2005[235]	×	×	×	×	×

DALY, disability-adjusted life-year; PSS, personal social services; SA, sensitivy analysis.
KEY: ✓ = yes/good; × = no/poor; /= partially; ? = uncertain/not stated.

Relapse – are all aspects of relapse modelled adequately?	Unwanted drug effects – are both short- and long-term effects properly modelled?	Comorbidities – are any comorbidities modelled?	Medication taking – can the effects of drug-taking behaviours be tested (e.g. via SA)?	Costs – are all relevant costs included (long-term NHS and PSS costs)?
/	×	×	/	×
/	×	×	/	
/	×	×	?	×
/	×	×	?	×
/	×	/ (costs)	?	×
/	×	/ (costs)	?	×
/	×	×	/	×
/	×	×	/	×
/	×	×	×	×
/	×	×	?	×
	×	×	×	/
/		×	?	×
/	×	×	/	×
?	?	?	?	? (or × as foreign)
/	×	×	?	×
/	×	×	/	×
?	×	×	?	×
/	×	×	/	×
×	×	×	×	×
?	×	×	?	×
?	?	?	?	? (or × as foreign)
/	×	×	/	/
?	×	×	?	×
?	×	×	?	×
/	×	×	?	×
/	×	×	/	/
/	×	×	/	×
?	×	×	?	×
?	?	×	?	? (or × as foreign)
?	×	×	?	×

Chapter 8
Discussion and conclusions

Clinical review

Analytical validity

A number of studies have now been published reporting on the analytical validity of genotype tests for *CYP* polymorphisms, particularly *CYP2D6*, although only one-third of all studies used sequencing (which is considered the gold standard) as a reference method, with very few samples from each study being actually compared in this manner.

As with a previous review of antidepressants[24] it was found that very few studies reported on all four aspects of analytical validity, with robustness and quality control in particular being commonly neglected, and thus no attempt was made by this review to formally assess study quality in this manner. Equally, very few studies actually explicitly reported sensitivity and specificity results, with general statements about concordance being common, although when this is 100% it would follow that sensitivity and specificity are also 100%. Indeed, it was not uncommon for studies to report 100% concordance between genotyping methods. Unfortunately less than half of the studies presented data to support their claims and, when they did, this was not always for genotypes but rather data on alleles such as allele frequencies. As has been noted in a previous review, correct allele counts do not necessarily reflect correct genotype calls (which are assumed to predict treatment outcomes) and they are therefore less relevant in the clinical context.[24] When genotype data were reported it was possible to calculate sensitivity and specificity and, with one exception, this was always 99% or higher.

It is noticeable that most of the *CYP2D6* studies assessing analytical validity were interested in testing for the loss of function alleles that are more prevalent in Caucasian and African American populations. Although very few studies reported on the ethnicity of their samples, another weakness in the reporting of the studies, the majority of *CYP2D6* studies were carried out in Europe and the USA where these populations are highly prevalent. This may, however, question the effectiveness of such tests in other populations, particularly those Asian populations in which the decreased function allele, *CYP2D6*10*, is more prevalent. It has been noted that even the AmpliChip, which targets the largest set of *CYP2D6* variants, fails to capture a large set of rare variants leading to deficient enzyme activity,[24] although this does test for the *CYP2D6*10* allele.

Notwithstanding these limitations, the studies suggest that genotyping for *CYP* polymorphisms has high analytical validity for all *CYP* polymorphisms, including *CYP2D6*, *CYP1A2*, *CYP2C9* and *CYP2C19*.

Clinical validity

CYP2D6 is arguably the most important CYP enzyme with regard to the metabolism of antipsychotics, with six typical antipsychotics (thioridazine, perphenazine, fluphenazine, zuclopenthixol, haloperidol and chlorpromazine) and two atypical antipsychotics (risperidone and olanzapine) metabolised by this enzyme. Thus it is unsurprising that most of the clinical validity studies also focused on CYP2D6 and, as with analytical validity studies, the loss of function alleles in particular. The only other CYP enzymes studied by more than one clinical validity study were CYP1A2, which also metabolises some antipsychotics (haloperidol and two atypicals, clozapine and olanzapine), and CYP2C19, which does not appear to metabolise any antipsychotic (a recent review highlighted this as a minor metabolic pathway for clozapine although such pathways are not likely to be relevant in most clinical circumstances[14]).

The majority of the studies that were concerned with clinical validity were either cross-sectional or prospective in design. Although the quality of these studies appeared to be of a generally adequate standard, it was apparent that key considerations, such as how patients were selected and the number of patients included in studies, were poorly reported indicating that there may have been some selection bias. Furthermore, in genetic association studies it is vital that tests for missingness at random are conducted to ensure that the missingness is independent of both true genotype and phenotype. When no mention

was made of any missing genotype data, but the numbers contributing to each analysis agreed with the sample size, it was not possible to distinguish between the situation in which no missing genotype data had occurred and that in which any patients with missing genotypes had been excluded from the number quoted as the sample size, in which case there was again a risk of bias if the data were not missing at random. This potentially limits the generalisability of the results.

A range of outcomes measuring metabolism, efficacy and ADRs was considered. For metabolism it was found that the *CYP2D6* genotype does affect the pharmacokinetics of the drugs when this represents the major pathway for elimination. Five studies were included in this analysis, assessing different drugs and reporting different outcomes. Each reports a link between genotype and drug metabolism. However, a complicating factor in relation to pharmacokinetic analysis (and therefore to response) for all of the antipsychotics is that: (1) multiple CYP isoforms are involved in their metabolism; (2) the fractional clearance via CYP2D6 is heavily dependent on the drug being studied, for example it represents a minor pathway of olanzapine; and (3) many of the CYP isoforms are prone to interference by concomitantly administered inducers and inhibitors (these may be drugs or, for CYP1A2, the effect of smoking). No studies undertook a comprehensive analysis of these factors.

Nine studies were identified that assessed an efficacy outcome for patients genotyped for *CYP2D6* but, although some suggest that there may be an association between genotype and efficacy, others also report data suggesting no effect. Given the contradictory findings from this small number of efficacy studies it is difficult to draw any firm conclusions regarding a link between genotype and drug efficacy. A complicating factor that needs to be considered in future studies is whether the drug being investigated has active metabolite(s) produced by the polymorphic pathway, for example as has been found with risperidone.[236] In such situations efficacy may well be dependent on the product of the parent drug and active metabolite, rather than only on the parent compound. An additional issue not considered with efficacy studies is an assessment of adherence to medications, which is known to be problematic in this group of patients.

The largest number of clinical validity studies examined a range of adverse events in patients using a variety of therapeutic agents (*CYP2D6*, $n = 34$; *CYP1A2*, $n = 9$; other *CYP* polymorphisms, $n = 2$). As in the other sections of this review the results are non-conclusive and there are significant limitations in the available data. Findings that failed to show any effect may well have occurred because across all of the studies included in this review very few patients possessed the *mut/mut* genotype. Given the low prevalence of such patients, even in Caucasian populations in which this PM phenotype is most common, this is not unexpected but it does suggest that studies were insufficiently powered to show any significant differences between genotypes.

Nevertheless, there were some significant findings for patients genotyped for *CYP2D6*, suggesting some relationship between genotype and TD and parkinsonism: patients with either the *wt/mut* or *mut/mut* + *wt/mut* genotype were found to be at an increased risk of TD in prospective studies (but not when other study designs were analysed) and patients with the *mut/mut* genotype showed statistically significantly higher AIMS scores than patients with the *wt/wt* genotype; patients with the *mut/mut* + *wt/mut* genotypes were at an increased risk of parkinsonism compared with those with the *wt/wt* genotype. The majority of the patients in these meta-analyses were taking typical antipsychotics. This could suggest that there may be a clinical argument for testing patients for *CYP2D6* to prevent the risk of TD, although as typical antipsychotics are increasingly used when atypicals are unsuitable there may be limited utility in this. Similarly, the findings should be interpreted with caution, not least because, although the odds ratios were statistically significant for some comparisons, they were perhaps too small to have clinical meaningfulness.

No significant differences were apparent for patients with *CYP1A2* genotypes. As noted, *CYP1A2* is thought to be more prone to variation from environmental influences, particularly the effect of smoking. However, studies in this review compared results for known smokers with TD with results for all patients with TD and found no differences between these groups. This suggests that the proportions of patients with TD by genotype would be similar in non-smoking patients and thus there is no evidence that smoking plays a significant role.

However, one study of *CYP2D6* also considered smoking status in patients with TD[137] and found that differences between genotype groups (*wt/wt* and *wt/mut*) were only significant in smokers.

Given that CYP2D6 is the only CYP which is not inducible and that genetic variation contributes largely to the interindividual variation in enzyme activity, this suggests that some other effect may be taking place and these study findings neatly encapsulate the complexity of the problems posed by pharmacogenetic studies in general. Although patients were taking any typical antipsychotic in this study, this was primarily haloperidol, which is not only metabolised by CYP2D6 but also by CYP1A2 and CYP3A4. Thus, the differences may have occurred not because of metabolism of haloperidol by CYP2D6 but because of metabolism of haloperidol by CYP1A2 and CYP3A4, reiterating the problems with metabolism highlighted above.

Overall, therefore, it is difficult to draw any firm conclusions about the clinical validity of *CYP* testing. When there are a greater number of patients included in the analysis, there is some evidence indicating that further study may be warranted to assess the link between genotype and clinical utility.

Clinical utility

Despite the encouraging results regarding analytical validity, given the lack of compelling evidence from the clinical validity studies it is disappointing, but not unexpected, that no completed and published studies were found that measured clinical utility. Thus, the potential benefit of *CYP* testing is still uncertain and it would be premature to recommend the use of pharmacogenetic testing for patients with schizophrenia. In the meantime there is clearly the need for further research, and recommendations for conducting this research are given in Chapter 9.

Given the limitations of the evidence base it is not currently possible to recommend the use of pharmacogenetic testing to inform guidance related to the management of therapeutic regimes for patients with schizophrenia.

Limitations

One of the major limitations of the current review is the lack of patients with the *mut/mut* genotype in the studies included. As discussed above, this may have been one of the major reasons for the general lack of conclusive evidence.

Another limitation is the fact that it was not possible to consider UMs separately to EMs in the current analysis. For the purposes of this review, patients with the UM phenotype have been classified as *wt/wt*, largely because not all studies themselves have made the distinction. This may in part be due to limitations of the test used for genotyping patients. Nevertheless, as UMs generally have a lower AUC and thus reduced efficacy at normal doses, including these patients with EMs will clearly dilute any evidence for differences with other genotypes. However, in the few studies that did report on UMs, the number of such patients was even fewer than the number of patients with the *mut/mut* genotype and so the impact on the overall results is likely to be minimal.

Aside from small numbers, another weakness of the current review is the wide range of antipsychotics being taken in the majority of the studies. Thus the lack of effects apparent in many of the studies may have occurred not because there were not enough patients in any particular genotype but because not all drugs taken were metabolised by the CYP being investigated, or because other factors were not taken into account. Arguably the area of pharmacogenetics in schizophrenia is even more complex because, although the aetiology of schizophrenia and causes of side-effects and/or ADRs are unclear, associations that are found may only be artefacts. For example, TD is not a typical dose-related effect although it could be assumed that cumulative drug exposure may contribute to its occurrence with this risk increased through CYP2D6.

It is important to note that the different targets that antipsychotics act on, for example dopamine and 5-HT receptors, are also polymorphically expressed, and their contribution to the overall efficacy of antipsychotics should be neither ignored nor underestimated. A comprehensive approach that therefore looks at environmental factors, and the genetic factors modulating both pharmacokinetic and pharmacodynamic pathways, will be important in the future, and appropriately powered studies will be able to dissect out the relative importance of each of these pathways in the overall response to antipsychotics.

A final limitation of the current review is that, because of the lack of published studies, it was not possible to consider evidence for clinical utility.

Economics

To develop an economic model and determine the cost-effectiveness of *CYP* pharmacogenetic

testing for prescribing antipsychotics in patients diagnosed with schizophrenia, two key issues must be considered:

- whether the clinical benefits of *CYP* pharmacogenetic testing for schizophrenia can be demonstrated (and at what place in the treatment pathway)
- whether the outcomes and costs of schizophrenia treatment can be robustly estimated.

In terms of the clinical benefits of the test, our clinical review has demonstrated that currently the data are very limited, thus it is not possible to link through from an individual's genotype to their phenotype and subsequently on to downstream sequelae such as response rates and adverse events. Nor were there any data on the clinical utility of the test, hence it is impossible to know how clinicians will handle test information and how it will be incorporated into a care pathway.

Additionally, the NICE schizophrenia guidelines[37] recommend the use of risperidone, olanzapine, quetiapine, amisulpride and zotepine for both initiation and acute episodes, but only risperidone and olanzapine are metabolised by CYP2D6, neither of which are particularly important, as the former has an active metabolite and the latter is primarily metabolised by other isoenzymes. This means that results from the test could, at best, only inform the choice of two out of the five currently recommended drugs. So, from a practical standpoint there is only a slight incentive to carry out the test.

In terms of the outcomes and costs of schizophrenia, our review of the published schizophrenia models identified that none of them would be appropriate for our purposes. A new schizophrenia model would need to be developed.

Therefore, as neither the evidence nor the guidelines support clinicians' use of *CYP* pharmacogenetic test results to determine the most appropriate treatment strategy for patients with schizophrenia it appears to be premature to attempt a full economic modelling and evaluation exercise for this technology at this time.

However, it is worth noting that the prospects of such a full economic evaluation finding in favour of *CYP* testing are probably quite positive. On the basis of a single test per patient costing around £300, the expected lifetime benefit per patient need be only about 0.01 QALYs per patient to achieve the current cost-effectiveness standard (≤ £30,000 per QALY gained). If any survival improvement can be shown to be supported by evidence then this level of gain appears to be modest, particularly if opportunities arise to target testing on those patients most likely to show improvements in their care and expected outcomes.

Summary

In summary, from this review of the literature it is possible say that tests for determining genotypes are highly accurate. However, not all aspects of analytical validity have been reported in the studies. In terms of clinical validity, research is being conducted to assess the links between genotype and metabolism and adverse events. However, to date the research is limited and no firm conclusions can be drawn. No studies assessing clinical utility have been reported.

In terms of assessing the cost-effectiveness of using such pharmacogenetic testing, in the authors' opinion it is too soon to tell. An economic model was not developed as part of this report but from previous work carried out in the area of pharmacogenetic testing in depression and through the assessment of published economic models of schizophrenia a suggested model framework has been developed. Our proposed model framework consists of four main modules: pharmacogenetic test module (assigning patient to phenotype), clinical effects module (linking phenotype to outcomes), transitional module (effect of test results on clinical decision) and schizophrenia module (projecting treatment effects over a patient's lifetime). Without all four components and the information to populate them it is not possible to determine the cost-effectiveness of *CYP* testing in schizophrenia.

The following section outlines the areas of research that are needed to inform future policy decisions regarding the use of pharmacogenetic testing in patients with schizophrenia.

Chapter 9
Research recommendations

Although the current evidence base does not support the use of pharmacogenetic testing in this area, it does indicate that further study in each of the key areas is needed to either demonstrate or refute the ability of pharmacogenetic testing to assist in the development of individualised patient care in the area of schizophrenia. Recommendations for future research cover both aspects of research quality and data that will be required to inform the development of future economic models.

Analytical validity

- Studies of analytical validity need to be explicit about patient selection, quality control, assay robustness and the sensitivity and specificity of tests. Study findings should not only report on allele frequencies but also on appropriate genotype data.

Clinical validity

- Further evidence is required to link phenotype to genotype. Such studies need to include larger numbers of patients with the UM and PM phenotypes and be prospective in design.
- Studies need to consider the impact of environmental factors such as smoking, concomitant medicines, medication adherence and ethnicity. In relation to medication adherence, genotypes need to be related not only to clinical parameters but also to pharmacokinetic parameters.
- Studies need to ensure that all currently used antipsychotics are investigated. However, given the uncertainty about the full extent of the role played by CYP2D6, further studies focusing on patients taking risperidone and olanzapine would also be useful.
- Future research will need to consider a comprehensive approach that considers not only CYP isoforms involved in the metabolism of antipsychotics but also other targets such as dopamine and 5-HT receptors.

Clinical utility

- Prospective clinical utility studies are needed. As with clinical validity they should ensure that all currently used antipsychotics are investigated although, given their importance to the NHS (and the uncertainty about the full extent of the role played by CYP2D6), further studies focusing on patients taking risperidone and olanzapine would be particularly useful.

Economic evaluation

- Improved evidence should be sought on the link between improved schizophrenia care and life expectancy.
- Collection of longitudinal data that identifies patterns of adherence, length of time in relapse and cost of care (including care provided in the community) is required.
- A common approach to the measurement and reporting of adherence, relapse and quality of life in schizophrenia is needed.

Acknowledgements

The review team is pleased to acknowledge Professor Paula Williamson, who provided input to the research protocol design; Ms Janet Atkinson, who provided administrative support (including obtaining bibliographic sources); and Dr Shon Lewis, who provided background information on schizophrenia.

Contribution of authors (alphabetically)

Professor Adrian Bagust had input into all aspects of the economic components of the review. Dr Sophie Beale carried out the economic evaluation and had input into all aspects of the economic review. Dr Angela Boland had input into the economic review and contributed to peer review of report. Ms Rumona Dickson had input into all aspects of the clinical components of the review. Dr Yenal Dundar was responsible for development of the search strategies and study selection and had input into aspects of the clinical component of the review. Mr Nigel Fleeman was responsible for review co-ordination, background and data management and had input into all aspects of the clinical review. Dr Andrea Jorgensen provided statistical advice and had input into aspects of the clinical review. Ms Claire McLeod co-ordinated the economic review and had input into the economic evaluation. Dr Katherine Payne had input into all aspects of the economic components of the review. Professor Munir Pirmohamed was responsible for data assessment and interpretation of clinical data. Dr Sudeep Pushpakom had input into the background and clinical components of the review and authored the background information. Professor Tom Walley contributed to data assessment and interpretation of clinical data. Dr Phillip De Warren-Penny had input into the background and clinical component of the review and authored the background information. All contributors took part in the editing and production of the final report.

About the assessment group

The Liverpool Reviews and Implementation Group (LR*i*G) was established at the University of Liverpool in April 2001. It is a multidisciplinary research group whose purpose, in the first instance, is to conduct health technology assessments (HTAs) commissioned by the NIHR Health Technology Assessment programme.

References

1. Grossman I. Routine pharmacogenetic testing in clinical practice: dream or reality? *Pharmacogenomics* 2007;**8**:1449–59.

2. Palomaki G, McClain M, Haddow J. ACCE reviews of genetic tests: BRC1, BRC2, and CFTR. In Gwinn M, Bedrosian B, Ottmann D, Khoury M, eds. *Genomics and population health*. Atlanta, GA: Centers for Disease Control and Prevention, Office of Genomics and Disease Prevention; 2005. pp. 27–33. URL: http://origin.cdc.gov/genomics/activities/ogdp/2005/chap05.htm.

3. Thakur M, Grossman I, McCrory D, Orlando L, Steffens D, Cline K, *et al*. Review of evidence for genetic testing for CYP450 polymorphisms in management of patients with nonpsychotic depression with selective serotonin reuptake inhibitors. *Genet Med* 2007;**9**:826–35.

4. Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group. Recommendations from the EGAPP Working Group: testing for cytochrome P450 polymorphisms in adults with nonpsychotic depression treated with selective serotonin reuptake inhibitors. *Genet Med* 2007;**9**:819–25.

5. Roche Molecular Systems. *US Food and Drug Administration 510(k) substantial equivalence determination decision summary for Roche AmpliChip CYP450 microarray for identifying CYP2C19 genotype (510(k) Number k043576)*. 2005 URL: www.fda.gov/cdrh/reviews/k043576.pdf. Cited 19 April 2006.

6. Roche's AmpliChip test gets EU approval. *Pharmacogenomics* 2004;**5**:763.

7. de Leon J, Susce M, Pan R, Koch W, Wedlund P. Polymorphic variations in GSTM1, GSTT1, PgP, CYP2D6, CYP3A5, and Dopamine D_2 and D_3 receptors and their association with tardive dyskinesia in severe mental illness. *J Clin Psychopharmacol* 2005;**25**:448–56.

8. Pirmohamed M, Park BK. Cytochrome P450 enzyme polymorphisms and adverse drug reactions. *Toxicology* 2003;**192**:23–32.

9. National Library of Medicine Genetics Home Reference. *CYP gene family*. URL: http://ghr.nlm.nih.gov/geneFamily=cyp. Cited 29 July 2008.

10. Blower PR. 5-HT3-receptor antagonists and the cytochrome P450 system: clinical implications. *Cancer J* 2002;**8**:405–14.

11. de Leon J, Armstrong SC, Cozza KL. Clinical guidelines for psychiatrists for the use of pharmacogenetic testing for CYP450 2D6 and CYP450 2C19. *Psychosomatics* 2006;**47**:75–85.

12. Kirchheiner J, Brosen K, Dahl ML, Gram LF, Kasper S, Roots I, *et al*. CYP2D6 and CYP2C19 genotype-based dose recommendations for antidepressants: a first step towards subpopulation-specific dosages. *Acta Psychiatr Scand* 2001;**104**:173–92.

13. Kirchheiner J, Nickchen K, Bauer M, Wong M-L, Licinio J, Roots I, *et al*. Pharmacogenetics of antidepressants and antipsychotics: the contribution of allelic variations to the phenotype of drug response. *Mol Psychiatry* 2004;**9**:442–73.

14. Arranz MJ, de Leon J. Pharmacogenetics and pharmacogenomics of schizophrenia: a review of last decade of research. *Mol Psychiatry* 2007;**12**:707–47.

15. The Doctors Laboratory. Pharmacogenetics: using genotyping in the development of personalised medicine. *TDL Lab Report*, Autumn 2005. URL: www.tdlpathology.com/.

16. Ingelman-Sundberg M, Sim SC, Gomez A, Rodriguez-Antona C. Influence of cytochrome P450 polymorphisms on drug therapies: pharmacogenetic, pharmacoepigenetic and clinical aspects. *Pharmacol Ther* 2007;**116**:496–526.

17. Kim E, Yu KS, Cho JY, Shin YW, Yoo SY, Kim YY, *et al*. Effects of DRD2 and CYP2D6 genotypes on delta EEG power response to aripiprazole in healthy male volunteers: a preliminary study. *Hum Psychopharmacol* 2006;**21**:519–28.

18. Cupp M, Tracey T. Cytochrome P450: new nomenclature and clinical implications. *Fam Phys* 1998;**57**:107–16.

19. Kirchheiner J. CYP2D6 phenotype prediction from genotype: which system is best. *Clin Pharmacol Ther* 2008;**83**:225–7.

20. Gaedigk A, Simon S, Pearce R, Bradford LD, Kennedy M, Leeder J. The CYP2D6 activity score: translating genotype information into qualitative measure of phenotype. *Clin Pharmacol Ther* 2008;**83**:234–42.

21. Cai WM, Chen B, Zhang WX. Frequency of CYP2D6*10 and *14 alleles and their influence on the metabolic activity of CYP2D6 in a healthy Chinese population. *Clin Pharmacol Ther* 2007;**81**:95–8.

22. Bradford LD. CYP2D6 allele frequency in European Caucasians, Asians, Africans and their descendants. *Pharmacogenomics* 2002;**3**:229–43.

23. Garcia-Barcelo M, Chow LY, Chiu HF, Wing YK, Lee DT, Lam KL, *et al*. Genetic analysis of the CYP2D6 locus in a Hong Kong Chinese population [erratum appears in *Clin Chem* 2000;**46**:1873]. *Clin Chem* 2000;**46**:18–23.

24. Matchar D, Thakur M, Grossman I, McCroy D, Orlando L, Steffens D, *et al*. *Testing for cytochrome P450 polymorphisms in adults with non-psychotic depression treated with SSRIs*. Rockville, MD: Agency for Healthcare and Research Quality; 2006.

25. Zackrisson A, Holmgren P, Gladh A, Ahlner J, Lindblom B. Fatal intoxication cases: cytochrome P450 2D6 and 2C19 genotype distributions. *Eur J Pharmacol* 2004;**60**:547–52.

26. Human Cytochrome P450 (CYP) Allele Nomenclature Committee. *Allele nomenclature for cytochrome P450 enzymes*. URL: www.cypalleles.ki.se/. Cited 30 July 2008.

27. The Doctors Laboratory. AmpliChip CYP450 test: breast cancer and tamoxifen response. *TDL Lab Report*, Spring 2007. URL: www.tdlpathology.com/.

28. National Health Service (UK). *Mental Health National Service Framework*. 1999. URL: www.dh.gov.uk/assetRoot/04/07/72/09/04077209.pdf. Cited 2008.

29. World Health Organization. *ICD-10: the ICD-10 classification of mental and behavioural disorders: clinical descriptions and diagnostic guidelines*. Geneva: World Health Organization; 1992.

30. Osby U, Correia N, Brandt L, Ekbom A, Sparen P. Mortality and causes of death in schizophrenia in Stockholm county, Sweden. *Schizophr Res* 2000;**45**:21–8.

31. Saha S, Chant D, McGrath J. A systematic review of mortality in schizophrenia: is the differential mortality gap worsening over time? *Arch Gen Psychiatry* 2007;**64**:1123–31.

32. Palmer BA, Pankratz VS, Bostwick JM. The lifetime risk of suicide in schizophrenia: a reexamination [see comment]. *Arch Gen Psychiatry* 2005;**62**:247–53.

33. Department for Work and Pensions. *Prevalence of schizophrenia*. URL: www.dwp.gov.uk/medical/med_conditions/major/schizophrenia/prevalence_schizophrenia.asp. Cited 26 June 2008.

34. Goldner EM, Hsu L, Waraich P, Somers JM. Prevalence and incidence studies of schizophrenic disorders: a systematic review of the literature. *Can J Psychiatry* 2002;**47**:833–43.

35. MIND. *Statistics 1: how common is mental distress?* 2008. URL: www.mind.org.uk/Information/Factsheets/Statistics/Statistics+1.htm#ftnref36. Cited 28 July 2008.

36. Jablensky A, Sartorius N, Ernberg G, Anker M, Korten A, Cooper JE, *et al*. *Schizophrenia: manifestations and course in different cultures. A World Health Organization ten-country study*. Psychological Medicine Monograph Supplement 20. Cambridge: Cambridge University Press; 1992.

37. National Institute for Clinical Excellence. *Schizophrenia: core interventions in the treatment and management of schizophrenia in primary and secondary care*. London: National Institute for Clinical Excellence; 1992.

38. Correll CU, Leucht S, Kane JM. Lower risk for tardive dyskinesia associated with second-generation antipsychotics: a systematic review of 1-year studies. *Am J Psychiatry* 2004;**161**:414–25.

39. Kerwin RW. The new atypical antipsychotics. A lack of extrapyramidal side-effects and new routes in schizophrenia research. *Br J Psychiatry* 1994;**164**:141–8.

40. Geddes J, Freemantle N, Harrison P, Bebbington P. Atypical antipsychotics in the treatment of schizophrenia: systematic overview and meta-regression analysis. *BMJ* 2000;**321**:1371–6.

41. Rosenheck RA, Leslie DL, Busch S, Rofman ES, Sernyak M. Rethinking antipsychotic formulary policy. *Schizophr Bull* 2008;**34**:375–80.

42. Casey DE, Haupt DW, Newcomer JW, Henderson DC, Sernyak MJ, Davidson M, *et al*. Antipsychotic-induced weight gain and metabolic abnormalities: implications for increased mortality in patients with schizophrenia. *J Clin Psychiatry* 2004;**65**(Suppl. 7):4–18.

43. Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, *et al*. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med* 2005;**353**:1209–23.

44. Mehta D. *British national formulary*. London: Pharmaceutical Press; 2007.

45. Iqbal MM, Rahman A, Husain Z, Mahmud SZ, Ryan WG, Feldman JM. Clozapine: a clinical review of adverse effects and management. *Ann Clin Psychiatry* 2003;**15**:33–48.

46. Taylor D, Paton C, Kerwin R. *The Maudsley prescribing guidelines*. 9th edn. London: Routledge; 2007.

47. Bagnall AM, Jones L, Ginnelly L, Lewis R, Glanville J, Gilbody S, *et al*. A systematic review of atypical antipsychotic drugs in schizophrenia. *Health Technol Assess* 2003;**7**:1–193.

48. Jones PB, Barnes TRE, Davies L, Dunn G, Lloyd H, Hayhurst KP, *et al*. Randomized controlled trial of the effect on quality of life of second- vs first-generation antipsychotic drugs in schizophrenia: Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1). *Arch Gen Psychiatry* 2006;**63**:1079–87.

49. Lewis S, Lieberman J. CATIE and CUtLASS: can we handle the truth? *Br J Psychiatry* 2008;**192**:161–3.

50. Hegarty JD, Baldessarini RJ, Tohen M, Waternaux C, Oepen G. One hundred years of schizophrenia: a meta-analysis of the outcome literature. *Am J Psychiatry* 1994;**151**:1409–16.

51. Tsoi WF, Wong KE. A 15-year follow-up study of Chinese schizophrenic patients. *Acta Psychiatr Scand* 1991;**84**:217–20.

52. Johnstone E, Lawrie S, Cunningham-Owens DG, Sharpe MD. *Companion to psychiatric studies (MRCPsy study guides)*. 7th edn. Oxford: Churchill Livingstone; 2004.

53. Meltzer HY. Treatment of the neuroleptic-nonresponsive schizophrenic patient. *Schizophr Bull* 1992;**18**:515–42.

54. Johnstone EC, Owens DG, Leary J. Disabilities and circumstances of schizophrenic patients – a follow-up study. Comparison of the 1975–85 cohort with the 1970–75 cohort. *Br J Psychiatry* 1991;**13**(Suppl.):34–6.

55. Mason P, Harrison G, Glazebrook C, Medley I, Dalkin T, Croudace T. Characteristics of outcome in schizophrenia at 13 years. *Br J Psychiatry* 1995;**167**:596–603.

56. Lieberman J, Jody D, Geisler S, Alvir J, Loebel A, Szymanski S, *et al*. Time course and biologic correlates of treatment response in first-episode schizophrenia. *Arch Gen Psychiatry* 1993;**50**:369–76.

57. Conley RR, Buchanan RW. Evaluation of treatment-resistant schizophrenia. *Schizophr Bull* 1997;**23**:663–74.

58. Kane JM. Management strategies for the treatment of schizophrenia. *J Clin Psychiatry* 1999;**60**(Suppl. 12):13–17.

59. Pantelis C, Barnes TR. Drug strategies and treatment-resistant schizophrenia [see comment]. *Aust N Z J Psychiatry* 1996;**30**:20–37.

60. Pantelis C, Lambert TJR. Managing patients with 'treatment-resistant' schizophrenia. *Med J Aust* 2003;**178**(Suppl.):S62–6.

61. Herz MI, Glazer WM, Mostert MA, Sheard MA, Szymanski HV, Hafez H, *et al*. Intermittent vs maintenance medication in schizophrenia. Two-year results. *Arch Gen Psychiatry* 1991;**48**:333–9.

62. Jolley AG, Hirsch SR, Morrison E, McRink A, Wilson L. Trial of brief intermittent neuroleptic prophylaxis for selected schizophrenic outpatients: clinical and social outcome at two years. *BMJ* 1990;**301**:837–42.

63. Weiden PJ. Understanding and addressing adherence issues in schizophrenia: from theory to practice. *J Clin Psychiatry* 2007;**68**(Suppl. 14):14–19.

64. Wyatt RJ. Neuroleptics and the natural course of schizophrenia. *Schizophr Bull* 1991;**17**:325–51.

65. Leucht S, Heres S. Epidemiology, clinical consequences, and psychosocial treatment of nonadherence in schizophrenia. *J Clin Psychiatry* 2006;**67(**Suppl. 5):3–8.

66. Kikkert MJ, Barbui C, Koeter MW, David AS, Leese M, Tansella M, *et al*. Assessment of medication adherence in patients with schizophrenia: the Achilles heel of adherence research. *J Nerv Ment Dis* 2008;**196**:274–81.

67. Nose M, Barbui C, Tansella M. How often do patients with psychosis fail to adhere to treatment programmes? A systematic review. *Psychol Med* 2003;**33**:1149–60.

68. Lacro JP, Dunn LB, Dolder CR, Leckband SG, Jeste DV. Prevalence of and risk factors for medication nonadherence in patients with schizophrenia: a comprehensive review of recent literature. *J Clin Psychiatry* 2002;**63**:892–909.

69. Awad G. Antipsychotic medications: compliance and attitudes towards treatment. *Curr Opin Psychiatry* 2004;**17**:75–80.

70. Farran-Ridge C. Dementia praecox and epidemic encephalitis. *J Med Sci* 1926;**72**:513–23.

71. Owens DG, Johnstone EC, Frith CD. Spontaneous involuntary disorders of movement: their prevalence, severity, and distribution in chronic schizophrenics with and without treatment with neuroleptics. *Arch Gen Psychiatry* 1982;**39**:452–61.

72. Correll CU, Schenk EM. Tardive dyskinesia and new antipsychotics. *Curr Opin Psychiatry* 2008;**21**:151–6.

73. Keshava C, McCanlies EC, Weston A. CYP3A4 polymorphisms – potential risk factors for breast and prostate cancer: a HuGE review. *Am J Epidemiol* 2004;**160**:825–41.

74. Yu AM, Fukamachi K, Krausz KW, Cheung C, Gonzalez FJ. Potential role for human cytochrome P450 3A4 in estradiol homeostasis. *Endocrinology* 2005;**146**:2911–9.

75. Thummel KE, Wilkinson GR. In vitro and in vivo drug interactions involving human CYP3A. *Annu Rev Pharmacol Toxicol* 1998;**38**:389–430.

76. Faber MS, Jetter A, Fuhr U. Assessment of CYP1A2 activity in clinical practice: Why, how, and when? *Basic Clin Pharmacol Toxicol* 2005;**97**:125–34.

77. Patsopoulos NA, Ntzani EE, Zintzaras E, Ioannidis JPA. CYP2D6 polymorphisms and the risk of tardive dyskinesia in schizophrenia: a meta-analysis. *Pharmacogenet Genomics* 2005;**15**:151–8.

78. Davies T. Psychosocial factors and relapse of schizophrenia. *BMJ* 1994;**309**:353–4.

79. HM Treasury. *Budget 2008: stability and opportunity: building a strong, sustainable future: economic and fiscal strategy report and financial statement and budget report*. London: London Stationery Office; 2008.

80. Moher D, Cook J, Eastwood S, Olkin I, Rennie D, Stroup D. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. *Lancet* 1999;**354**:1896–900.

81. Little J, Higgins J, editors. *The HuGENet HUGE Review Handbook, version 1.0*. 2006. URL: www.genesens.net/_intranet/doc_nouvelles/HuGE%20Review%20Handbook%20v11.pdf. Cited 30 June 2008.

82. Khan K, Ter Riet G, Glanville J, Sowdon A, Kleijnen J. *Undertaking systematic reviews of research on effectiveness. CRD's guidance for carrying out or commissioning reviews*. CRD Report Number 4. 2nd edn. York: Centre for Reviews and Dissemination, University of York; 2001.

83. Jorgensen AL, Williamson PR. Methodological quality of pharmacogenetic studies: issues of concern. *Stat Med* 2008. Published online in Wiley InterScience (www.interscience.wiley.com); DOI 10.1002/sim.3420.

84. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analysis. *BMJ* 2003;**327**:557–60.

85. Drummond M, Jefferson T. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working. *BMJ* 1996;**313**:275–83.

86. Chou WH, Yan FX, Robbins-Weilert DK, Ryder TB, Liu WW, Perbost C, *et al*. Comparison of two CYP2D6 genotyping methods and assessment of genotype–phenotype relationships. *Clin Chem* 2003;**49**:542–51.

87. Crescenti A, Mas S, Gasso P, Baiget M, Bernardo M, Lafuente A. Simultaneous genotyping of CYP2D6*3, *4, *5 and *6 polymorphisms in a Spanish population through multiplex long polymerase chain reaction and minisequencing multiplex single base extension analysis. *Clin Exp Pharmacol Physiol* 2007;**34**:992–7.

88. Dukek BA, O'Kane DJ. Comparison of Roche diagnostics AmpliChip CYP450IVD test with TM Bioscience Tag-It cytochrome P450 2D6 and 2C19 tests. *Clin Chem* 2006;**52**:A52-A.

89. Eriksson S, Berg LM, Wadelius M, Alderborn A. Cytochrome P450 genotyping by multiplexed real-time DNA sequencing with pyrosequencing technology. *Assay Drug Dev Technol* 2002;**1**:49–59.

90. Heller T, Kirchheiner J, Armstrong VW, Lathe H, Brockmoller J, Oellerich M. Assessment of Amplichip CYP450-based CYP2D6-genotyping and phenotype prediction compared to PCR-RFLP-genotyping and phenotyping by metoprolol pharmacokinetics. *Ther Drug Monit* 2005;**27**:221.

91. Heller T, Kirchheiner J, Armstrong VW, Luthe H, Tzvetkov M, Brockmoller J, *et al*. AmpliChip CYP450 GeneChip®: a new gene chip that allows rapid and accurate CYP2D6 genotyping. *Ther Drug Monit* 2006;**28**:673–7.

92. Hersberger M, Marti-Jaun J, Rentsch K, Hanseler E. Rapid detection of the CYP2D6*3, CYP2D6*4, and CYP2D6*6 alleles by tetra-primer PCR and of the CYP2D6*5 allele by multiplex long PCR. *Clin Chem* 2000;**46**:1072–7.

93. James HM, Coller JK, Gillis D, Bahnisch J, Sallustio BC, Somogyi AA. A new simple diagnostic for the identification of the major CYP2D6 genotypes by DNA sequencing analysis. *Int J Clin Pharmacol Ther* 2004;**42**:719–23.

94. Lee HK, Lewis LD, Tsongalis GJ, Schur BC, Jannetto PJ, Wong SH, *et al*. Validation of a CYP2D6 genotyping panel on the NanoChip Molecular Biology Workstation. *Clin Chem* 2007;**53**:823–8.

95. Melis R, Lyon E, McMillin GA. Determination of CYP2D6, CYP2C9 and CYP2C19 genotypes with Tag-It mutation detection assays. *Exp Rev Mol Diagn* 2006;**6**:811–20.

96. Muller B, Zopf K, Bachofer J, Steimer W. Optimized strategy for rapid cytochrome P450 2D6 genotyping by real-time long PCR. *Clin Chem* 2003;**49**:1624–31.

97. Neville M, Selzer R, Aizenstein B, Maguire M, Hogan K, Walton R, *et al*. Characterization of cytochrome P450 2D6 alleles using the Invader system. *Biotechniques* 2002;(Suppl.):34–8.

98. Nielsen KA, Hansen EL, Gille S. Genotyping of the cytochrome P450 2D6 4469 C>T polymorphism using SimpleProbes. *Scand J Clin Lab Invest* 2007;**67**:280–90.

99. Roberts R, Sullivan P, Joyce P, Kennedy MA. Rapid and comprehensive determination of cytochrome P450 CYP2D6 poor metabolizer genotypes by multiplex polymerase chain reaction. *Hum Mutat* 2000;**16**:77–85.

100. Roche Molecular Systems. *US Food and Drug Administration 510(k) substantial equivalence determination decision summary for Roche AmpliChip CYP450 microarray for identifying CYP2D6 genotype (510(k) Number k042259)*. 2004 19 April 2006 cited; URL: www.fda.gov/cdrh/reviews/k042259.pdf.

101. Schaeffeler E, Schwab M, Eichelbaum M, Zanger UM. CYP2D6 genotyping strategy based on gene copy number determination by TaqMan real-time PCR. *Hum Mutat* 2003;**22**:476–85.

102. Soderback E, Zackrisson A-L, Lindblom B, Alderborn A. Determination of CYP2D6 gene copy number by pyrosequencing. *Clin Chem* 2005;**51**: 522–31.

103. Stamer UM, Stuber F. Genetic factors in pain and its treatment. *Curr Opin Anaesthesiol* 2007;**20**:478–84.

104. Stuven T, Griese EU, Kroemer HK, Eichelbaum M, Zanger UM. Rapid detection of CYP2D6 null alleles by long distance- and multiplex-polymerase chain reaction. *Pharmacogenetics* 1996;**6**:417–21.

105. Zackrisson A-L, Lindblom B. Identification of CYP2D6 alleles by single nucleotide polymorphism analysis using pyrosequencing. *Eur J Clin Pharmacol* 2003;**59**:521–6.

106. Casley WL, LeBlanc-Westwood CA. Assay for the simultaneous detection of the *1C and *1F alleles of the CYP1A2 gene by real-time polymerase chain reaction and melting curve analysis. *Psychiatr Genet* 2006;**16**:81–3.

107. Popp J, Messner B, Steimer W. High-speed genotyping of CYP1A2*1F mutation with fluorescent hybridization probes using the LightCycler. *Pharmacogenomics* 2003;**4**:643–6.

108. Burian M, Grosch S, Tegeder I, Geisslinger G. Validation of a new fluorogenic real-time PCR assay for detection of CYP2C9 allelic variants and CYP2C9 allelic distribution in a German population. *Br J Clin Pharmacol* 2002;**54**:518–21.

109. Pickering JW, McMillin GA, Gedge F, Hill HR, Lyon E. Flow cytometric assay for genotyping cytochrome P450 2C9 and 2C19: comparison with a microelectronic DNA array. *Am J Pharmacogenomics* 2004;**4**:199–207.

110. Toriello M, Meccariello P, Mazzaccara C, Di Fiore R, Esposito C, Sacchetti L. Comparison of the TaqMan and LightCycler systems in pharmacogenetic testing: evaluation of CYP2C9*2/*3 polymorphisms. *Clin Chem Lab Med* 2006;**44**:285–7.

111. Wen SY, Wang H, Sun OJ, Wang SQ. Rapid detection of the known SNPs of CYP2C9 using oligonucleotide microarray. *World J Gastroenterol* 2003;**9**:1342–6.

112. Zainuddin Z, Teh LK, Suhaimi AWM, Salleh MZ, Ismail R. A simple method for the detection of CYP2C9 polymorphisms: nested allele-specific multiplex polymerase chain reaction. *Clin Chim Acta* 2003;**336**:97–102.

113. Mizugaki M, Hiratsuka M, Agatsuma Y, Matsubara Y, Fujii K, Kure S, *et al*. Rapid detection of CYP2C18 genotypes by real-time fluorescence polymerase chain reaction. *J Pharm Pharmacol* 2000;**52**:199–205.

114. Bruning T, Abel J, Koch B, Lorenzen K, Harth V, Donat S, *et al*. Real-time PCR-analysis of the cytochrome P450 1B1 codon 432-polymorphism. *Arch Toxicol* 1999;**73**:427–30.

115. Fredericks S, Moreton M, MacPhee IAM, Mohamed M, Marlowe S, Jorga A, *et al*. Genotyping cytochrome P450 3A5 using the light cycler. *Ann Clin Biochem* 2005;**42**:376–81.

116. Harth V, Bruning T, Abel J, Koch B, Berg I, Sachinidis A, *et al*. Real-time genotyping of cytochrome P4501A1 A4889G and T6235C polymorphisms. *Mol Cell Probes* 2001;**15**:93–7.

117. Innocenti C, Accorsi A, Cerreta V, Mantovani V, Violante FS. Fast CYP2E1 genotyping using automated fluorescent detection. *Med Lav* 2006;**97**:799–804.

118. Labuda D, Krajinovic M, Richer C, Skoll A, Sinnett H, Yotova V, *et al*. Rapid detection of CYP1A1, CYP2D6, and NAT variants by multiplex polymerase chain reaction and allele-specific oligonucleotide assay. *Anal Biochem* 1999;**275**:84–92.

119. Muthiah YD, Lee WL, Teh LK, Ong CE, Salleh MZ, Ismail R. A simple multiplex PCR method for the concurrent detection of three CYP2C8 variants. *Clin Chim Acta* 2004;**349**:191–8.

120. Oyama T, Mitsudomi T, Kawamoto T, Ogami A, Osaki T, Kodama Y, *et al*. Detection of CYP1A1 gene polymorphism using designed RFLP and distributions of CYP1A1 genotypes in Japanese. *Int Arch Occup Environ Health* 1995;**67**:253–6.

121. Rohrbacher M, Kirchhof A, Geisslinger G, Lotsch J. Pyrosequencing-based screening for genetic polymorphisms in cytochrome P450 2B6 of potential clinical relevance. *Pharmacogenomics* 2006;**7**:995–1002.

122. Weise A, Grundler S, Zaumsegel D, Klotzek M, Grondahl B, Forst T, *et al*. Development and evaluation of a rapid and reliable method for cytochrome P450 2C8 genotyping. *Clin Lab* 2004;**50**:141–8.

123. Weise A, Lambertz U, Thome N, Bartz U, Krefft M, Mockenhaupt F, *et al*. A fast and reliable single-run method for genotyping of the human cytochrome P450 2C8 gene for different ethnic groups. *Clin Lab* 2006;**52**:599–603.

124. Wen S, Wang H, Ding Y, Liang H, Wang S. Screening of 12 SNPs of CYP3A4 in a Chinese population using oligonucleotide microarray. *Genet Test* 2004;**8**:411–6.

125. Wu X, Zhou Y, Xu S. Detection of CYP I A1 polymorphisms with a colorimetric method based on mismatch hybridization. *Clin Chim Acta* 2002;**323**:103–9.

126. Aitchison KJ, Munro J, Wright P, Smith S, Makoff AJ, Sachse C, *et al*. Failure to respond to treatment with typical antipsychotics is not associated with CYP2D6 ultrarapid hydroxylation. *Br J Clin Pharmacol* 1999;**48**:388–94.

127. Andreassen OA, MacEwan T, Gulbrandsen AK, McCreadie RG, Steen VM. Non-functional CYP2D6 alleles and risk for neuroleptic-induced movement disorders in schizophrenic patients. *Psychopharmacology (Berl)* 1997;**131**:174–9.

128. Armstrong M, Daly AK, Blennerhassett R, Ferrier N, Idle JR. Antipsychotic drug-induced movement disorders in schizophrenics in relation to CYP2D6 genotype [see comment]. *Br J Psychiatry* 1997;**170**:23–6.

129. Arranz MJ, Dawson E, Shaikh S, Sham P, Sharma T, Aitchison K, *et al*. Cytochrome P4502D6 genotype does not determine response to clozapine. *Br J Clin Pharmacol* 1995;**39**:417–20.

130. Arthur H, Dahl ML, Siwers B, Sjoqvist F. Polymorphic drug metabolism in schizophrenic patients with tardive dyskinesia. *J Clin Psychopharmacol* 1995;**15**:211–6.

131. Brockmoller J, Kirchheiner J, Schmider J, Walter S, Sachse C, Muller-Oerlinghausen B, *et al*. The impact of the CYP2D6 polymorphism on haloperidol pharmacokinetics and on the outcome of haloperidol treatment. *Clin Pharmacol Ther* 2002;**72**:438–52.

132. Culav-Sumic J, Topic E, Baric V, Stefanovic M, Martic-Biocina S, Skocic D, *et al*. CYP2D6 polymorphism and side effects in schizophrenia and schizoaffective psychosis. *Period Biol* 2001;**103**:315–9.

133. de Leon J, Diaz FJ, Wedlund P, Josiassen RC, Cooper TB, Simpson GM. Haloperidol half-life after chronic dosing. *J Clin Psychopharmacol* 2004;**24**:656–60.

134. Dettling M, Sachse C, Muller-Oerlinghausen B, Roots I, Brockmoller J, Rolfs A, *et al*. Clozapine-induced agranulocytosis and hereditary polymorphisms of clozapine metabolizing enzymes: no association with myeloperoxidase and cytochrome P450206. *Pharmacopsychiatry* 2000;**33**:218–20.

135. Ellingrod VL, Schultz SK, Arndt S. Association between cytochrome P4502D6 (CYP2D6) genotype, antipsychotic exposure, and abnormal involuntary movement scale (AIMS) score. *Psychiatr Genet* 2000;**10**:9–11.

136. Ellingrod VL, Miller D, Schultz SK, Wehring H, Arndt S. CYP2D6 polymorphisms and atypical antipsychotic weight gain. *Psychiatr Genet* 2002;**12**:55–8.

137. Ellingrod VL, Schultz SK, Arndt S. Abnormal movements and tardive dyskinesia in smokers and nonsmokers with schizophrenia genotyped for cytochrome P450 2D6. *Pharmacotherapy* 2002;**22**:1416–9.

138. Fu Y, Fan C-H, Deng H-H, Hu S-H, Lv D-P, Li L-H, *et al*. Association of CYP2D6 and CYP1A2 gene polymorphism with tardive dyskinesia in Chinese schizophrenic patients. *Acta Pharm Sinica* 2006;**27**:328–32.

139. Hamelin BA, Dorson PG, Pabis D, Still D, Bouchard RH, Pourcher E, *et al*. CYP2D6 mutations and

therapeutic outcome in schizophrenic patients. *Pharmacotherapy* 1999;**19**:1057–63.

140. Inada T, Senoo H, Iijima Y, Yamauchi T, Yagi G. Cytochrome P450 II D6 gene polymorphisms and the neuroleptic-induced extrapyramidal symptoms in Japanese schizophrenic patients. *Psychiatr Genet* 2003;**13**:163–8.

141. Iwahashi K, Isobe C, Waga C. The influence that the polymorphisms of cytochrome P450 (CYP) gene, thrifty gene and pharmacodynamic-related gene give to a side effect of olanzapine. *Int Clin Psychopharmacol* 2007;**22**:P21.

142. Jaanson P, Marandi T, Kiivet RA, Vasar V, Vaan S, Svensson JO, *et al*. Maintenance therapy with zuclopenthixol decanoate: associations between plasma concentrations, neurological side effects and CYP2D6 genotype. *Psychopharmacology (Berl)* 2002;**162**:67–73.

143. Jeon JY, Kim JR, Lim KS, Kim JW, Kim BH, Tae YM, *et al*. CYP2D6 genotype affects aripiprazole clearance in Korean patients: population pharmacokinetic analysis. *Clin Pharmacol Ther* 2007;**81**:S80.

144. Jerling M, Dahl ML, Aberg-Wistedt A, Liljenberg B, Landell NE, Bertilsson L, *et al*. The CYP2D6 genotype predicts the oral clearance of the neuroleptic agents perphenazine and zuclopenthixol. *Clin Pharmacol Ther* 1996;**59**:423–8.

145. Kakihara S, Yoshimura R, Shinkai K, Matsumoto C, Goto M, Kaji K, *et al*. Prediction of response to risperidone treatment with respect to plasma concentrations of risperidone, catecholamine metabolites, and polymorphism of cytochrome P450 2D6. *Int Clin Psychopharmacol* 2005;**20**:71–8.

146. Kapitany T, Meszaros K, Lenzinger E, Schindler SD, Barnas C, Fuchs K, *et al*. Genetic polymorphisms for drug metabolism (CYP2D6) and tardive dyskinesia in schizophrenia. *Schizophr Res* 1998;**32**:101–6.

147. Lam LC, Garcia-Barcelo MM, Ungvari GS, Tang WK, Lam VK, Kwong SL, *et al*. Cytochrome P450 2D6 genotyping and association with tardive dyskinesia in Chinese schizophrenic patients. *Pharmacopsychiatry* 2001;**34**:238–41.

148. Lane HY, Liu YC, Huang CL, Chang YC, Wu PL, Lu CT, *et al*. Risperidone-related weight gain – genetic and nongenetic predictors. *J Clin Psychopharmacol* 2006;**26**:128–34.

149. Liou YJ, Wang YC, Bai YM, Lin CC, Yu SC, Liao DL, *et al*. Cytochrome P-450 2D6*10 C188T polymorphism is associated with antipsychotic-induced persistent tardive dyskinesia in Chinese schizophrenic patients. *Neuropsychobiology* 2004;**49**:167–73.

150. Lohmann PL, Bagli M, Krauss H, Muller DJ, Schulze TG, Fangerau H, *et al*. CYP2D6 polymorphism and tardive dyskinesia in schizophrenic patients. *Pharmacopsychiatry* 2003;**36**:73–8.

151. Mihara K, Kondo T, Higuchi H, Takahashi H, Yoshida K, Shimizu T, *et al*. Tardive dystonia and genetic polymorphisms of cytochrome P4502D6 and dopamine D-2 and D-3 receptors: a preliminary finding. *Am J Med Genet* 2002;**114**:693–5.

152. Nikoloff D, Shim JC, Fairchild M, Patten N, Fijal BA, Koch WH, *et al*. Association between CYP2D6 genotype and tardive dyskinesia in Korean schizophrenics. *Pharmacogenomics J* 2002;**2**:400–7.

153. Ohmori O, Suzuki T, Kojima H, Shinkai T, Terao T, Mita T, *et al*. Tardive dyskinesia and debrisoquine 4-hydroxylase (CYP2D6) genotype in Japanese schizophrenics. *Schizophr Res* 1998;**32**:107–13.

154. Ohmori O, Kojima H, Shinkai T, Terao T, Suzuki T, Abe K. Genetic association analysis between CYP2D6*2 allele and tardive dyskinesia in schizophrenic patients. *Psychiatry Res* 1999;**87**:239–44.

155. Panagiotidis G, Arthur HW, Lindh JD, Dahl ML, Sjoqvist F. Depot haloperidol treatment in outpatients with schizophrenia on monotherapy: impact of CYP2D6 polymorphism on pharmacokinetics and treatment outcome. *Ther Drug Monit* 2007;**29**:417–22.

156. Plesnicar BK, Zalar B, Breskvar K, Dolzan V. The influence of the CYP2D6 polymorphism on psychopathological and extrapyramidal symptoms in the patients on long-term antipsychotic treatment. *J Psychopharmacol (Oxf)* 2006;**20**:829–33.

157. Riedel M, Schwarz MJ, Strassnig M, Spellmann I, Muller-Arends A, Weber K, *et al*. Risperidone plasma levels, clinical response and side-effects. *Eur Arch Psychiatry Clin Neurosci* 2005;**255**:261–8.

158. Scordo MG, Spina E, Romeo P, Dahl ML, Bertilsson L, Johansson I, *et al*. CYP2D6 genotype and antipsychotic-induced extrapyramidal side effects in schizophrenic patients. *Eur J Clin Pharmacol* 2000;**56**:679–83.

159. Thanacoody RHK, Daly AK, Reilly JG, Ferrier IN, Thomas SHL. Factors affecting drug concentrations and QT interval during thioridazine therapy. *Clin Pharmacol Ther* 2007;**82**:555–65.

160. Thanacoody HKR, Daly AK, Thomas SHL. Influence of CYP2D6 and CYP2C19 genotypes

on the QTc intervals of psychiatric patients taking thioridazine. *Br J Clin Pharmacol* 2003;**55**:445.

161. Tiwari AK, Deshpande SN, Rao AR, Bhatia T, Lerer B, Nimgaonkar VL, *et al*. Genetic susceptibility to tardive dyskinesia in chronic schizophrenia subjects: III. Lack of association of CYP3A4 and CYP2D6 gene polymorphisms. *Schizophr Res* 2005;**75**:21–6.

162. Topic E, Stefanovic M, Ivanisevic AM, Blazinic F, Culav J, Skocilic Z. CYP2D6 genotyping in patients on psychoactive drug therapy. *Clin Chem Lab Med* 2000;**38**:921–7.

163. Wang L, Yu L, Zhang AP, Fang C, Du J, Gu NF, *et al*. Serum prolactin levels, plasma risperidone levels, polymorphism of cytochrome P450 2D6 and clinical response in patients with schizophrenia. *J Psychopharmacol (Oxf)* 2007;**21**:837–42.

164. Basile VS, Ozdemir V, Masellis M, Walker ML, Meltzer HY, Lieberman JA, *et al*. A functional polymorphism of the cytochrome P450 1A2 (CYP1A2) gene: association with tardive dyskinesia in schizophrenia. *Mol Psychiatry* 2000;**5**:410–17.

165. Boke O, Gunes S, Kara N, Aker S, Sahin AR, Basar Y, *et al*. Association of serotonin 2A receptor and lack of association of CYP1A2 gene polymorphism with tardive dyskinesia in a Turkish population. *DNA Cell Biol* 2007;**26**:527–31.

166. Matsumoto C, Ohmori O, Shinkai T, Hori H, Nakamura J. Genetic association analysis of functional polymorphisms in the cytochrome P450 1A2 (CYP1A2) gene with tardive dyskinesia in Japanese patients with schizophrenia. *Psychiatr Genet* 2004;**14**:209–13.

167. Schulze TG, Schumacher J, Muller DJ, Krauss H, Alfter D, Maroldt A, *et al*. Lack of association between a functional polymorphism of the cytochrome P450 1A2 (CYP1A2) gene and tardive dyskinesia in schizophrenia. *Am J Med Genet* 2001;**105**:498–501.

168. Tay JKX, Tan CH, Chong SA, Tan EC. Functional polymorphisms of the cytochrome P450 lA2 (CYPlA2) gene and prolonged QTc interval in schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry* 2007;**31**:1297–302.

169. Tiwari AK, Deshpande SN, Rao AR, Bhatia T, Mukit SR, Shriharsh V, *et al*. Genetic susceptibility to tardive dyskinesia in chronic schizophrenia subjects. I. Association of CYP1A2 gene polymorphism. *Pharmacogenomics J* 2005;**5**:60–9.

170. Tiwari AK, Deshpande SN, Lerer B, Nimgaonkar VL, Thelma BK. Genetic susceptibility to tardive dyskinesia in chronic schizophrenia subjects. V. Association of CYP1A2 1545 C > T polymorphism. *Pharmacogenomics J* 2007;**7**:305–11.

171. Yasar U, Babaoglu MO, Balibey H, Cetin M, Lundgren S, Rane A, *et al*. Association of the cytochrome P450 1A2*1F polymorphism with clozapine response in schizophrenic patients. *FASEB J* 2007;**21**:A196.

172. Segman RH, Heresco-Levy U, Yakir A, Goltser T, Strous R, Greenberg DA, *et al*. Interactive effect of cytochrome P450 17alpha-hydroxylase and dopamine D3 receptor gene polymorphisms on abnormal involuntary movements in chronic schizophrenia. *Biol Psychiatry* 2002;**51**:261–3.

173. Hutton JL, Williamson PR. Bias in meta-analysis due to outcome variable selection within studies. *J R Stat Soc Ser C* 2000;**49**:359–70.

174. Miles W, Sheridan J, Wheeler A. The effect of knowing the CYP 450 metaboliser status on clinician prescribing behaviour when treating psychosis with risperidone. *Aust N Z J Psychiatry* 2007;**41**:A60.

175. Danish Institute for Health Services Research. *Does genotyping for cytochrome P450 polymorphisms improve individual antipsycotic drug treatment? (2007–2011)*. Participants in the project: Bispebjerg hospital: Clinical Pharmacological Unit, Sct. Hans Hospital: research institute and DSI (project 2087) (brief record). Ongoing (2007–2011). URL: www.mrw.interscience.wiley.com/cochrane/clhta/articles/HTA-20061224/frame.html.

176. Mulder H, Herder A, Wilmink FW, Tamminga WJ, Belitser SV, Egberts ACG. The impact of cytochrome P450–2D6 genotype on the use and interpretation of therapeutic drug monitoring in long-stay patients treated with antidepressant and antipsychotic drugs in daily psychiatric practice. *Pharmacoepidemiol Drug Saf* 2006;**15**:107–14.

177. Charlier C, Broly F, Lhermitte M, et al,. Polymorphisms in the CYP 2D6 gene: association with plasma concentrations of fluoxetine and paroxetine. *Ther Drug Monit* 2003;**25**:738–42.

178. Grasmader K, Verwohlt PL, Rietschel M, Dragicevic A, Müller M, Hiemke C, *et al*. Impact of polymorphisms of cytochrome-P450 isoenzymes 2C9, 2C19 and 2D6 on plasma concentrations and clinical effects of antidepressants in a naturalistic clinical setting. *Eur J Clin Pharmacol* 2004;**60**:329–36.

179. Rossini D, Serretti A, Franchini L, Mandelli L, Smeraldi E, Rondi D, *et al*. Sertraline versus fluvoxamine in the treatment of elderly patients with major depression: a double-blind, randomized trial. *J Clin Psychopharmacol* 2005;**25**:471–5.

180. Anon. URL: www.costco.com/pharmacy. Cited 11 September 2006.

181. Palylyk Colwell E. *CYP450 genotyping for determining drug metabolizer status (structured abstract)*. URL: www.mrw.interscience.wiley.com/cochrane/clhta/articles/HTA-20060238/frame.html. Cited 2006.

182. Bennett KJ, Torrance GW, Boyle MH, Guscott R, Moran LA. Development and testing of a utility measure for major, unipolar depression. *Q Life Res* 2000;**9**:109–20.

183. Kind P, Hardman G, Macran S. *UK population norms for EQ-5D*. Discussion Paper 172. York: Centre for Health Economics, University of York; 1999.

184. Hatziandreu EJ, Brown RE, Revicki DA, Turner R, Martindale J, Levine S. Cost utility of maintenance treatment of recurrent depression with sertraline versus episodic treatment with dothiepin. *Pharmacoeconomics* 1994;**5**:249–68.

185. Anton SF, Revicki DA. The use of decision analysis in the pharmacoeconomic evaluation of an antidepressant: a cost-effectiveness study of nefazodone. *Psychopharmacol Bull* 1995;**31**:249–58.

186. Tarrier N, Barrowclough C, Bamrah JS. Prodromal signs of relapse in schizophrenia. *Soc Psychiatry Psychiatr Epidemiol* 1991;**26**:157–61.

187. Lieberman J, Alvir J, Geisler S, Ramos-Lorenzi J, Woerner M, Novacenko H. Methylphenidate response, psychopathology and tardive dyskinesia as predictors of relapse in schizophrenia. *Neuropsychopharmacology* 1994;**11**:107–18.

188. Doering S, Müller E, Köpcke W, Pietzcker A, Gaebel W, Linden M. Predictors of relapse and rehospitalization in schizophrenia and schizoaffective disorder. *Schizophr Bull* 1998;**24**:87–98.

189. Swofford CD, Kasckow JW, Scheller-Gilkey G, Inderbitzin L. Substance use: a powerful predictor of relapse in schizophrenia. *Schizophr Res* 1996;**20**:145–51.

190. Goff DC, Shader RI. Non-neurological side-effects of antipsychotic drugs. In Hirsch SR, Weinberger D, editors. *Schizophrenia*. 2nd edn. Oxford: Blackwell Publishing; 2003. pp. 573–88.

191. Phelan N, Stradins L, Morrison S. Physical health of people with severe mental illness. *BMJ* 2001;**322**:442–4.

192. Newman SC, Bland RC. Mortality in a cohort of patients with schizophrenia: a record linkage study. *Can J Psychiatry* 1991;**36**:239–54.

193. Brown S, Inskip H, Barraclough B. Causes of the excess mortality of schizophrenia. *Br J Psychiatry* 2000;**177**:212–7.

194. Barnes TR, Kerwin R. Mortality and sudden death in schizophrenia. In Camm J, editor. *Cardiovascular risk associated with schizophrenia and its treatment*. London: Galliard Healthcare Communications; 2003. pp. 7–23.

195. Cooper D, Moisan J, Grégoire JP. Adherence to atypical antipsychotic treatment among newly treated patients: a population-based study in schizophrenia. *J Clin Psychiatry* 2007;**68**:818–25.

196. Morken G, Widen JH, Grawe RW. Non-adherence to antipsychotic medication, relapse and rehospitalisation in recent-onset schizophrenia. *BMC Psychiatry* 2008;**8**:32.

197. Tunis SL, Faries DE, Stensland MD, Hay DP, Kinon BJ. An examination of factors affecting persistence with initial antipsychotic treatment in patients with schizophrenia. *Curr Med Res Opin* 2007;**23**:97–104.

198. Gee L, Pearce E, Jackson M. Quality of life in schizophrenia: a grounded theory approach. *Health Qual Life Outcomes* 2003;**1**:31.

199. National Collaborating Centre for Mental Health. *Schizophrenia: full national clinical guideline on core interventions in primary and secondary care*. London: Royal College of Psychiatrists and British Psychological Society; 2002.

200. Almond S, O'Donnell O. Cost analysis of the treatment of schizophrenia in the UK: a simulation model comprising olanzapine, risperidone and haloperidol. *Pharmacoeconomics* 2000;**17**:383–9.

201. Almond S, O'Donnell O. Cost analysis of the treatment of schizophrenia in the UK: a comparison of olanzapine and haloperidol. *Pharmacoeconomics* 1998;**13**:575–88.

202. Beard AM, Maciver F, Clouth J, Ruther E. A decision model to compare health care costs of olanzapine and risperidone treatment of schizophrenia in Germany. *Eur J Health Econ* 2006;**7**:165–72.

203. Bernardo M, Azanza JR, Rubio-Terres C, Rejas J. Cost-effectiveness analysis of schizophrenia relapse prevention: an economic evaluation of the ZEUS (Ziprasidone-Extended-Use-in-Schizophrenia) study in Spain. *Clin Drug Investig* 2006;**26**:447–57.

204. Bernardo M, Azanza JR, Rubio-Terres C, Rejas J. Cost-effectiveness analysis of the prevention of relapse of schizophrenia in the longitudinal study Ziprasidone Extended Use in Schizophrenia (ZEUS). *Actas Esp Psiquiatr* 2007;**35**:259–62.

205. Bobes J, Canas F, Rejas J, Mackell J. Economic consequences of the adverse reactions related with antipsychotics: an economic model comparing tolerability of ziprasidone, olanzapine, risperidone, and haloperidol in Spain. *Prog Neuropsychopharmacol Biol Psychiatry* 2004;**28**:1287–97.

206. Bounthavong M, Okamoto MP. Decision analysis model evaluating the cost-effectiveness of risperidone, olanzapine and haloperidol in the treatment of schizophrenia. *J Eval Clin Pract* 2007;**13**:453–60.

207. Byrom BD, Garratt CJ, Kilpatrick AT. Influence of antipsychotic profile on cost of treatment of schizophrenia: a decision analysis approach. *Int J Psychiatry Clin Pract* 1998;**2**:129–38.

208. Davies L, Lewis S. *Antipsychotic medication for people with first episode schizophrenia: an exploratory economic analysis of alternative treatment algorithms*. CHE Discussion Paper 178. York: Centre for Health Economics and School of Psychiatry and Behavioural Sciences, University of Manchester; 2000.

209. Davies A, Langley PC, Keks NA, Catts SV, Lambert T, Schweitzer I. Risperiodone versus haloperidol. II. Cost-effectiveness. *Clin Ther* 1998;**20**:196–213.

210. De Graeve D, Smet A, Mehnert A, Caleo S, Miadi-Fargier H, Mosqueda GJ, *et al*. Long-acting risperidone compared with oral olanzapine and haloperidol depot in schizophrenia: a Belgian cost-effectiveness analysis. *Pharmacoeconomics* 2005;**23**:35–47.

211. Glazer WM, Ereshefsky L. A pharmacoeconomic model of outpatient antipsychotic therapy in 'revolving door' schizophrenic patients. *J Clin Psychiatry* 1996;**57**:337–45.

212. Edwards NC, Rupnow MFT, Pashos CL, Botteman MF, Diamond RJ. Cost-effectiveness model of long-acting risperidone in schizophrenia in the US. *Pharmacoeconomics* 2005;**23**:299–314.

213. Obradovic M, Mrhar A, Kos M. Cost-effectiveness of antipsychotics for outpatients with chronic schizophrenia. *Int J Clin Pract* 2007;**61**:1979–88.

214. Ganguly R, Miller LS, Martin BC. Future employability, a new approach to cost-effectiveness analysis of antipsychotic therapy. *Schizophr Res* 2003;**63**:111–9.

215. Glennie JL. *Pharmacoeconomic evaluations of clozapine in treatment resistant schizophrenia and risperidone in chronic schizophrenia*. Ottawa: Canadian Coordinating Office for Health Technology Assessment; 1997.

216. Gutierrez-Recacha P, Chisholm D, Haro JM, Salvador-Carulla L, Ayuso-Mateos JL. Cost-effectiveness of different clinical interventions for reducing the burden of schizophrenia in Spain. *Acta Psychiatr Scand* 2006;**114**:29–38.

217. Hansen K, Francois C, Toumi M, Lancon C. A pharmacoeconomic evaluation of zuclopenthixol compared with haloperidol and risperidone in the treatment of schizophrenia. *Eur J Health Econ* 2002;**3**:173–9.

218. Heeg BM, Buskens E, Knapp M, van Aalst G, Dries PJ, de Haan L, *et al*. Modelling the treated course of schizophrenia: development of a discrete event simulation model. *Pharmacoeconomics* 2005;**23**:17–33.

219. Kongsakon R, Leelahanaj T, Price N, Birinyi-Strachan L, Davey P. Cost analysis of the treatment of schizophrenia in Thailand: a simulation model comparing olanzapine, risperidone, quetiapine, ziprasidone and haloperidol. *J Med Assoc Thai* 2005;**88**:1267–77.

220. Launois R, von der Schulenberg MG, Knapp M, Toumi M. Cost-effectiveness of sertindole versus olanzapine or haloperidol: a comprehensive model. *Int J Psychiatry Clin Pract* 1998;**2**:S79–S86.

221. Laurier C, Kennedy W, Lachaine J, Gariepy L, Tessier G. Economic evaluation of zuclopenthixol acetate compared with injectable haloperidol in schizophrenic patients with acute psychosis. *Clin Ther* 1997;**19**:316–29.

222. Lecomte P, De Hert M, van Dijk M, Nuijten M, Nuyts G, Persson U. A 1-year cost-effectiveness model for the treatment of chronic schizophrenia with acute exacerbations in Belgium. *Value Health* 2000;**3**:1–11.

223. Magnus A, Carr V, Mihalopoulos C, Carter R, Vos T. Assessing cost-effectiveness of drug interventions for schizophrenia. *Aust N Z J Psychiatry* 2005;**39**:44–54.

224. Mortimer A, Williams P, Meddis D. Impact of side-effects of atypical antipsychotics on non-compliance, relapse and cost. *J Int Med Res* 2003;**31**:188–96.

225. Oh PI, Iskedjian M, Addis A, Lanctot K, Einarson TR. Pharmacoeconomic evaluation of clozapine in treatment-resistant schizophrenia: a cost-utility analysis. *Can J Clin Pharmacol* 2001;**8**:199–206.

226. Oh PI, Lanctot KL, Mittmann N, Iskedjian M, Einarson TR. Cost-utility of risperidone compared with standard conventional antipsychotics in chronic schizophrenia. *J Med Econ* 2001;**4**:137–56.

227. Palmer CS, Revicki DA, Genduso LA, Hamilton SH, Brown RE. A cost-effectiveness clinical decision analysis model for schizophrenia. *Am J Manag Care* 1998;**4**:345–55.

228. Palmer CS, Brunner E, Ruiz-Flores LG, Paez-Agraz F, Revicki DA. A cost-effectiveness clinical decision analysis model for treatment of Schizophrenia. *Arch Med Res* 2002;**33**:572–80.

229. Sacristan JA, Gomez JC, Salvador-Carulla L. Cost effectiveness analysis of olanzapine versus haloperidol in the treatment of schizophrenia in Spain. *Actas Luso Esp Neurol Psiquiatr Cienc Afines* 1997;**25**:225–34.

230. Perlis RH, Ganz DA, Avorn J, Schneeweiss S, Glynn RJ, Smoller JW, *et al*. Pharmacogenetic testing in the clinical management of schizophrenia: a decision-analytic model. *J Clin Psychopharmacol* 2005;**25**:427–34.

231. Tilden D, Aristides M, Meddis D, Burns T. An economic assessment of quetiapine and haloperidol in patients with schizophrenia only partially responsive to conventional antipsychotics. *Clin Ther* 2002;**24**:1648–67.

232. Vera-Llonch M, Delea TE, Richardson E, Rupnow M, Grogg A, Oster G. Outcomes and costs of risperidone versus olanzapine in patients with chronic schizophrenia or schizoaffective disorders: a Markov model. *Value Health* 2004;**7**:569–84.

233. Vera-Llonch M, Delea TE, Richardson E, Oster G, Rupnow M, Grogg A. Authors' response to comments regarding risperidone versus olanzapine Markov model. *Value Health* 2005;**8**:613–14.

234. Wang PS, Ganz DA, Benner JS, Glynn RJ, Avorn J. Should clozapine continue to be restricted to third-line status for schizophrenia: a decision-analytic model. *J Ment Health Pol Econ* 2004;**7**:77–85.

235. Yang YK, Tarn YH, Wang TY, Liu CY, Laio YC, Chou YH, *et al*. Pharmacoeconomic evaluation of schizophrenia in Taiwan: model comparison of long-acting risperidone versus olanzapine versus depot haloperidol based on estimated costs. *Psychiatry Clin Neurosci* 2005;**59**:385–94.

236. Risperidone package insert (Risperdal; Janssen, US), Rev. 11/97, Rec. 07/98.

237. Duggan A, Warner J, Knapp M, Kerwin R. Modelling the impact of clozapine on suicide in patients with treatment-resistant schizophrenia in the UK. *Br J Psychiatry* 2003;**182**:505–8.

Appendix 1

Search strategies: clinical evidence

Analytical validity

Ovid MEDLINE® 1995 to January Week 2 2008

#	Search history	Results
1	(CYP2D6 or CYP 2D6 or CYP2C19 or CYP 2C19 or CYP2C8 or CYP 2C8 or CYP2C9 or CYP 2C9 or CYP1A1 or CYP 1A1 or CYP1A2 or CYP 1A2 or CYP3A4 or CYP 3A4).mp.	13,589
2	exp Cytochrome P-450 Enzyme System/	51,223
3	amplichip$.tw.	14
4	microarray analysis/	1607
5	(genotyp$adj test$).tw.	329
6	pharmacogenetic$.tw. or Pharmacogenetics/	5573
7	(genetic$adj test$).tw.	5545
8	or/1–7	64,658
9	"Reproducibility of Results"/	149,174
10	"Sensitivity and Specificity"/	176,921
11	(valid$or reliab$).tw.	332,968
12	*"Predictive Value of Tests"/	691
13	or/9–12	547,567
14	8 and 13	2658
15	or/3,14	2669
16	limit 15 to (english language and humans and yr="1995 – 2008")	1768

PsycINFO 1995 to January Week 2 2008

#	Search history	Results
1	(CYP2D6 or CYP 2D6 or CYP2C19 or CYP 2C19 or CYP2C8 or CYP 2C8 or CYP2C9 or CYP 2C9 or CYP1A1 or CYP 1A1 or CYP1A2 or CYP 1A2 or CYP3A4 or CYP 3A4).mp.	388
2	cytochrome$.tw.	811
3	amplichip.tw.	3
4	(genotyp$adj test$).tw.	9
5	(pharmacogenetic$adj test$).tw.	10
6	or/1–5	979
7	(valid$or reliab$).tw.	113,287
8	Test Reliability/	19,455
9	Test Validity/	27,623
10	or/7–9	115,340
11	6 and 10	21
12	limit 11 to (human and english language and yr="1995 – 2008")	9

Cochrane Library 2007 Issue 4

(Cytochrome P-450 Enzyme System or genotyp* test* or CYP2D6 or CYP 2D6 or CYP2C19 or CYP 2C19 or CYP2C8 or CYP 2C8 or CYP2C9 or CYP 2C9 or CYP1A1 or CYP 1A1 or CYP1A2 or CYP 1A2 or CYP3A4 or CYP 3A4) and (valid* or rehab*), from 1995 to 2008

Results:

- Cochrane Database of Systematic Reviews (CDSR): 62 hits
- Database of Abstracts of Reviews of Effectiveness (DARE): 13 hits
- Cochrane Controlled Trials Register (CCTR): 66 hits
- Health Technology Assessment database (HTA): 9 hits
- NHS Economic Evaluation Database (NHS EED): 48 hits.

ISI Web of Knowledge

Science Citation Index Expanded (SCI-EXPANDED) 1995–present

TS=((Cytochrome P-450 or genotyp* or amplichip* or CYP2D6 or CYP 2D6 or CYP2C19 or CYP 2C19 or CYP2C8 or CYP 2C8 or CYP2C9 or CYP 2C9 or CYP1A1 or CYP 1A1 or CYP1A2 or CYP 1A2 or CYP3A4 or CYP 3A4) and validity)

Results: 373.

ISI Proceedings

TS=(((Cytochrome P-450 or genotyp* or amplichip* or CYP2D6 or CYP 2D6 or CYP2C19 or CYP 2C19 or CYP2C8 or CYP 2C8 or CYP2C9 or CYP 2C9 or CYP1A1 or CYP 1A1 or CYP1A2 or CYP 1A2 or CYP3A4 or CYP 3A4) and validity))

Results: 35.

Clinical validity

Ovid MEDLINE 1995 to January Week 2 2008

#	Search history	Results
1	exp Genotype/	164,126
2	exp Phenotype/	148,209
3	(genotype$or phenotype$).tw.	229,979
4	exp cytochrome p-450 enzyme system/	51,223
5	(CYP2D6 or CYP 2D6 or CYP2C19 or CYP 2C19 or CYP2C8 or CYP 2C8 or CYP2C9 or CYP 2C9 or CYP1A1 or CYP 1A1 or CYP1A2 or CYP 1A2 or CYP3A4 or CYP 3A4).mp.	13,589
6	amplichip$.tw.	14
7	or/1–6	451,909
8	exp Antipsychotic Agents/	102,469
9	(antipsychotic$or neuroleptic$).tw.	28,312
10	(risperidone or olanzapine or thioridazine or perphenazine or fluphenazine or zuclopenthixol or haloperidol or chlorpromazine or clozapine or quetiapine or ziprasidone or flupentixol or flupenthixol or benperidol or levomepromazine or methotrimeprazine or pericyazine or periciazine or pimozide or promazine or sulpiride or trifluoperazine or amisulpride or aripiprazole or sertindole or zotepine).tw.	41,738
11	or/8–10	116,792
12	7 and 11	1772
13	limit 12 to (english language and humans and yr="1995 – 2008")	1150

PsycINFO 1995 to January Week 2 2008

#	Search history	Results
1	exp Genotypes/	1894
2	exp Phenotypes/	2260
3	(genotype$or phenotype$).tw.	8680
4	(CYP2D6 or CYP 2D6 or CYP2C19 or CYP 2C19 or CYP2C8 or CYP 2C8 or CYP2C9 or CYP 2C9 or CYP1A1 or CYP 1A1 or CYP1A2 or CYP 1A2 or CYP3A4 or CYP 3A4).mp.	388
5	amplichip$.tw.	3
6	cytochrome$.tw.	811
7	or/1–6	10,120
8	exp Neuroleptic Drugs/	15,762
9	(antipsychotic$or neuroleptic$).tw.	18,879
10	(risperidone or olanzapine or thioridazine or perphenazine or fluphenazine or zuclopenthixol or haloperidol or chlorpromazine or clozapine or quetiapine or ziprasidone or flupentixol or flupenthixol or benperidol or levomepromazine or methotrimeprazine or pericyazine or periciazine or pimozide or promazine or sulpiride or trifluoperazine or amisulpride or aripiprazole or sertindole or zotepine).tw.	15,465
11	or/8–10	26,887
12	7 and 11	472
13	limit 12 to (human and english language and yr="1995 – 2008")	369

ISI Web of Knowledge

Science Citation Index Expanded (SCI-EXPANDED) 1995–present
((genotype* or phenotype* or cytochrome*) and (neuroleptic* or antipsychotic* or risperidone or olanzapine or thioridazine or perphenazine or fluphenazine or zuclopenthixol or haloperidol or chlorpromazine or clozapine or quetiapine or ziprasidone or flupentixol or flupenthixol or benperidol or levomepromazine or methotrimeprazine or pericyazine or periciazine or pimozide or promazine or sulpiride or trifluoperazine or amisulpride or aripiprazole or sertindole or zotepine))

Results: 1210.

ISI Proceedings
Results: 88

((genotype* or phenotype* or cytochrome*) and (neuroleptic* or antipsychotic* or risperidone or olanzapine or thioridazine or perphenazine or fluphenazine or zuclopenthixol or haloperidol or chlorpromazine or clozapine or quetiapine or ziprasidone or flupentixol or flupenthixol or benperidol or levomepromazine or methotrimeprazine or pericyazine or periciazine or pimozide or promazine or sulpiride or trifluoperazine or amisulpride or aripiprazole or sertindole or zotepine))

Cochrane Library *2007 Issue 4*
(genotype* or phenotype* or cytochrome*) and (neuroleptic* or antipsychotic* or risperidone or olanzapine or thioridazine or perphenazine or fluphenazine or zuclopenthixol or haloperidol or chlorpromazine or clozapine or quetiapine or ziprasidone or flupentixol or flupenthixol or benperidol or levomepromazine or methotrimeprazine or pericyazine or periciazine or pimozide or promazine or sulpiride or trifluoperazine or amisulpride or aripiprazole or sertindole or zotepine)

Results:

- Cochrane Database of Systematic Reviews (CDSR): 10 hits
- Database of Abstracts of Reviews of Effectiveness (DARE): 0 hits
- Cochrane Controlled Trials Register (CCTR): 55 hits
- Health Technology Assessment database (HTA): 2 hits
- NHS Economic Evaluation Database (NHS EED): 1 hit.

PubMed 2007–8

175 references found (above search terms used).

EMBASE 1995 to 2008 Week 3

#	Search history	Results
1	exp GENOTYPE/or exp PHENOTYPE/	176,758
2	(genotype$or phenotype$).tw.	188,916
3	CYTOCHROME P450/	23,159
4	(CYP2D6 or CYP 2D6 or CYP2C19 or CYP 2C19 or CYP2C8 or CYP 2C8 or CYP2C9 or CYP 2C9 or CYP1A1 or CYP 1A1 or CYP1A2 or CYP 1A2 or CYP3A4 or CYP 3A4).mp.	10,397
5	amplichip$.tw.	15
6	or/1–5	275,194
7	Neuroleptic Agent/or ATYPICAL ANTIPSYCHOTIC AGENT/	32,118
8	(antipsychotic$or neuroleptic$).tw.	23,460
9	(risperidone or olanzapine or thioridazine or perphenazine or fluphenazine or zuclopenthixol or haloperidol or chlorpromazine or clozapine or quetiapine or ziprasidone or flupentixol or flupenthixol or benperidol or levomepromazine or methotrimeprazine or pericyazine or periciazine or pimozide or promazine or sulpiride or trifluoperazine or amisulpride or aripiprazole or sertindole or zotepine).tw.	27,354
10	or/7–9	56,061
11	6 and 10	1777
12	limit 11 to (human and english language and yr="1995 – 2008")	1325

Clinical utility

Ovid MEDLINE® 1995 to March Week 1 2008

#	Search history	Results
1	exp Cytochrome P-450 Enzyme System/	51,811
2	(CYP2D6 or CYP 2D6 or CYP2C19 or CYP 2C19 or CYP2C8 or CYP 2C8 or CYP2C9 or CYP 2C9 or CYP1A1 or CYP 1A1 or CYP1A2 or CYP 1A2 or CYP3A4 or CYP 3A4 or CYP 450 or cytochrome P450).af.	27,446
3	(genotype adj test$).mp.	70
4	(pharmacogenetic$adj test$).mp.	124
5	amplichip.af.	15
6	1 or 2 or 4 or 5	57,695
7	(effectiv$or impact$or utilit$or outcome$or manag$or decision$or feasib$or implement$or predict$or influenc$or improv$or efficacy$or effect$or decision making$or harm$or clinical response$or disease management$or clinical outcome$or clinical impact$or management decision$).mp.	5,304,482
8	exp Decision Making/	75,729
9	exp Treatment Outcome/	339,633
10	7 or 8 or 9	5,327,364
11	6 and 10	28,691
12	exp Antipsychotic Agents/	104,231
13	(antipsychotic$or neuroleptic$).tw.	28,910
14	(risperidone or olanzapine or thioridazine or perphenazine or fluphenazine or zuclopenthixol or haloperidol or chlorpromazine or clozapine or quetiapine or ziprasidone or flupentixol or flupenthixol or benperidol or levomepromazine or methotrimeprazine or pericyazine or periciazine or pimozide or promazine or sulpiride or trifluoperazine or amisulpride or aripiprazole or sertindole or zotepine).af.	58,771
15	12 or 13 or 14	119,008
16	11 and 15	573
17	limit 16 to (english language and humans and yr="1995 – 2008")	428

PsycINFO 1995 to March Week 2 2008

#	Search history	Results
1	(CYP2D6 or CYP 2D6 or CYP2C19 or CYP 2C19 or CYP2C8 or CYP 2C8 or CYP2C9 or CYP 2C9 or CYP1A1 or CYP 1A1 or CYP1A2 or CYP 1A2 or CYP3A4 or CYP 3A4 or CYP 450 or cytochrome P450).af.	2212
2	(genotype adj test$).mp.	6
3	(pharmacogenetic$adj test$).mp.	10
4	amplichip.af.	13
5	(genotype adj test$).mp.	6
6	1 or 2 or 3 or 4 or 5	2222
7	(effectiv$ or impact$ or utilit$ or outcome$ or manag$ or decision$ or feasib$ or implement$ or predict$ or influenc$ or improv$ or efficacy$ or effect$ or decision making$ or clinical response$ or disease management$ or clinical outcome$ or clinical impact$ or clinical tool$ or benefit$ or management decision$).mp.	1,012,132
8	exp Treatment Outcomes/	18,763
9	exp Decision Making/	32,786
10	7 or 8 or 9	1,014,171
11	6 and	1746
12	exp Neuroleptic Drugs/	16,093
13	(antipsychotic$ or neuroleptic$).tw.	19,247
14	(risperidone or olanzapine or thioridazine or perphenazine or fluphenazine or zuclopenthixol or haloperidol or chlorpromazine or clozapine or quetiapine or ziprasidone or flupentixol or flupenthixol or benperidol or levomepromazine or methotrimeprazine or pericyazine or periciazine or pimozide or promazine or sulpiride or trifluoperazine or amisulpride or aripiprazole or sertindole or zotepine).tw.	15,859
15	12 or 13 or 14	27,523
16	11 and 15	438
17	limit 16 to(human and english language and yr="1995 – 2008")	383

ISI Web of Knowledge

Science Citation Index Expanded (SCI-EXPANDED) 1995–present

(((genotype test* or cytochrome* or CYP 450 or cytochrome P450) and (effectiv* or impact* or utilit* or outcome* or manag* or decision* or feasib*or implement* or predict* or influenc* or improv* or efficacy* or effect* or decision making* or clinical response* or disease management* or clinical outcome* or clinical impact* or management decision*) and (neuroleptic* or antipsychotic* or risperidone or olanzapine or thioridazine or perphenazine or fluphenazine or zuclopenthixol or haloperidol or chlorpromazine or clozapine or quetiapine or ziprasidone or flupentixol or flupenthixol or benperidol or levomepromazine or methotrimeprazine or pericyazine or periciazine or pimozide or promazine or sulpiride or trifluoperazine or amisulpride or aripiprazole or sertindole or zotepine)))

Results: 506.

ISI Proceedings

((((genotype test* or cytochrome* or CYP 450 or cytochrome P450) and (effectiv* or impact* or utilit* or outcome* or manag* or decision* or feasib*or implement* or predict* or influenc* or improv* or efficacy* or effect* or decision making* or clinical response* or disease management* or clinical outcome* or clinical impact* or management decision*) and (neuroleptic* or antipsychotic* or risperidone or olanzapine or thioridazine or perphenazine or fluphenazine or zuclopenthixol or haloperidol or chlorpromazine or clozapine or quetiapine or ziprasidone or flupentixol or flupenthixol or benperidol or levomepromazine or methotrimeprazine or pericyazine or periciazine or pimozide or promazine or sulpiride or trifluoperazine or amisulpride or aripiprazole or sertindole or zotepine))))

Results: 35.

Cochrane Library 2008 Issue 1 (from 1995 to 2008)

(genotype test* or cytochrome* or CYP 450 or cytochrome P450) and (effectiv* or impact* or utilit* or outcome* or manag* or decision* or feasib*or implement* or predict* or influenc* or improv* or efficacy* or effect* or decision making* or clinical response* or disease management* or clinical outcome* or clinical impact* or management decision*) and (neuroleptic* or antipsychotic* or risperidone or olanzapine or thioridazine or perphenazine or fluphenazine or zuclopenthixol or haloperidol or chlorpromazine or clozapine or quetiapine or ziprasidone or flupentixol or flupenthixol or benperidol or levomepromazine or methotrimeprazine or pericyazine or periciazine or pimozide or promazine or sulpiride or trifluoperazine or amisulpride or aripiprazole or sertindole or zotepine)

Results in: Cochrane reviews (7), other reviews (0), clinical trials (35), technology assessments (1), economic evaluations (1).

EMBASE 1995 to 2008 Week 11

#	Search history	Results
1	exp CYTOCHROME P450/	27,865
2	(CYP2D6 or CYP 2D6 or CYP2C19 or CYP 2C19 or CYP2C8 or CYP 2C8 or CYP2C9 or CYP 2C9 or CYP1A1 or CYP 1A1 or CYP1A2 or CYP 1A2 or CYP3A4 or CYP 3A4 or CYP 450 or cytochrome P450).af.	48,696
3	(genotype adj test$).mp.	489
4	(pharmacogenetic$adj test$).mp.	172
5	amplichip.af.	52
6	1 or 2 or 3 or 4 or 5 or 6	49,236
7	(effectiv$or impact$or utilit$or outcome$or manag$or decision$or feasib$or implement$or predict$or influenc$or improv$or efficacy$or effect$or decision making$or harm$or clinical response$or disease management$or clinical outcome$or clinical impact$or management decision$).mp.	4,651,844
8	exp TREATMENT OUTCOME/or exp OUTCOME ASSESSMENT/or exp ADVERSE OUTCOME/	427,199
9	exp CLINICAL DECISION MAKING/	1746
10	7 or 8 or 9	4,660,639
11	6 and 10	27,698
12	(antipsychotic$or neuroleptic$).tw.	28,655
13	Neuroleptic Agent/or ATYPICAL ANTIPSYCHOTIC AGENT/	36,504
14	(risperidone or olanzapine or thioridazine or perphenazine or fluphenazine or zuclopenthixol or haloperidol or chlorpromazine or clozapine or quetiapine or ziprasidone or flupentixol or flupenthixol or benperidol or levomepromazine or methotrimeprazine or pericyazine or periciazine or pimozide or promazine or sulpiride or trifluoperazine or amisulpride or aripiprazole or sertindole or zotepine).tw.	36,381
15	12 or 13 or 14	70,553
16	11 and 15	1018
17	limit 16 to (human and english language and yr="1995 – 2008")	780

Appendix 2
Included studies

Analytical validity

Papers identified for screening stage 1 = 2844

- From original analytical validity search = 2840
- From AHRQ review = 2
- From clinical utility search = 2

Total papers identified for screening stage 2 = 66

- From original analytical validity search = 62
- From AHRQ review =2
- From clinical utility search = 2

Papers included in review = 41

- From original analytical validity search = 39
- From AHRQ review = 2
- From clinical utility search = 0

Clinical validity

Papers identified for screening stage 1 = 2161

- From original clinical validity search = 2153
- From analytical validity search = 2
- From clinical utility search = 6

Total papers identified for screening stage 2 = 169

- From original clinical validity search = 161 (including 6 originally rejected but flagged up in clinical utility search)
- Additional papers identified from analytical validity search = 2
- Additional papers identified from additional clinical utility search = 6

Papers included in review = 47

- From original clinical validity search = 46
- From analytical validity search = 0
- From clinical utility search = 1

Clinical utility

Papers identified for screening stage 1 = 1236

- From original clinical utility search = 1233
- From clinical validity search = 2
- From member of advisory panel =1

Total papers identified for screening stage 2 = 13

- From original clinical utility search = 11
- From clinical validity search = 1
- From member of advisory panel =1

Papers included in review = 2*

- From original clinical utility search = 2
- From clinical validity search = 0
- From member of advisory panel =0

*An additional 2 studies that were rejected at screening stage 2 were also briefly reported on

Appendix 3

Searches: economic evidence

Identification of the available economic evaluations of *CYP* testing for psychiatry

Summary table

Database	Years	Search strategy	References identified
MEDLINE	1950 to April Week 3 2008	See below	91
EMBASE	1980 to Week 17 2008	See below	153
ISI Web of Science		See below	20
ISI Proceedings		See below	6
Cochrane		See below	1
PsycINFO	1967 to April Week 4 2008	See below	7
Total			278
Total after duplicates removed			199

Search strategies

Ovid MEDLINE® 1950 to April Week 3 2008

#	Searche history	Results
1	((cyp 450 or cytochrome P450 or pharmacogenetic$or genetic$or genotype$) adj test$).tw.	6093
2	*Cytochrome P-450 Enzyme System/ge	3985
3	amplichip.af.	15
4	exp Genetic Screening/	16,572
5	or/1–4	23,890
6	exp "Costs and Cost Analysis"/or exp Cost-Benefit Analysis/or exp models, economic/	139,172
7	economics/	25,641
8	(cost$adj2 (effective$or utilit$or benefit$or minimi$)).ti,ab.	52,776
9	cost$.ti.	55,447
10	(value adj2 (money or monetary)).tw.	682
11	or/6–10	206,285
12	exp Mental Disorders/or exp Antipsychotic Agents/or exp Antidepressive Agents/or exp Psychiatry/or exp Schizophrenia/	880,297
13	(antipsychotic$or neuroleptic$or schizophrenia$).tw.	69,259
14	or/12–13	886,576
15	5 and 11 and 14	91

EMBASE 1980 to 2008 Week 17

#	Search history	Results
1	((cyp 450 or cytochrome P450 or pharmacogenetic$or genetic$or genotype$) adj test$).tw.	5408
2	amplichip.af.	52
3	Genetic Screening/	16,606
4	or/1–3	20,662
5	cost$.ti.	37,406
6	(cost$adj2 (effective$or utilit$or benefit$or minimi$)).ab.	43,968
7	cost minimization analysis/or cost utility analysis/or health care cost/or cost-effectiveness analysis/or cost benefit analysis/	123,232
8	(cost$adj2 effective$).ti,ab.	40,428
9	(cost$adj2 benefit$).ti,ab.	8075
10	health economics/or economic evaluation/or economics/or pharmacoeconomics/	19,802
11	or/5–10	163,065
12	exp MENTAL DISEASE/or exp MENTAL HEALTH/or exp Antidepressant Agent/ or exp Neuroleptic Agent/or exp ATYPICAL ANTIPSYCHOTIC AGENT/or exp PSYCHIATRY/or exp Schizophrenia/	829,498
13	(antipsychotic$or neuroleptic$or schizophrenia).tw.	61,539
14	12 or 13	831,533
15	4 and 11 and 14	153

SCI-EXPANDED

ISI Web of Knowledge Science Citation Index Expanded

((genetic SAME test*) or ((cyp 450 or cytochrome P450 or pharmacogenetic* or genetic* or genotype*) SAME test*)) AND Topic=((economic* or price* or pricing or pharmacoeconomic* or pharma economic* or cost* or budget*)) AND Topic=((antidepressant* or antipsychotic* or neuroleptic* or schizophrenia or psychiatr* or psychotic*))

Results: 20.

ISI Proceedings

(genetic test* or ((cyp 450 or cytochrome P450 or pharmacogenetic* or genetic* or genotype*) test*)) AND Topic=(economic* or price* or pricing or pharmacoeconomic* or pharma economic* or cost* or budget*) AND Topic=(antidepressant* or antipsychotic* or neuroleptic* or schizophrenia or psychiatr* or psychotic*)

Results: 6.

PsycINFO 1967 to April Week 4 2008

#	Search history	Results
1	((cyp 450 or cytochrome P450 or pharmacogenetic$or genetic$or genotype$) adj test$).tw.	803
2	amplichip.af.	14
3	exp Genetic Testing/	458
4	or/1–3	902
5	exp health care economics/or pharmacoeconomics/or exp "cost containment"/or exp "costs and cost analysis"/or exp health care costs/	11,284
6	(cost$adj2 (effective$or utilit$or benefit$or minimi$)).ab.	8873
7	cost$.ti,ab.	37,125
8	exp "Costs and Cost Analysis"/	11,058
9	or/5–8	40,780
10	exp MENTAL DISORDERS/or exp CHRONIC MENTAL ILLNESS/	308,137
11	exp SCHIZOPHRENIA/or schizophrenia.mp.	69,051
12	exp Neuroleptic Drugs/	18,325
13	exp ANTIDEPRESSANT DRUGS/	25,031
14	(antipsychotic$or neuroleptic$).tw.	22,351
15	exp Serotonin Reuptake Inhibitors/	8121
16	or/10–15	332,865
17	4 and 9 and 16	7

Cochrane

There is one result out of 5320 records for: "(cyp 450 or cytochrome P450 or pharmacogenetic* or genetic* or genotype*) test* in Title, Abstract or Keywords and (antidepressant* or antipsychotic* or neuroleptic* or schizophrenia or psychiatr* or psychotic*) in Title, Abstract or Keywords and (economic* or price* or pricing or pharmacoeconomic* or pharma economic* or cost* or budget*) in Title, Abstract or Keywords in Cochrane Database of Systematic Reviews"

Identification of the available economic models for schizophrenia

Summary table

Database	Years	Search strategy
MEDLINE	2000 to November Week 2 2007	See below
EMBASE	2000 to Week 52 2007	See below
NHS EED	To December 2007	See below
HEED	Issue December 2007	See below
CEA registry	See below	See below
CHE	To January 2008	See below
HTA database	To May 2008	See below
Total after duplicates removed		93

Search strategies

MEDLINE and Pre-MEDLINE (Ovid gateway) 2000 to November Week 2 2007

Searched 3 January 2008.

1. exp SCHIZOPHRENIA/
2. schizophre$.ti,ab.
3. dementia praecox.ti,ab.
4. hebephre$.ti,ab.
5. or/1–4
6. exp Decision Support Techniques/

7. exp models, economic/
8. Markov chains/
9. *Cost-Benefit Analysis/
10. ((economic or econometric or pharmacoeconomic or cost$) adj2 model$).ti,ab.
11. ((mathematical or stochastic or statistical or theoretical) adj2 model$).ti,ab.
12. (decision adj2 (analy$or tree or triage or data or model$)).ti,ab.
13. (crystal adj2 ball).ti,ab.
14. markov.ti,ab.
15. or/6–14
16. 5 and 15
17. limit 16 to yr="2000 – 2008"
18. limit 17 to english language
19. Animals/
20. Humans/
21. 19 not (19 and 20)
22. 18 not 21

EMBASE (Ovid gateway) 2000 to 2007 Week 52
Searched 3 January 2008.

1. exp Schizophrenia/
2. schizophre$.ti,ab.
3. dementia praecox.ti,ab.
4. hebephre$.ti,ab.
5. or/1–4
6. decision support system/
7. statistical model/or stochastic model/or mathematical model/
8. Probability/
9. ((economic or econometric or pharmacoeconomic or cost$) adj2 model$).ti,ab.
10. ((mathematical or stochastic or statistical or theoretical) adj2 model$).ti,ab.
11. (decision adj2 (analy$or tree or triage or data or model$)).ti,ab.
12. (crystal adj2 ball).ti,ab.
13. markov.ti,ab.
14. or/6–13
15. 5 and 14
16. limit 15 to yr="2000 – 2008"
17. limit 16 to english language
18. Animal/or Animal Experiment/or Nonhuman/
19. (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,sh.
20. 18 or 19
21. exp Human/or Human Experiment/
22. 20 not (20 and 21)
23. 17 not 22

NHS EED
CRD database interface (www.crd.york.ac.uk/crdweb/), updated to December 2007.

Searched 3 January 2008.

s schizophre$
s dementia(w)praecox
s hebephre$
s s1 or s2 or s3
s $/xmo
s s4 and s5

HEED
Wiley Interscience online, Issue December 2007.

Searched 3 January 2008.

AX=schizophre*
AX=dementia praecox
AX=hebephr*
CS=1 or 2 or 3
OU=model*
CS=4 and 5

CEA registry
https://research.tufts-nemc.org/cear/default.aspx.

Searched 3 January 2008.

Searched for 'schizophrenia' in the following databases: cost–utility ratios 2002–2003, cost–utility ratios 1976–2001, preference weights 1998–2001, and Preference weights 1976–1997.

CHE website
www.york.ac.uk/inst/che/.

Searched 3 January 2008.

HTA database
www.crd.york.ac.uk/crdweb/.

Searched on 1 May 2008 Search term: 'schizophrenia'.

Appendix 4

Summary of analytical validity studies

Study	*CYP* and alleles tested	Method under study and number tested	Reference methods(s) and number tested	Geographic location/ ethnicity of population	Findings			Brief summary of findings relating to sensitivity and specificity
					Genotype	Number of matching calls (test/reference)	Percent agreement	
Bruning 1997[114]	*1B1* Codon position 432	Real-time PCR; *n* = 300	Sequencing; *n* = NS	Germany/NS	**1/*1*	110/110	100.0	Genotype frequencies presented
					**1/*2*	139/139	100.0	Genotype frequencies show 100% sensitivity and specificity
					**2/*2*	51/51	100.0	
					Total	300/300	100.0	
Burian 2002[108]	*2C9* **1*, **2*, **3*	Real-time PCR; *n* = 118	PCR-RFLP; *n* = 118	Germany/NS	NS	NS	100.0	No relevant genotype data presented
								Stated that the concordance rate between methods was 100% for both polymorphic sites (**2* and **3*)
Casley 2006[106]	*1A2* **1C*, **1F*	Real-time PCR (LightCycler); *n* = NS	PCR-RFLP; *n* = 62	Canada/NS	NS	NS	100.0	No relevant genotype data presented
								Stated accuracy of allelic discrimination was confirmed by 100% concordance with PCR-RFLP methods in genotyping 62 individuals with genotypes represented
Chou 2003[86]	*2D6* **3*, **4*, **5*, **6*, **7*, **9*, **17*, **41*, **1XN*, **2XN/*35XN*, **4XN*	GeneChip; *n* = 232 (AmpliChip forerunner)	AS-PCR; *n* = 232	USA/NS	NS	NS	NS	Allele frequencies provided by each method
								For all alleles, concordance ≥ 99.8%
Crescenti 2007[87]	*2D6* **3*, **4*, **5*, **6*	Multiplex long PCR + SBE; *n* = 290	Allelic discrimination (TaqMan) for **4* and **6*; *n* = 100 PCR-RFLP for **3*; *n* = 100	Spain/NS	*2D6*3*			Genotype frequencies presented for each allele
					**1/*1*	95/95	100.0	Genotype frequencies show 100% sensitivity and specificity with both reference methods
					**1/*3*	5/5	100.0	
					**3/*3*	0/0	100.0	
					Total	100/100	100.0	
					*2D6*4*			
					**1/*1*	51/51	100.0	
					**1/*4*	44/44	100.0	

DOI: 10.3310/hta14030

Study	*CYP* and alleles tested	Method under study and number tested	Reference methods(s) and number tested	Geographic location/ ethnicity of population	Findings			Brief summary of findings relating to sensitivity and specificity
					Genotype	Number of matching calls (test/reference)	Percent agreement	
					*4/*4	5/5	100.0	
					Total	100/100	100.0	
					*2D6*6*			
					*1/*1	96/96	100.0	
					*1/*6	4/4	100.0	
					*6/*6	0/0	100.0	
					Total	100/100	100.0	
Dukek 2006[88] (abstract only)	2C19 2D6	AmpliChip; *n* = 207	Tag-It; *n* = 207 Sequencing for *CYP2D6*41*; *n* = NS	USA/NS	*All 2C19* *All 2D6*	206/207 207/207	99.5 100.0	Limited relevant genotype data presented Stated that there was perfect correlation in 206/207 samples for alleles for *CYP2C19* (99.5% concordance) Stated that there was perfect correlation in 207/207 samples for alleles for *CYP2D6* Stated that AmpliChip improved discrimination between similar alleles (i.e. *41 vs *2 and *35 vs *2)
Eriksson 2002[89]	*2C19* *2, *3, *4* *2C9* *2, *3* *2D6* *2, *3, *4, *6, *7, *8, *14*	Pyrosequencing; *n* = 138 (*2C19*), *n* = 28 (*2C9*), *n* = 117 (*2D6*)	PCR-RFLP; *n* = 138 (*2C19*), *n* = 28 (*2C9*), *n* = 117 (*2D6*)	Sweden/NS	*2C19* *1/*1 *2 homozygous *2 heterozygous *3 homozygous *3 heterozygous *4 homozygous *4 heterozygous	 108/108 5/5 24/24 0/0 0/0 0/0 1/1	 100.0 100.0 100.0 100.0 100.0 100.0 100.0	Genotype frequencies presented for each allele Stated that the two methods were in complete agreement Genotype frequencies show 100% sensitivity and specificity except for *2D6* for which specificity appears to be only 30.8%

continued

Study	*CYP* and alleles tested	Method under study and number tested	Reference methods(s) and number tested	Geographic location/ ethnicity of population	Findings			Brief summary of findings relating to sensitivity and specificity
					Genotype	Number of matching calls (test/reference)	Percent agreement	
					2C9			
					*1/*1	9/9	100.0	
					*2 homozygous	0/0	100.0	
					*2 heterozygous	14/14	100.0	
					*3 homozygous	0/0	100.0	
					*3 heterozygous	10/10	100.0	
					2D6			
					*1/*1	24/78	30.8	
					*2	NA	NA	
					*3 homozygous	1/1	100.0	
					*3 heterozygous	4/4	100.0	
					*4 homozygous	5/5	100.0	
					*4 heterozygous	32/32	100.0	
					*6	NA	NA	
					*7	NA	NA	
					*8,*14	NA	NA	
						NA because PCR-RFLP does not determine these alleles	NA because PCR-RFLP does not determine these alleles	
Fredericks 2005[115]	*3A5* *1, *3	Real-time PCR (LightCycler); *n* = 263	Sequencing; *n* = 21	UK/Middle Eastern = 13, Indian = 145, Black = 29, Caucasian = 130, Nepalese = 13, Ethiopian = 33	NS	NS	100.0	No relevant genotype data presented Stated 100% concordance between test and reference in subset of 21 samples compared

Study	*CYP* and alleles tested	Method under study and number tested	Reference methods(s) and number tested	Geographic location/ ethnicity of population	Findings			Brief summary of findings relating to sensitivity and specificity
					Genotype	Number of matching calls (test/reference)	Percent agreement	
Harth 2001[116]	*1A1* **1, *2, *3*	Real-time PCR (LightCycler); *n* = 300	PCR-RFLP; *n* = 300 Sequencing; *n* = 20	Germany/ Caucasian	NS	NS	95.0% with PCR-RFLP and 100% with sequencing	No relevant genotype data presented Stated that there was a 5% discordancy rate between the methods
Heller 2005[90]	*2D6*	AmpliChip; *n* = 47	PCR-RFLP; *n* = 47	Germany/NS	NS	NS	NS	No relevant genotype data presented
Heller 2006[91]	*2D6* 29 SNPs tested	AmpliChip; *n* = 159	PCR-RFLP; *n* = 159 SNaPshot for duplications; *n* = 43 Sequencing; *n* = 1 (discordant cases)	Germany/NS	**1/*1*	18/18	100	Stated that genotype frequencies identical in 45/47 samples In other 2/47 samples, allele assignment also consistent Genotype frequencies presented for AmpliChip and corresponding readings by PCR-RFLP, SNaPshot and sequencing Stated concordance between AmpliChip and PCR-RFLP is 95.6% Genotype frequencies show overall concordance with RFLP is 152/159 (95.6%) Genotype frequencies show 100% sensitivity and 95% specificity with RFLP Of discordant cases, 6/7 agreed with SNaPshot with remaining 1/7 agreeing with sequencing
					**1/*2*	15/15	100.0	
					**1/*3*	3/3	100.0	
					**1/*4*	11/11	100.0	
					**1/*5*	8/8	100.0	
					**1/*6*	3/3	100.0	
					**1/*9*	1/1	100.0	
					**1/*10*	5/5	100.0	
					**1/*35*	4/4	100.0	
					**1/*41*	7/7	100.0	
					**2/*2*	3/3	100.0	
					**2/*4*	2/2	100.0	
					**2/*5*	4/4	100.0	
					**2/*35*	3/3	100.0	
					**5/*35*	1/1	100.0	
					**35/*35*	4/4	100.0	
					**35/*41*	1/1	100.0	
					**1XN/*4*	3/3	100.0	

continued

Study	*CYP* and alleles tested	Method under study and number tested	Reference methods(s) and number tested	Geographic location/ ethnicity of population	Findings			Brief summary of findings relating to sensitivity and specificity
					Genotype	Number of matching calls (test/reference)	Percent agreement	
					*1XN/*5	1/1	100.0	Findings are also presented by phenotype and genotype – in the samples, when genotyping by AmpliChip and PCR-RFLP differed, the different genotypes did not affect the classification into one of the phenotypic groups (PM, IM, EM or UM). However, the semiquantitative gene dose was different in 6/7 samples when PCR-RFLP overestimated these in comparison with AmpliChip
					*1XN/*9	1/1	100.0	
					*1XN/*41	3/3	100.0	
					*2XN/*4	3/3	100.0	
					*2XN/*6	1/1	100.0	
					*2XN/*41	2/2	100.0	
					*4XN/*1	1/1	100.0	
					*35XN/*5	1/1	100.0	
					*4/*41	3/3	100.0	
					*5/*41	3/3	100.0	
					*1XN/*1	11/11	100.0	
					*1XN/*2	1/1	100.0	
					*2XN/*1	5/5	100.0	
					*2XN/*2	1/1	100.0	
					*2XN/*35	3/3	100.0	
					*2XN/*41	1/1 (a)	100.0	
					*3/*3	1/1	100.0	
					*3/*4	3/3	100.0	
					*3/*5	1/1	100.0	
					*4/*4	3/3	100.0	
					*4/*5	3/3	100.0	
					*4/*6	3/3	100.0	
					*4XN/*41	0/0	100.0	
					*5/*5	1/1	100.0	
					*5/*6	1/1	100.0	
					*10XN/*1	1/1 (b)	100.0	
					*35XN/*1	1/1 (b)	100.0	
					*41XN/*1	1/1 (b)	100.0	

Study	*CYP* and alleles tested	Method under study and number tested	Reference methods(s) and number tested	Geographic location/ ethnicity of population	Findings			Brief summary of findings relating to sensitivity and specificity
					Genotype	Number of matching calls (test/reference)	Percent agreement	
					*41XN/*1	1/1 (b)	100.0	
					*41XN/*2	1/1 (b)	100.0	
					*41XN/*4	1/1 (b)	100.0	
					Total	159/159	100.0	
						NB: All with PCR-RFLP except for: (a) sequencing, (b) SNaPshot		
Hersberger 2000[92]	*2D6* *3, *4, *5, *6	Tetra-primer PCR for *3, *4 and *6; *n* = 57 Multiplex long PCR for *5; *n* = 57	PCR-RFLP; *n* = 57 Sequencing; *n* = 5 (*2D6*3*), n = 8 (*2D6*4*), n = 6 (*2D6*6*)	Switzerland/ NS (stated only 'European subjects')	*2D6*3*			Genotype data presented only for that confirmed by sequencing Genotype frequencies show 100% sensitivity and specificity Stated that reanalysis by reference methods confirmed allele frequencies by test
					*3/*3	0/0	100.0	
					*3/*1	3/3	100.0	
					*1/*1	2/2	100.0	
					Total	5/5	100.0	
					*2D6*4*			
					*4/*4	2/2	100.0	
					*4/*1	4/4	100.0	
					*1/*1	2/2	100.0	
					Total	8/8	100.0	
					*2D6*6*			
					*6/*6	0/0	100.0	
					*6/*1	2/2	100.0	
					*1/*1	4/4	100.0	
					Total	6/6	100.0	

continued

Study	*CYP* and alleles tested	Method under study and number tested	Reference methods(s) and number tested	Geographic location/ ethnicity of population	Findings			Brief summary of findings relating to sensitivity and specificity
					Genotype	Number of matching calls (test/reference)	Percent agreement	
Innocenti 2006[117]	*2E1* **1*, **5B*	SNuPE; *n* = 114	PCR-RFLP; *n* = 114	Italy/Caucasian	With PCR-RFLP	With PCR-RFLP	With PCR-RFLP	Limited genotype data presented
					**1/*1*	113/113	100.0	Stated results consistent (100% accuracy) with reference methods
					**1/*5B*	1/1	100.0	
					**5B/*5B*	0/0	100.0	Genotype frequencies show 100% sensitivity and specificity
					Total	114/114	100.0	
James 2004[93]	*2D6* **2*, **3*, **4*, **5*, **6*, **7*, **8*, **9*, **10*, **16*, **41*	Direct sequencing; *n* = 64	AS-PCR; *n* = 39	Australia/ Caucasian	NS	NS	NS	No relevant genotype data presented Stated that with the exception of two samples, for which the AS-PCR result was uncertain, there was 'agreement' between methods
Labuda 1999[118]	*1A1* **1*, **2A*, **2B* *2D6* **3*, **4*	Multiplex PCR + ASO; *n* = 428	PCR-RFLP; *n* = 428	Canada/French Canadian	NS	NS	NS	No relevant genotype data presented Stated that there is 'good agreement' between methods
Lee 2007[94]	*2D6* **3*, **4*, **5*, **6*, **7*, **8*	Pyrosequencing; *n* = 200	NanoChip Molecular Biology Workstation; *n* = 200 Sequencing; *n* = 8	USA/NS	NS	NS	99.4% (1392/1400)	Only data on genotype discrepancies presented (8/1400 samples) Stated found 99.4% concordance between methods

Study	*CYP* and alleles tested	Method under study and number tested	Reference methods(s) and number tested	Geographic location/ ethnicity of population	Findings			Brief summary of findings relating to sensitivity and specificity
					Genotype	Number of matching calls (test/reference)	Percent agreement	
Melis 2006[95]	*2C19* *2, *3, *4, *5, *6, *7, *8 *2C9* *2, *3, *4, *5, *6 *2D6* *2, *3, *4, *5, *6, *7, *8, *9, *10, *11, *12, *17, *Xn	Tag-It; *n* = 150	AmpliChip; *n* = 150	USA/Caucasian (*n* = 100), Japanese (*n* = 10), Chinese (*n* = 10), African American (*n* = 10), SE Asia (*n* = 10), Middle East (*n* = 10)	*2C19*			Stated that no discrepancies found with AmpliChip indicating > 99% analytical sensitivity and specificity Stated that *2D6* assays less robust than *2C9* and *2C19* assays Genotype frequencies show 100% sensitivity and specificity
					**1/*1*	95/95	100.0	
					**2/*1*	41/41	100.0	
					**2/*2*	6/6	100.0	
					**2/*3*	2/2	100.0	
					**2/*4*	1/1	100.0	
					**3/*1*	3/3	100.0	
					**8/*1*	2/2	100.0	
					2C9			
					**1/*1*	99/99	100.0	
					**2/*1*	30/30	100.0	
					**2/*2*	1/1	100.0	
					**2/*3*	4/4	100.0	
					**3/*1*	15/15	100.0	
					**3/*3*	1/1	100.0	
					2D6			
					**1/*1*	24/24	100.0	
					**2A/*1*	14/14	100.0	
					**2A/*2A*	7/7	100.0	
					**2A/*3*	1/1	100.0	
					**2A/*4*	11/11	100.0	
					**2A/*9*	1/1	100.0	
					**2A/*10*	4/4	100.0	
					**2A/*17*	2/2	100.0	
					**2A/2850C>T*	7/7	100.0	
					**4/*1*	15/15	100.0	

continued

Study	*CYP* and alleles tested	Method under study and number tested	Reference methods(s) and number tested	Geographic location/ ethnicity of population	Findings			Brief summary of findings relating to sensitivity and specificity
					Genotype	Number of matching calls (test/reference)	Percent agreement	
					**4/*4*	3/3	100.0	
					**4/*10*	2/2	100.0	
					**4/2850C>T*	7/7	100.0	
					**5/*1*	2/2	100.0	
					**5/*2A*	2/2	100.0	
					**5/*4*	2/2	100.0	
					**5/*9*	1/1	100.0	
					**5*10*	1/1	100.0	
					**5/*17*	1/1	100.0	
					*2850C>T/*1*	8/8	100.0	
					2850C>T/2850C>T	1/1	100.0	
					**6/*1*	1/1	100.0	
					**9/*1*	2/2	100.0	
					**10/*1*	14/14	100.0	
					**10/*10*	5/5	100.0	
					**10/2850C>T*	2/2	100.0	
					**17/*1*	1/1	100.0	
					**17/*17*	1/1	100.0	
					**17/2850C>T*	1/1	100.0	
					*DUP *1/*1*	1/1	100.0	
					*DUP *2A/*1*	1/1	100.0	
					*DUP *2A/*2A*	1/1	100.0	
					*DUP *2A/*4*	1/1	100.0	
					*DUP *2A/17*	1/1	100.0	
					*DUP *10/*1*	1/1	100.0	
					*DUP 2850C>T/*1*	1/1	100.0	

Study	*CYP* and alleles tested	Method under study and number tested	Reference methods(s) and number tested	Geographic location/ ethnicity of population	Findings			Brief summary of findings relating to sensitivity and specificity
					Genotype	Number of matching calls (test/reference)	Percent agreement	
Mizugaki 2000[113]	*2C19*	Real-time PCR (AS TaqMan); *n* = 144	PCR-RFLP; *n* = 144	Japan/Japanese	NS	NS	NS	No relevant genotype data presented Stated that all of the genotypes determined by both methods were consistent
Muller 2003[96]	*2D6* **2, *3, *4, *6, *7, *8, *35*	Real-time PCR (LightCycler); *n* = 105 (deletion and duplication), *n* = 116 (preamplification)	Multiplex PCR for **3, *4, *6, *7* and **8*; *n* = NS PCR-RFLP for **2*; *n* = NS Real-time PCR for **5* and deletions/ duplications; *n* = NS Nearest neighbour model for **35*; *n* = 69	Germany/NS	**35* *31G* *31A* *G/A* Total	60/60 2/2 7/7 69/69	100.0 100.0 100.0 100.0	Limited relevant genotype data presented Stated identical results obtained between methods Genotype frequencies show 100% sensitivity
Muthiah 2004[119]	*2C8* **1, *2, *3, *4*	Multiplex PCR; *n* = NS	Sequencing; *n* = 57	Malaysia/ Malaysian Indian	**1/*1* **1/*2* **1/*3* **1/*4* Total	52/52 2/2 3/3 0/0 57/57	100.0 100.0 100.0 100.0 100.0	Genotype frequencies presented for controls Stated that these confirmed test results Genotype frequencies show 100% sensitivity and specificity
Neville 2002[97]	*2D6* **2, *3, *4, *6, *10, *11, *18, *33, *35, *37*	Invader assay; *n* = 174/181	Long-range PCR; *n* = 171/181 (10 samples generated no visible product)	USA/NS	NS	NS	NS	No relevant genotype data presented Stated 16/17 deletions and 11/17 duplications detected by Invader test confirmed by long-range PCR

continued

Study	*CYP* and alleles tested	Method under study and number tested	Reference methods(s) and number tested	Geographic location/ ethnicity of population	Findings			Brief summary of findings relating to sensitivity and specificity
					Genotype	Number of matching calls (test/reference)	Percent agreement	
Nielsen 2007[98]	*2D6* 4469 C>T **1*, **2*, **3*, **4*, **5*, **6*, **9*, **10*, **15*, **41*	One-step SimpleProbes analysis; *n* = 144	PCR-RFLP *n* = 144	Germany/NS	**1/*1*	29/29	100.0	Genotype frequencies presented Stated that the results of the test correspond completely with the PCR-RFLP results Genotype frequencies show 100% sensitivity and specificity
					**1/*2*	21/21	100.0	
					**1/*4*	23/23	100.0	
					**1/*5*	3/3	100.0	
					**1/*9*	5/5	100.0	
					**1/*10*	1/1	100.0	
					**1/*15*	1/1	100.0	
					**1/*41*	4/4	100.0	
					**2/*2*	15/15	100.0	
					**2/*3*	2/2	100.0	
					**2/*4*	8/8	100.0	
					**2/*5*	4/4	100.0	
					**2/*6*	1/1	100.0	
					**2/*9*	1/1	100.0	
					**2/*41*	9/9	100.0	
					**4/*4*	7/7	100.0	
					**4/*6*	2/2	100.0	
					**4/*9*	2/2	100.0	
					**4/*10*	1/1	100.0	
					**6/*6*	1/1	100.0	
					**6/*9*	1/1	100.0	
					**9/*41*	3/3	100.0	
					Total	144/144	100.0	

DOI: 10.3310/hta14030

Study	*CYP* and alleles tested	Method under study and number tested	Reference methods(s) and number tested	Geographic location/ ethnicity of population	Findings			Brief summary of findings relating to sensitivity and specificity
					Genotype	Number of matching calls (test/reference)	Percent agreement	
Oyama 1995[120]	*1A1*	PCR-RFLP; *n* = 240	AS-PCR; *n* = 6	Japan/Japanese	*Val/Val*	2/2	100.0	Genotype frequencies presented for controls
					Ile/Val	2/2	100.0	Stated that these confirmed test results
					Ile/Ile	2/2	100.0	Genotype frequencies show 100% sensitivity and specificity
					Total	6/6	100.0	
Pickering 2004[109]	*2C9* **2*, **3*	Multiplex PCR + Luminex XMap System; *n* = 101	Microarray (eSensor); *n* = 49	USA/NS	NS	NS	100.0	No relevant genotype data presented
								Stated that there was 100% agreement between the two methods for all 49 samples
Popp 2003[107]	*1A2* **1F*	Real-time PCR; *n* = 101	PCR-RFLP; *n* = 101	Germany/ Caucasian	*–164C/C*	6/6	100.0	Genotype frequencies presented
					–164C/A	41/41	100.0	Stated genotypes determined by both methods in 100% concordance
					–164A/A	54/54	100.0	Genotype frequencies show 100% sensitivity and specificity
					Total	101/101	100.0	
Roberts 2000[99]	*2D6* **3*, **4*, **6*, **8*, **11*, **12*, **14*, **15*, **19*, **20*	Multiplex PCR; *n* = NS	PCR-RFLP; *n* = 100	New Zealand/ NS	**1/*1*	84/84	100.0	Applicable genotype frequencies from controls (i.e. those possessing alleles detectable by test) presented for test (i.e. those genotypes that the test could ascertain)
					**1/*4*	17/17	100.0	
					**4/*4*	5/5	100.0	
					**1/*3*	2/2	100.0	
					**1/*6*	3/3	100.0	
					**2/*3, *4 or *6*	16/16	100.0	Stated that test found alleles in controls with 100% accuracy
								Genotype frequencies show 100% sensitivity and specificity

continued

Study	*CYP* and alleles tested	Method under study and number tested	Reference methods(s) and number tested	Geographic location/ ethnicity of population	Findings			Brief summary of findings relating to sensitivity and specificity
					Genotype	Number of matching calls (test/reference)	Percent agreement	
Roche 2004[100]	*2D6* **1*, **2*, **3*, **4ABDJK*, **5*, **6ABC*, **7*, **8*, **9*, **10AB*, **11*, **15*, **17*, **19*, **20*, **29*, **35*, **36*, **41*, **1XN*, **2XN*, **10XN*, **17XN*, **35XN*, **41XN*	AmpliChip; $n=403$	Sequencing; $n=246$ AS-PCR; $n=343$ PCR-RFLP; $n=58$ PCR size (**5* only); $n=2$ NB: $n \neq 403$ as some samples tested by a combination of methods	NS/NS	**1/*1*	31/31	100	Genotype frequencies presented Genotype frequencies show 99.2% sensitivity and 100% specificity
					**1/*1XN*	5/5	100	
					**1/*2A*	30/30	100	
					**1/*2AXN*	1/2	50	
					**1/*2D*	1/1	100	
					**1/*2DXN*	1/1	100	
					**1/*3*	2/2	100	
					**1/*4A*	30/30	100	
					**1/*4AXN*	1/1	100	
					**1/*4D*	1/1	100	
					**1/*4DXN*	1/1	100	
					**1/*5*	15/15	100	
					**1/*6B*	3/3	100	
					**1/*9*	2/2	100	
					**1/*10B*	16/16	100	
					**1/*10BXN*	1/1	100	
					**1/*17*	13/13	100	
					**1/*17XN*	1/1	100	
					**1/*29*	2/2	100	
					**1/*35*	13/13	100	
					**1/*35XN*	1/1	100	
					**1/*40*	1/1	100	
					**1/*41*	14/14	100	
					**1XN/*2A*	2/3	66.7	

Study	*CYP* and alleles tested	Method under study and number tested	Reference methods(s) and number tested	Geographic location/ ethnicity of population	Findings			Brief summary of findings relating to sensitivity and specificity
					Genotype	Number of matching calls (test/reference)	Percent agreement	
					*1XN/*4A	4/4	100	
					*1XN/*10A	1/1	100	
					*1XN/*35	1/1	100	
					*1XN/*41	2/2	100	
					*2A/*2A	16/16	100	
					*2A/*3	1/1	100	
					*2A/*4A	20/20	100	
					*2A/*5	4/4	100	
					*2A/*6B	2/2	100	
					*2A/*9	2/2	100	
					*2A/*10B	2/2	100	
					*2A/*35	8/8	100	
					*2A/*41	5/5	100	
					*2AXN/*17	2/2	100	
					*2AXN/*41	2/2	100	
					*3/*3	2/2	100	
					*3/*4A	3/3	100	
					*3/*5	2/2	100	
					*3/*35	1/1	100	
					*3/*41	1/1	100	
					*4A/*4A	23/23	100	
					*4A/*4D	1/1	100	
					*4A/*5	2/2	100	
					*4A/*6B	2/2	100	
					*4A/*9	2/2	100	
					*4A/*15	1/1	100	
					*4A/*35	4/4	100	

continued

Study	*CYP* and alleles tested	Method under study and number tested	Reference methods(s) and number tested	Geographic location/ ethnicity of population	Findings			Brief summary of findings relating to sensitivity and specificity
					Genotype	Number of matching calls (test/reference)	Percent agreement	
					**4A/*41*	11/11	100	
					**4D/*5*	1/1	100	
					**4D/*41*	2/2	100	
					**4DXN/*5*	1/1	100	
					**4DXN/*17*	1/1	100	
					**5/*5*	2/2	100	
					**5/*9*	2/2	100	
					**5/*10B*	1/1	100	
					**5/*10BXN*	2/2	100	
					**5/*17*	4/4	100	
					**5/*29*	1/1	100	
					**5/*35*	2/2	100	
					**5/*41*	7/7	100	
					**6B/*41*	1/1	100	
					**9/*17*	1/1	100	
					**9/*41*	1/1	100	
					**10B/*10B*	16/17	94.1	
					**10B/*10BXN*	2/2	100	
					**10B/*17*	2/2	100	
					**10B/*35*	1/1	100	
					**10B/*36*	1/1	100	
					**10B/*40*	1/1	100	
					**10B/*41*	2/2	100	
					**10BXN/*4*	1/1	100	
					**17/*17*	4/4	100	
					**17/*29*	2/2	100	
					**17/*41*	3/3	100	
					**29/*29*	1/1	100	

Study	*CYP* and alleles tested	Method under study and number tested	Reference methods(s) and number tested	Geographic location/ ethnicity of population	Findings			Brief summary of findings relating to sensitivity and specificity
					Genotype	Number of matching calls (test/reference)	Percent agreement	
					**29/*36*	1/1	100	
					**29/*41*	4/4	100	
					**35/*35*	1/1	100	
					**35/*41*	4/4	100	
					**41/*41*	9/9	100	
					**41/*41XN*	1/1	100	
					Total	400/403	99.3%	
Roche 2005[5]	*2C19* **1, *2, *3*	AmpliChip; *n* = 399	Sequencing; *n* = 122	NS/NS	By PCR-RFLP	By PCR-RFLP	By PCR-RFLP	Genotype frequencies presented
			PCR-RFLP; *n* = 399		**1/*1*	270/270	100.0	Genotype frequencies show 99.6% sensitivity and 100% specificity
					**1/*2*	101/101	100.0	
					**1/*3*	6/6	100.0	
					**2/*2*	14/14	100.0	
					**2/*3*	6/6	100.0	
					**2/*10*	0/1	0%	
					**3/*3*	1/1	100.0%	
					Total	398/399	99.7%	
Rohrbacher 2006[121]	*2B6* **1, *4, *5, *6, *7*	Pyrosequencing; *n* = 273	Sequencing; *n* = 31	Germany/ Caucasian	NS	NS	100.0%	No relevant genotype data presented Stated that results were in 'complete agreement' between methods
Schaeffeler 2003[101]	*2D6* **1, *2, *2XN, *3, *4, *5, *6, *7, *8, *9, *10, *16, *17, *35, *41*	Real-time PCR (TaqMan); *n* = NS	Previously determined genotypes by method NS; *n* = 64	Germany/ Caucasian	NS	NS	NS	No relevant genotype data presented Stated that test results were in complete agreement with controls except in one instance in which an unclear result was obtained

continued

Study	*CYP* and alleles tested	Method under study and number tested	Reference methods(s) and number tested	Geographic location/ ethnicity of population	Findings			
					Genotype	Number of matching calls (test/reference)	Percent agreement	Brief summary of findings relating to sensitivity and specificity
Soderback 2005[102]	*2D6* **1, *2, *3, *4, *5, *6*	Pyrosequencing; *n* = 470	Long-range PCR; *n* = 270	Sweden/NS	All	267/270	96.3%	Limited relevant genotype data presented Stated that reference method verified these findings
Stamer 2002[103]	*2D6* **3, *4, *5, *6, *7, *8*	Real-time PCR; *n* = 323	AS-PCR; *n* = 323	Germany/ Caucasian	**5* homozygous	1/1	100.0	Allele frequencies presented Stated found 14 genotypes
					**5* heterozygous	12/12	100.0	Limited relevant genotype data presented
					Total	13/13	100.0	Stated that test presented 100% reliable results as confirmed by sequencing (unlike AS-PCR, which was 89.9%) Genotype frequencies show 100% sensitivity for **5*
Stuven 1996[104]	*2D6* **3, *4, *6, *7, *8*	Long-distance multiplex AS-PCR; *n* = NS	Multiplex PCR; *n* = 84	Germany/ Caucasian	NS	NS	NS	No relevant genotype data presented Stated that 12 genotypes found and all were correctly identified by test Stated that all 5 null alleles tested for were correctly identified
Toriello 2006[110]	*2C9* **1, *2, *3*	Real-time PCR (TaqMan); *n* = 114	Real-time PCR (LightCycler) *n* = 114	Italy/Caucasian	NS	NS	NS	No relevant genotype data presented Stated that there was 100% concordance in the genotyping results obtained with the two methods

Study	*CYP* and alleles tested	Method under study and number tested	Reference methods(s) and number tested	Geographic location/ ethnicity of population	Findings			Brief summary of findings relating to sensitivity and specificity
					Genotype	Number of matching calls (test/reference)	Percent agreement	
Weise 2004[122]	*2C8* **2*, *3, *4*	Real-time PCR; *n* = 122	PCR-RFLP; *n* = 122	Germany/ Caucasian	**1* homozygous	95/95	100.0	Genotype and allele frequencies presented
			'Some' samples had to be repeated with classical PCR because of incomplete enzymatic digestion		**2* heterozygous	2/2	100.0	Stated that results of all analysed samples were identical for both methods except that some had to be repeated with classical PCR because of incomplete enzymatic digestion
					**2* homozygous	0/0	100.0	
					**3* heterozygous	16/16	100.0	
					**3* homozygous	0/0	100.0	
					*3/*4	1/1	100.0	
					**4* heterozygous	8/8	100.0	Genotype frequencies show 100% sensitivity and specificity
					**5* homozygous	0/0	100.0	
Weise 2006[123]	*2C8* **2*, *3, *4*	Triplex real-time PCR; *n* = 200	Real-time PCR; *n* = 200	NS/African	NS	NS	NS	No relevant genotype data presented
								Stated that repeated runs by different investigators revealed same results (presumably with 'older method' but this unclear)
Wen 2003[111]	*2C9* **2*, *3, *4, *5*	Microarray; *n* = 62	Sequencing; *n* = 20	China/Chinese	NS	NS	NS	No relevant genotype data presented
								Stated that the same genotype results were obtained with the 20 DNA samples typed with the two methods
Wen 2004[124]	*3A4* **1B, *1C, *2, *4, *5, *6, *8, *11, *12, *13, *17, *18*	Microarray; *n* = 387	Sequencing; *n* = 30	China/Chinese	NS	NS	NS	No relevant genotype data presented
								'All samples were in concordance with the two genotyping methods'

continued

Study	*CYP* and alleles tested	Method under study and number tested	Reference methods(s) and number tested	Geographic location/ ethnicity of population	Findings			Brief summary of findings relating to sensitivity and specificity
					Genotype	Number of matching calls (test/reference)	Percent agreement	
Wu 2002[125]	*1A1*	Colorimetric hybridisation; n = NS	PCR-RFLP; *n* = NS	China/Chinese	NS	NS	NS	Presents effect of hybridisation temperature on ratios for wild-type and mutant samples in m1 and m2 sites and comparison of reference method (controls) with obtained ratios It is stated that the results demonstrate the feasibility of this assay to detect *CYP1A1* polymorphisms
Zackrisson 2003[105]	*2D6* **1*, **2*, **3*, **4*, **5*, **6*	Pyrosequencing for **1*, **2*, **3*, **4* and **6*; *n* = 282 Long multiplex PCR for **5*; *n* = 282	AS-PCR; *n* = 20	Sweden/NS	All *2D6*	19/20	95.0%	Limited relevant genotype data presented Identical genotype in 19/20 samples Failure due to lack of visible control elements in AS amplifications
Zainuddin 2003[112]	*2C9*	Multiplex PCR; *n* = 40	Sequencing; *n* = 40	Malaysia/ Malaysian Indian	*1/*1	28/28	100.0	Genotype frequencies presented for samples tested by both methods
					*1/*2	3/3	100.0	
					*1/*3	5/5	100.0	Test found to be reproducible and specific when tested against controls
					*2/*2	0/0	100.0	
					*2/*3	2/2	100.0	
					*3/*3	2/2	100.0	Genotype frequencies show 100% sensitivity and specificity
					Total	40/40	100.0	

NA, not applicable; NS, not stated.

Appendix 5

Clinical validity findings – forest plots for non-significant findings

Review: The clinical effectiveness and cost-effectiveness of testing for cytochrome P450 polymorphisms in patients treated with antipsychotics
Comparison: 01 CYP2D6 – total number of patients with tardive dyskinesia
Outcome: 01 mut/mut vs wt/wt

Study or subcategory	mut/mut n/N	wt/wt n/N	OR (random) 95% CI	Weight %	OR (random) 95% CI
01 Asian					
Ohmori 1998[153]	11/30	4/26		10.84	3.18 (0.87 to 11.67)
Nikoloff 2002[152]	26/49	20/43		15.93	1.30 (0.57 to 2.95)
Inada 2003[140]	4/39	10/78		11.48	0.78 (0.23 to 2.66)
Liou 2004[149]	27/48	39/87		17.29	1.58 (0.78 to 3.22)
Fu 2006[138]	15/35	37/50		14.74	0.26 (0.10 to 0.66)
Subtotal (95% CI)	201	284		70.28	1.03 (0.47 to 2.26)
Total events: 83 (mut/mut), 110 (wt/wt)					
Test for heterogeneity: $\chi^2 = 13.24$, df = 4 ($p = 0.010$), $I^2 = 69.8\%$					
Test for overall effect: $z = 0.08$ ($p = 0.93$)					
02 Caucasian					
Andreassen 1997[127]	5/10	30/61		10.50	1.03 (0.27 to 3.94)
Scordo 2000[158]	2/4	8/71		5.86	7.88 (0.97 to 63.89)
Jaanson 2002[142]	1/4	6/35		4.66	1.61 (0.14 to 18.26)
Lohmann 2003[150]	4/7	31/68		8.70	1.59 (0.33 to 7.66)
Subtotal (95% CI)	25	235		29.72	1.75 (0.74 to 4.11)
Total events: 12 (mut/mut), 75 (wt/wt)					
Test for heterogeneity: $\chi^2 = 2.62$, df = 3 ($p = 0.45$), $I^2 = 0\%$					
Test for overall effect: $z = 1.27$ ($p = 0.20$)					
Total (95% CI)	226	519		100.00	1.23 (0.69 to 2.21)
Total events: 95 (mut/mut), 185 (wt/wt)					
Test for heterogeneity: $\chi^2 = 16.98$, df = 8 ($p = 0.03$), $I^2 = 52.9\%$					
Test for overall effect: $z = 0.70$ ($p = 0.49$)					

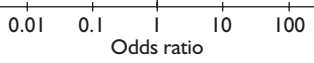


FIGURE 6 *Meta-analysis for patients tested for the* CYP2D6 *genotype – total number of patients with tardive dyskinesia: (a)* wt/wt *vs* mut/mut.

Review: The clinical effectiveness and cost-effectiveness of testing for cytochrome P450 polymorphisms in patients treated with antipsychotics
Comparison: 01 CYP2D6 – total number of patients with tardive dyskinesia
Outcome: 02 wt/mut vs wt/wt

Study or subcategory	wt/mut *n/N*	wt/wt *n/N*	OR (random) 95% CI	Weight %	OR (random) 95% CI
01 Asian					
Ohmori 1998[153]	9/43	4/26		6.54	1.46 (0.40 to 5.31)
Nikoloff 2002[152]	64/110	20/43		12.69	1.60 (0.79 to 3.25)
Inada 2003[140]	13/97	10/78		10.37	1.05 (0.43 to 2.55)
Liou 2004[149]	47/81	39/87		14.16	1.70 (0.92 to 3.13)
Fu 2006[138]	30/64	37/50		11.43	0.31 (0.14 to 0.69)
Subtotal (95% CI)	395	284		55.19	1.05 (0.55 to 2.02)
Total events: 163 (wt/mut), 110 (wt/wt)					
Test for heterogeneity: $\chi^2 = 12.85$, df = 4 ($p = 0.01$), $I^2 = 69.9\%$					
Test for overall effect: $z = 0.15$ ($p = 0.88$)					
02 Caucasian					
Andreassen 1997[127]	16/29	30/61		10.33	1.27 (0.52 to 3.09)
Kapitany 2007	13/16	13/28		5.51	5.00 (1.16 to 21.50)
Scordo 2000[158]	5/44	8/71		7.35	1.01 (0.31 to 3.31)
Ellingrod 2002b[137]	12/26	3/11		5.11	2.29 (0.49 to 10.61)
Jaanson 2002[142]	4/13	6/35		5.45	2.15 (0.49 to 9.34)
Lohmann 2003[150]	15/34	31/68		11.06	0.94 (0.41 to 2.16)
Subtotal (95% CI)	162	274		44.81	1.42 (0.90 to 2.24)
Total events: 65 (wt/mut), 91 (wt/wt)					
Test for heterogeneity: $\chi^2 = 4.86$, df = 5 ($p = 0.43$), $I^2 = 0\%$					
Test for overall effect: $z = 1.51$ ($p = 0.13$)					
Total (95% CI)	557	558		100.00	1.25 (0.84 to 1.86)
Total events: 228 (wt/mut), 201 (wt/wt)					
Test for heterogeneity: $\chi^2 = 18.42$, df = 10 ($p = 0.05$), $I^2 = 45.7\%$					
Test for overall effect: $z = 1.10$ ($p = 0.27$)					

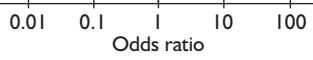


FIGURE 6 *Meta-analysis for patients tested for the* CYP2D6 *genotype – total number of patients with tardive dyskinesia: (b)* wt/wt *vs* wt/mut.

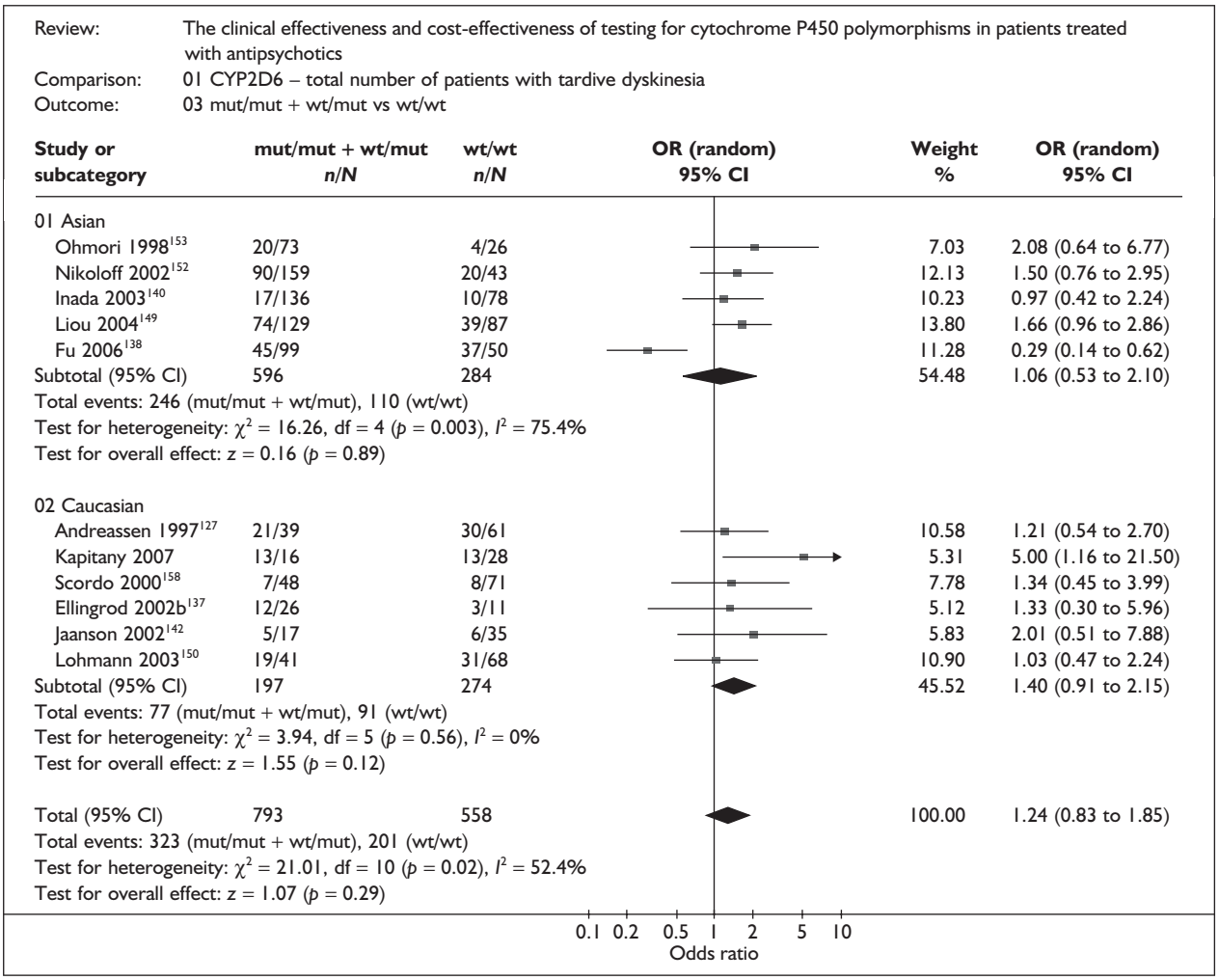


FIGURE 6 *Meta-analysis for patients tested for the* CYP2D6 *genotype – total number of patients with tardive dyskinesia: (c)* wt/wt *vs* mut/mut + wt/mut

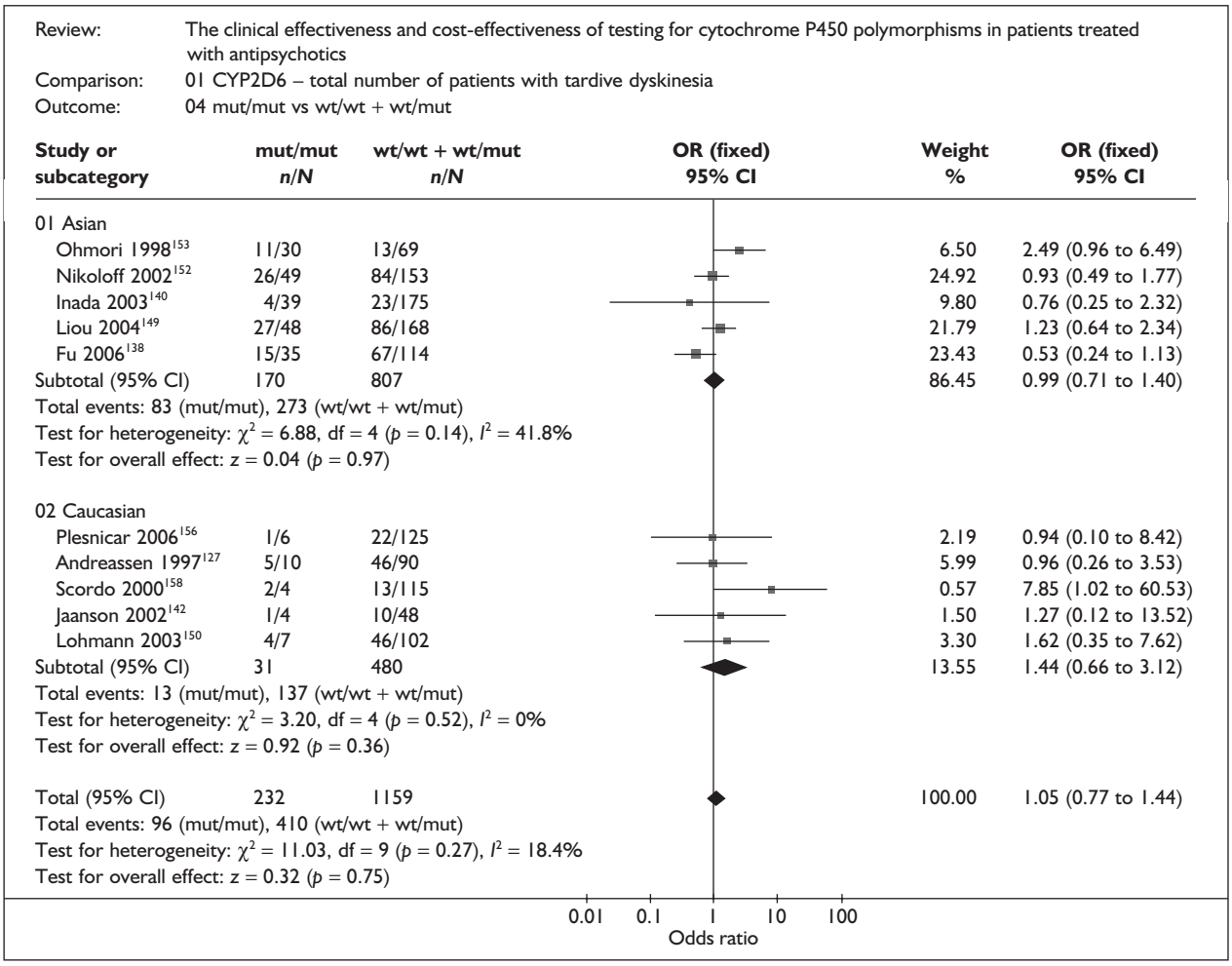
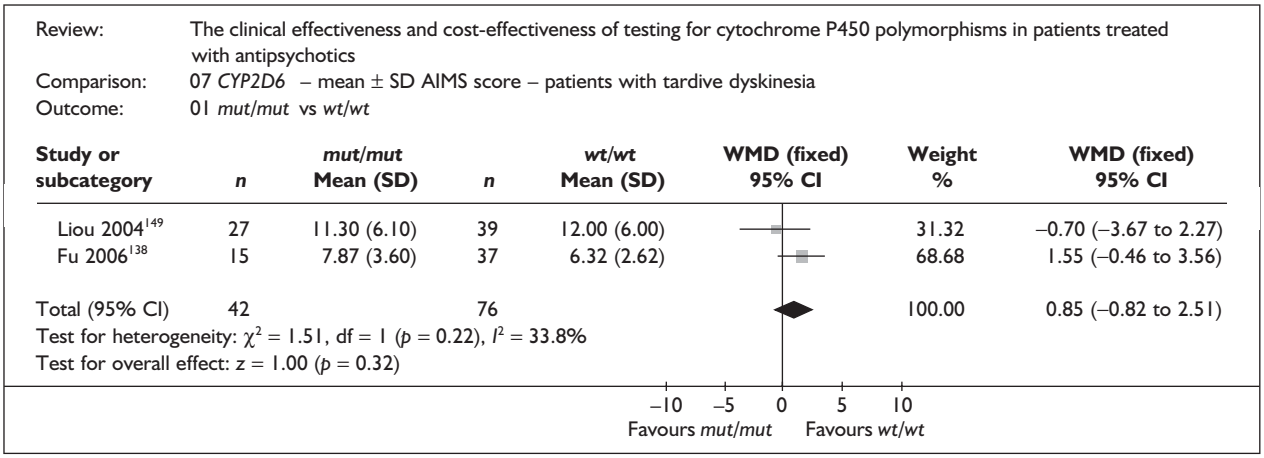
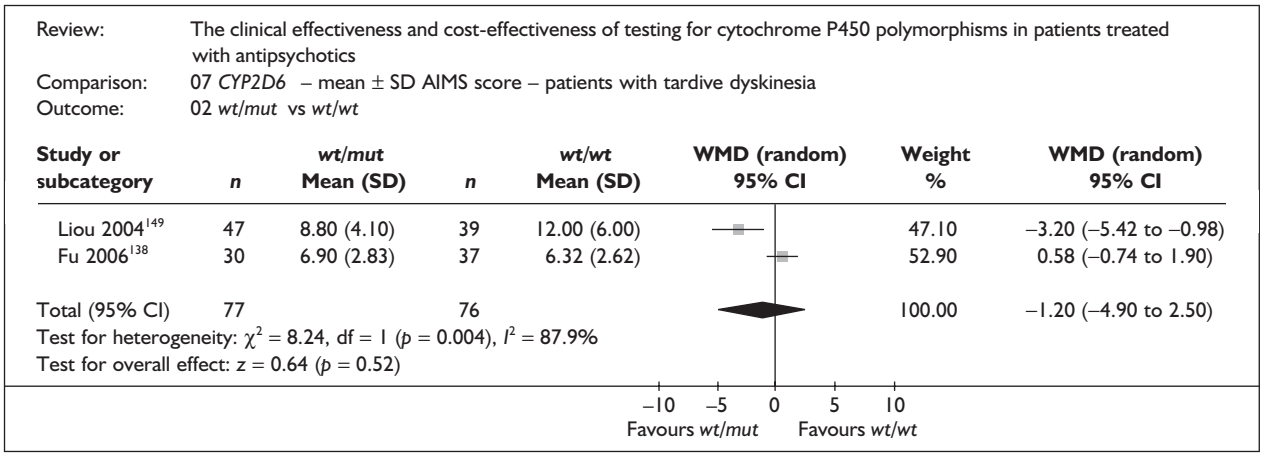


FIGURE 6 *Meta-analysis for patients tested for the* CYP2D6 *genotype – total number of patients with tardive dyskinesia: (d)* wt/wt + wt/mut *vs* mut/mut





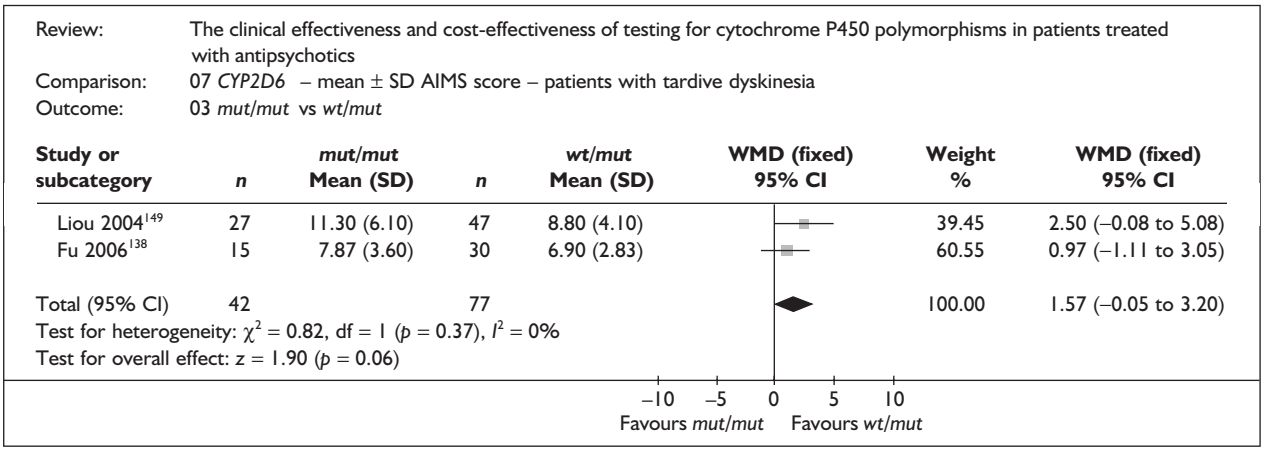
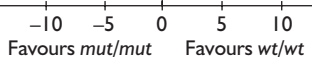


FIGURE 7 *Meta-analysis for patients tested for the* CYP2D6 *genotype – mean ± SD AIMS score for patients with tardive dyskinesia: (a)* wt/wt *vs* mut/mut*; (b)* wt/wt *vs* wt/mut*; (c)* wt/wt *vs* mut/mut + wt/mut.

Review: The clinical effectiveness and cost-effectiveness of testing for cytochrome P450 polymorphisms in patients treated with antipsychotics
Comparison: 11 *CYP2D6* – mean ± SD SAS score – all patients
Outcome: 01 *mut/mut* vs *wt/wt*

Study or subcategory	*mut/mut* n	*mut/mut* Mean (SD)	*wt/wt* n	*wt/wt* Mean (SD)	WMD (random) 95% CI	Weight %	WMD (random) 95% CI
Andreassen 1997[127]	10	0.56 (0.74)	61	0.37 (0.35)		59.98	0.19 (–0.28 to 0.66)
Kakihara 2005[145]	9	1.30 (1.50)	16	2.60 (2.00)		40.02	–1.30 (–2.69 to 0.09)
Total (95% CI)	19		77			100.00	–0.41 (–1.84 to 1.02)

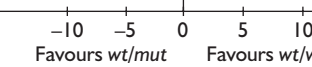
Test for heterogeneity: $\chi^2 = 3.99$, df = 1 ($p = 0.05$), $I^2 = 74.9\%$
Test for overall effect: $z = 0.56$ ($p = 0.58$)



Review: The clinical effectiveness and cost-effectiveness of testing for cytochrome P450 polymorphisms in patients treated with antipsychotics
Comparison: 11 *CYP2D6* – mean ± SD SAS score – all patients
Outcome: 02 *wt/mut* vs *wt/wt*

Study or subcategory	*wt/mut* n	*wt/mut* Mean (SD)	*wt/wt* n	*wt/wt* Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
Andreassen 1997[127]	21	0.36 (0.35)	61	0.37 (0.35)		98.31	–0.01 (–0.18 to 0.16)
Kakihara 2005[145]	14	2.00 (1.70)	16	2.60 (2.00)		1.69	–0.60 (–1.92 to 0.72)
Total (95% CI)	35		77			100.00	–0.02 (–0.19 to 0.15)

Test for heterogeneity: $\chi^2 = 0.75$, df = 1 ($p = 0.39$), $I^2 = 0\%$
Test for overall effect: $z = 0.23$ ($p = 0.82$)



Review: The clinical effectiveness and cost-effectiveness of testing for cytochrome P450 polymorphisms in patients treated with antipsychotics
Comparison: 11 *CYP2D6* – mean ± SD SAS score – all patients
Outcome: 03 *mut/mut* vs *wt/mut*

Study or subcategory	*mut/mut* n	*mut/mut* Mean (SD)	*wt/mut* n	*wt/mut* Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
Andreassen 1997[127]	10	0.56 (0.74)	21	0.36 (0.35)		88.28	0.20 (–0.28 to 0.68)
Kakihara 2005[145]	9	1.30 (1.50)	14	2.00 (1.70)		11.72	–0.70 (–2.02 to 0.62)
Total (95% CI)	19		35			100.00	0.09 (–0.36 to 0.55)

Test for heterogeneity: $\chi^2 = 1.57$, df = 1 ($p = 0.21$), $I^2 = 36.2\%$
Test for overall effect: $z = 0.41$ ($p = 0.68$)

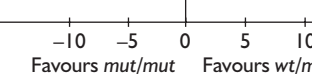
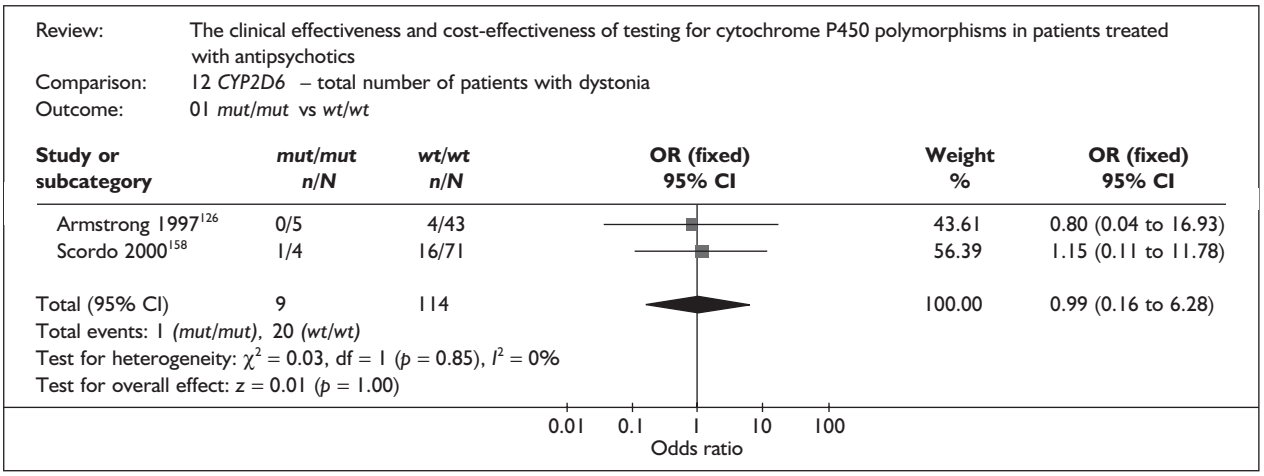
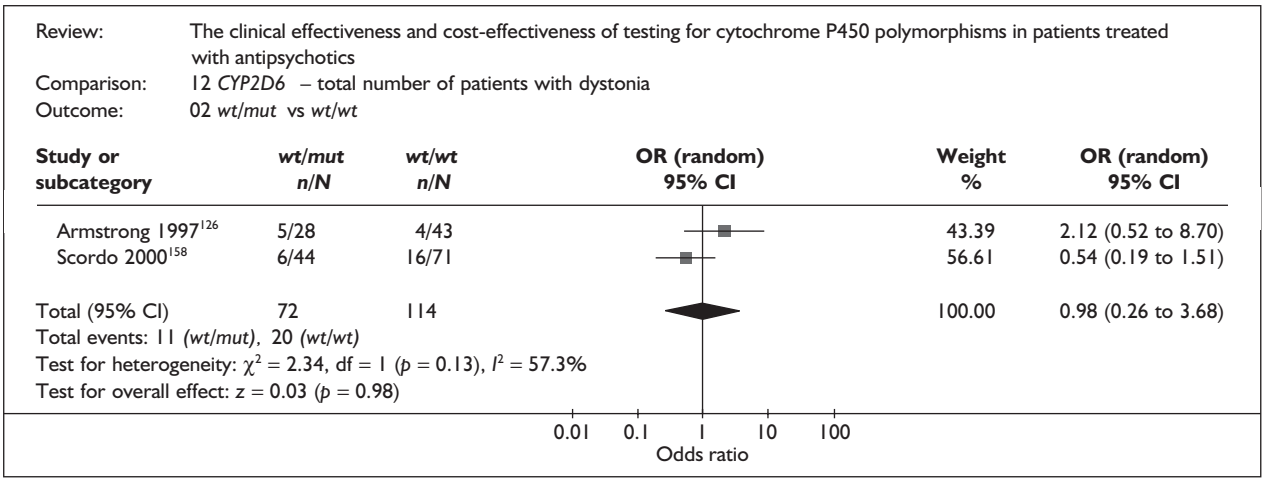


FIGURE 8 *Meta-analysis for patients tested for the* CYP2D6 *genotype – mean ± SAS score: (a)* wt/wt *vs* mut/mut; *(b)* wt/wt *vs* wt/mut; *(c)* wt/wt *vs* mut/mut + wt/mut.





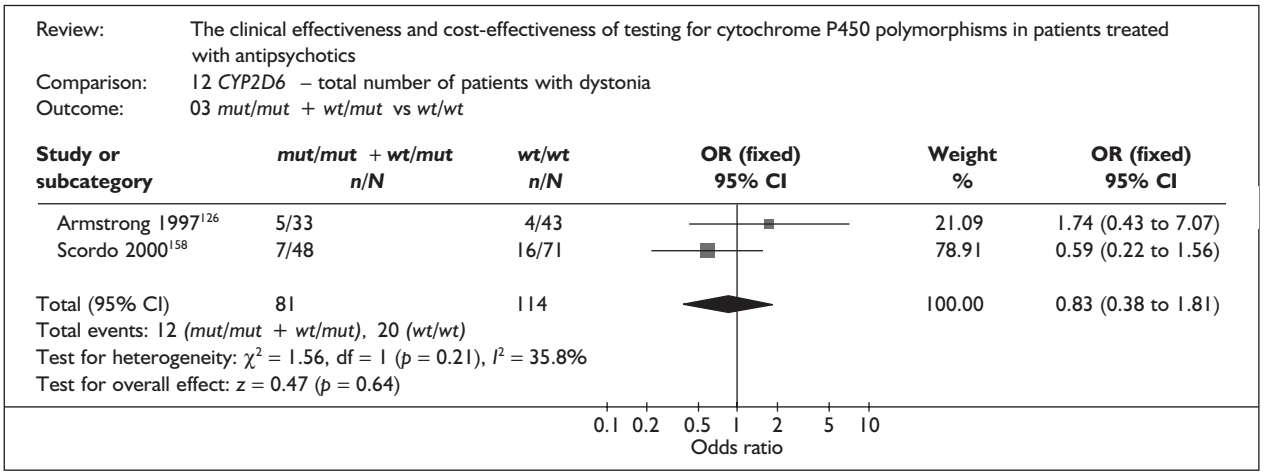


FIGURE 9 *Meta-analysis for patients tested for the* CYP2D6 *genotype – total number of patients with dystonia: (a)* wt/wt *vs* mut/mut*; (b)* wt/wt *vs* wt/mut*; (c)* wt/wt *vs* mut/mut + wt/mut*.*

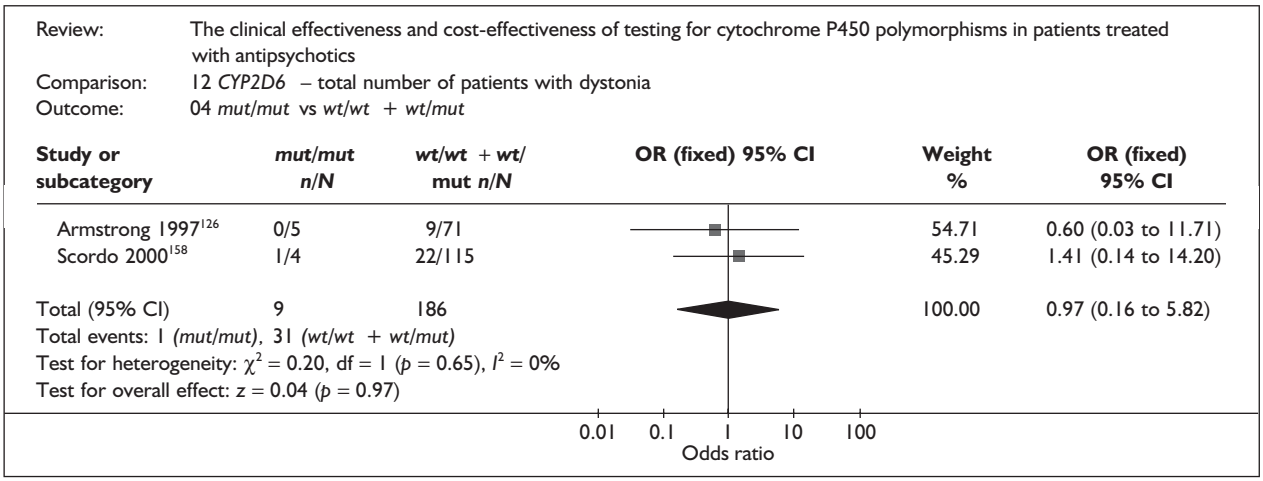


FIGURE 9 *Meta-analysis for patients tested for the* CYP2D6 *genotype – total number of patients with dystonia: (d)* wt/wt + wt/mut *vs* mut/mut.

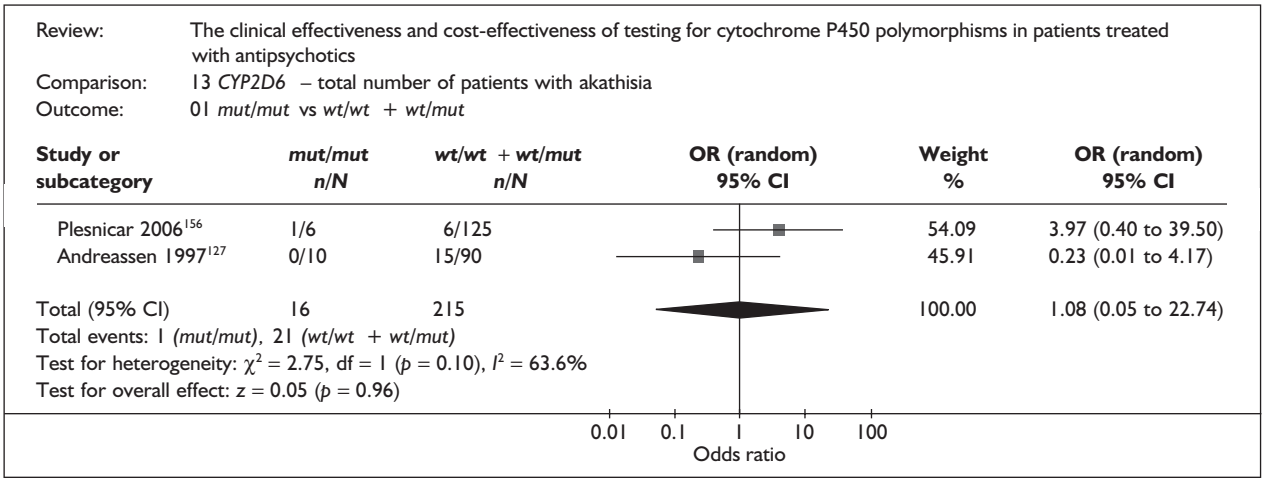
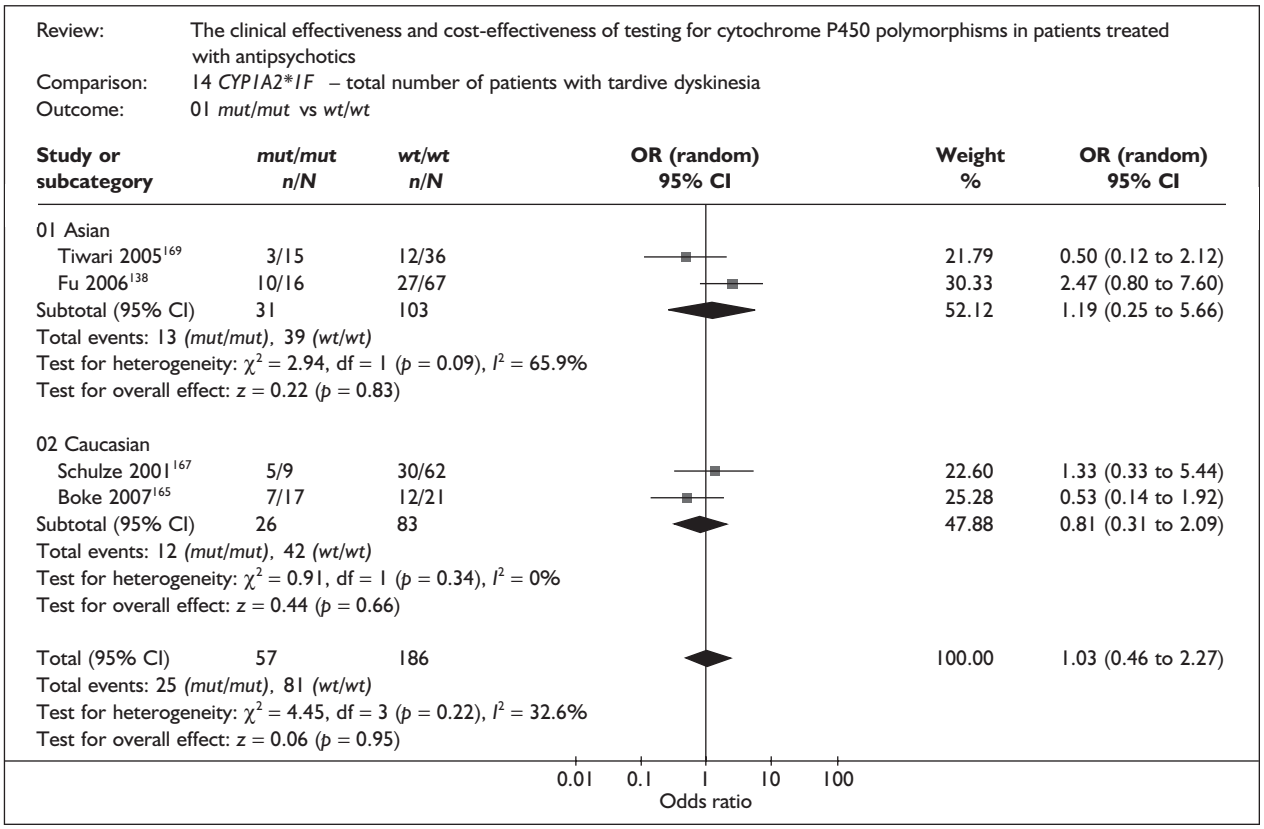


FIGURE 10 *Meta-analysis for patients tested for the* CYP2D6 *genotype – total number of patients with akathisia:* wt/wt + wt/mut *vs* mut/mut.



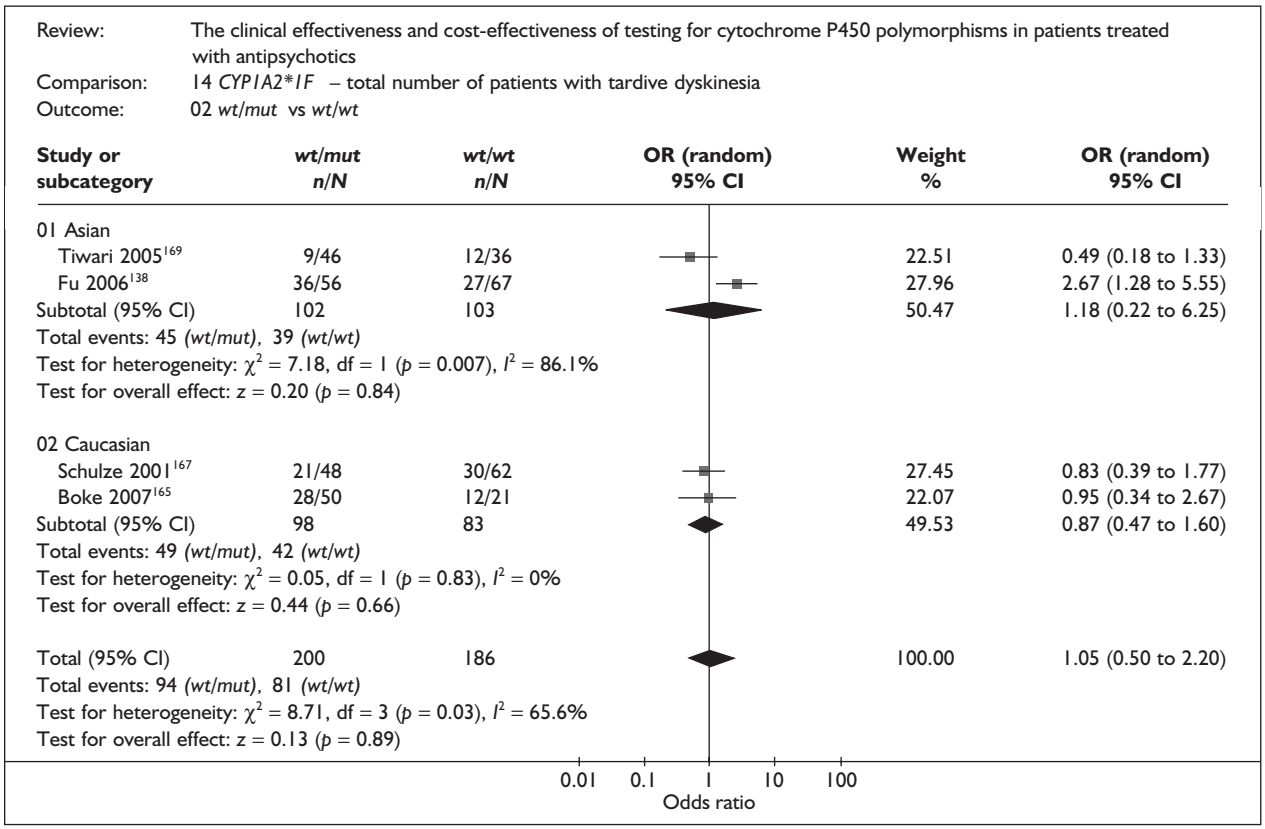
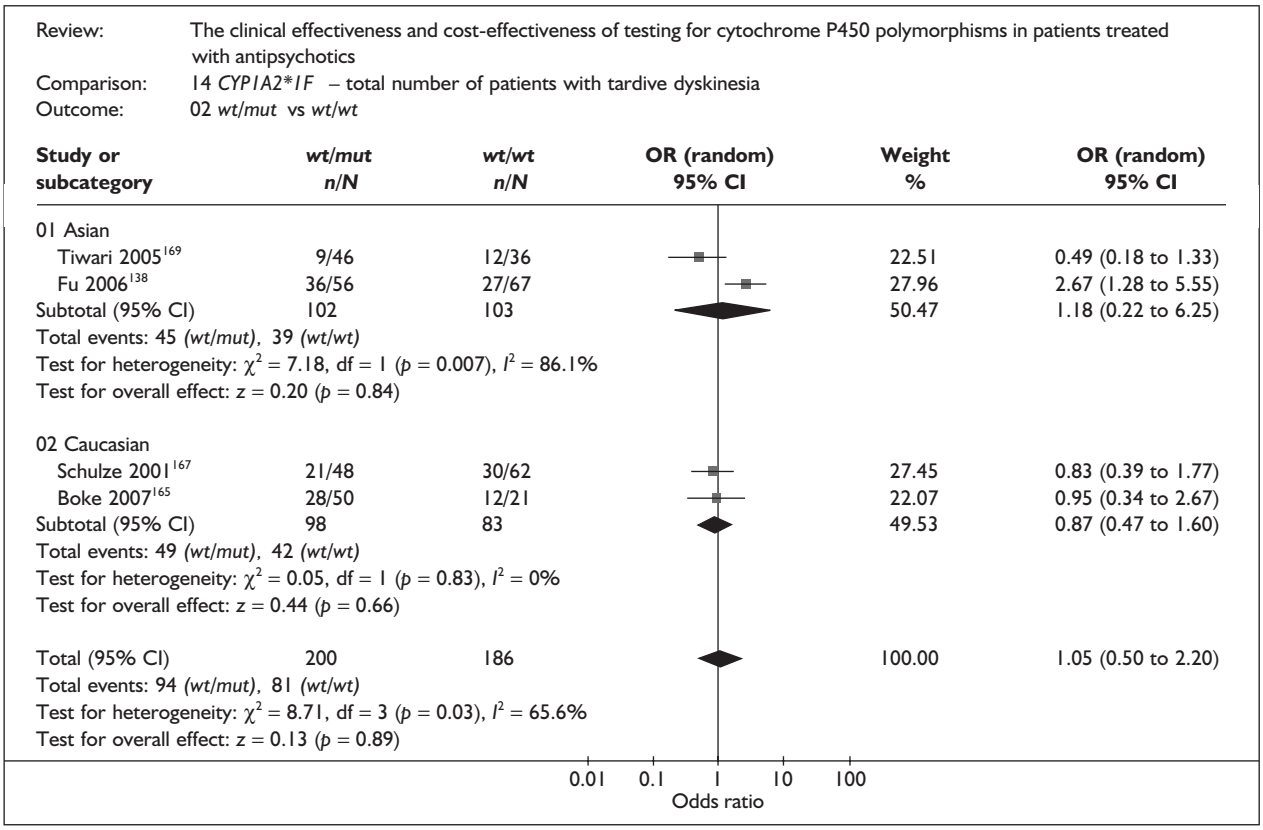


FIGURE 11 *Meta-analysis for patients tested for the* CYP1A2*1F *genotype – total number of patients with tardive dyskinesia: (a)* wt/wt *vs* mut/mut*; (b)* wt/wt *vs* wt/mut.



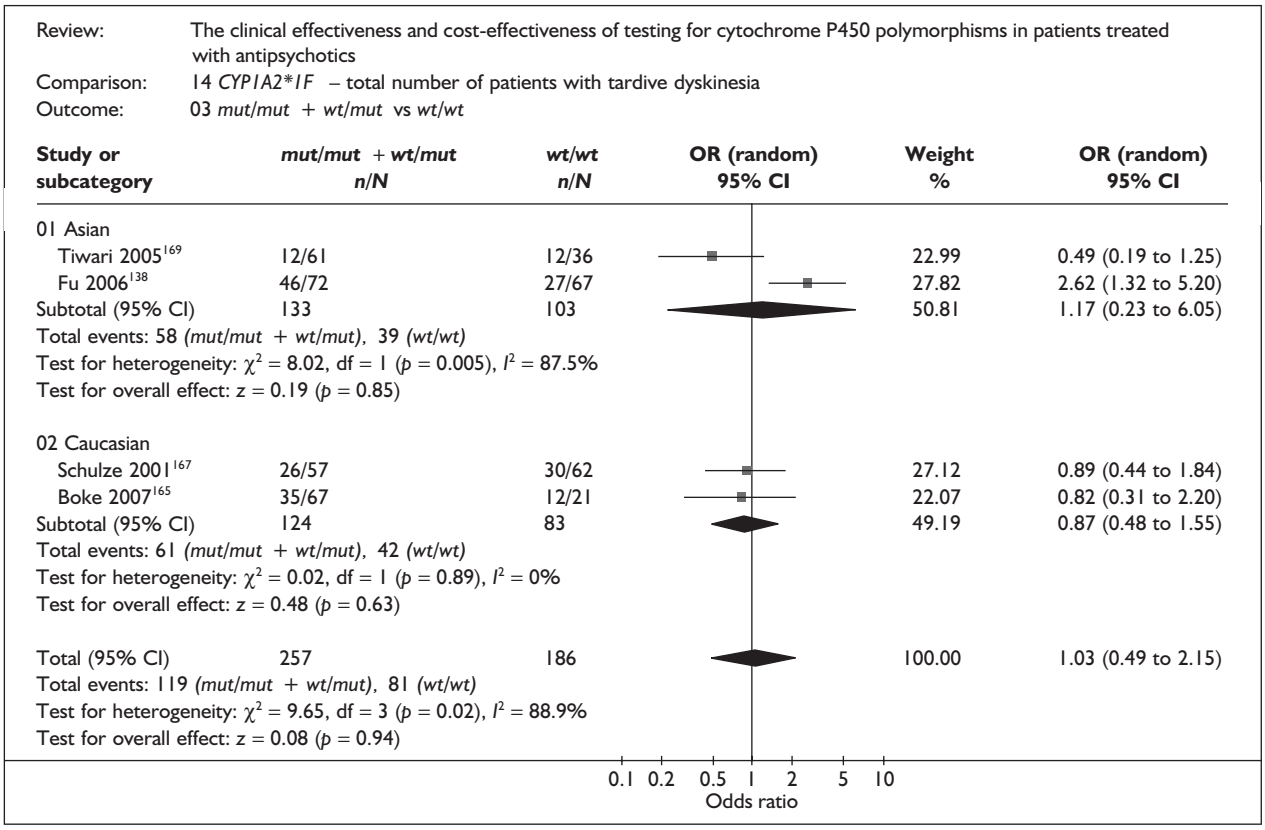


FIGURE 11 *Meta-analysis for patients tested for the* CYP1A2*1F *genotype – total number of patients with tardive dyskinesia: (c)* wt/wt *vs* mut/mut + wt/mut*; (d)* wt/wt + wt/mut *vs* mut/mut*.*

Appendix 6
Economic review

TABLE 43 *Study characteristics*

Study	Type of evaluation and synthesis	Interventions	Study population	Perspective	Time period of study	Industry author affiliation	Publication type
AHRQ[24]	Modelling exercise to determine the benefits (and to a degree costs) of testing for prescribing selective serotonin reuptake inhibitors (SSRIs). A decision tree model was developed in TreeAge ProSuite 2006	*CYP* testing under four scenarios: (1) do not test and treat with sertraline; (2) test and if PM or UM give sertraline, if EM/IM give fluoxetine; (3) test and if PM or UM alter dose of fluoxetine; (4) do not test and give fluoxetine	The study population was limited to treatment-naive adult patients who met DSM-IV criteria for major depression and who were not taking any other medications that could interact with SSRIs	US health-care system	6-week time frame	None declared	Full review

EM, extensive metaboliser; IM, intermediate metaboliser; PM, poor metaboliser; UM, ultrarapid metaboliser.

DOI: 10.3310/hta14030

TABLE 44 *Probabilities*

Study	Probabilities of linking genotype to phenotype (high correlation to low correlation)	Probabilities of responding to fluoxetine given a phenotype (high correlation – low correlation)	Probability of responding to sertraline	Data sources
AHRQ[24]	Probability PM phenotype will have a:	Probability of responding to high-dose fluoxetine if:	0.56	Probabilities of linking genotype to phenotype estimated using bootstrapping techniques, probabilities of responding to fluoxetine estimated using clinical opinion, and probability of responding to sertraline based on the response rate observed in a small RCT[179]
	PM genotype: 0.58–0.35	PM phenotype: 0.40–0.21		
	EM genotype: 0.37–0.39	EM phenotype: 0.50–0.45		
	UM genotype: 0.05–0.26	UM phenotype: 0.61–0.56		
	Probability EM phenotype will have a:	Probability of responding to medium-dose fluoxetine if:		
	PM genotype: 0.20–0.23	PM phenotype: 0.50–0.45		
	EM genotype: 0.45–0.35	EM phenotype: 0.61–0.56		
	UM genotype: 0.35–0.42	UM phenotype: 0.50–0.45		
	Probability UM phenotype will have a:	Probability of responding to low-dose fluoxetine if:		
	PM genotype: 0.14–0.13	PM phenotype: 0.61–0.56		
	EM genotype: 0.49–0.36	EM phenotype: 0.50–0.45		
	UM genotype: 0.50–0.38	UM phenotype: 0.40–0.21		

EM, extensive metaboliser; PM, poor metaboliser; UM, ultrarapid metaboliser.

TABLE 45 *Costs and utilities*

Study	Currency and year	Discount rate	Price of *CYP* test and data source	Costs of medication and data sources	Utilities and data sources
AHRQ[24]	Unclear, presumably US$, and no base year given	NA	*CYP* test = $1000 Taken from the published literature[181] but in publication one test is described as costing US$500	Costs of selective serotonin reuptake inhibitors (SSRIs) based on Costco website[180] prices, which could not be verified as this information does not appear to be available on the website anymore (prescription needed?). The price of sertraline was estimated as $130, and the cost of fluoxetine was stated to be $12. It is unclear if this is a monthly cost or the cost for 6 weeks	Utility of treated depression (0.99) based on expert opinion Utility of untreated depression (0.32) based on published literature[182]

TABLE 46 *Results*

Study	Response rate	Utility	Costs	Sensitivity analysis	Authors conclusion
AHRQ[24]	The response rate (56% taken from chart) was greatest with the non-test strategy followed by treatment with a non-CYP-metabolised selective serotonin reuptake inhibitor (SSRI)	The utility (0.695 taken from chart) was greatest with the non-test strategy followed by treatment with a non-CYP-metabolised SSRI	Results not shown, only brief narrative description, which discussed the fact that the costs of the test were not offset in the 6-week time frame but with longer time frames costs began to break even	Sensitivity analysis not presented but briefly discussed. It is stated that one-way sensitivity analysis was performed for prevalence of phenotype, utility of depression, probability of responding to sertraline, cost of fluoxetine and sertraline, and cost of testing. It is stated that the results of these analyses were robust	When non-CYP-metabolised SSRIs are available they should be used without testing. More data regarding the linkage level of genotype to clinical response are needed. But even if the linkage is high, *CYP* testing is unlikely to be cost-effective for treatment durations that are anticipated to be of less than 9 months because of the high costs of testing

Appendix 7
Overview of schizophrenia models

TABLE 47 *Study characteristics*

Author, year	Type of model	Time period of study	Population characteristics	Drugs studied	Funding/affiliation	Analytical perspective	Where model developed
Almond 2000[200] (and 1998[201])	Markov decision tree simulation model	5 years	Patients enter the model after an acute psychopathology episode. They are existing patients who have previously experienced multiple episodes of acute psychopathology. The model excludes new cases and treatment-resistant schizophrenia (TRS)	Olanzapine, haloperidol, risperidone (only in 2000 publication); oral formulations only	Grant from Lilly Industries (manufacturer of olanzapine)	UK NHS	Originally a US model built for Eli Lilly – Revicki 1998 data on file
Bagnall 2003[47]	Decision-analytical model	1 year	Population based on the trials included in their systematic review?? Doesn't tell us much – have to go back to trials	Chlorpromazine, haloperidol, clozapine, olanzapine, quetiapine, zotepine, risperipone, ziprasidone, amisulpride, sertindole	NHS funded	UK NHS	UK
Beard 2006[202]	Decision tree for acute phase with Markov model for maintenance phase	1-year results, but model may be 2 years and there is mention of 3 years in sensitivity analysis	Patients enter the model after an acute episode. They are assumed to have had schizophrenia for at least 10 years but to be naive to atypicals	Olanzapine, risperidone (clozapine is in there at the end for TRS but is not a comparator)	Eli Lilly (olanzapine)	German health-care payer perspective	UK
Bernardo 2006[203] (and 2007[204])	Deterministic model	1 year	Adult Spanish patients with chronic stable schizophrenia	Ziprasidone, placebo	Pfizer (ziprasidone)	Spanish health-care system	Spain
Bobes 2004[205]	Markov model	1 year	Patients with chronic schizophrenia	Haloperidol, risperidone, olanzapine, ziprasidone	Pfizer	Spanish health-care system	Based on a model developed to capture the importance of side effects (Russell)
Bounthavong 2007[206]	Decision-analytical model	16 weeks	Adult schizophrenia patients	Haloperidol, risperidone, olanzapine	None declared	USA health-care system	USA

DOI: 10.3310/hta14030

Author, year	Type of model	Time period of study	Population characteristics	Drugs studied	Funding/affiliation	Analytical perspective	Where model developed
Byrom 1998[207]	Decision tree model. The model is divided into two modules, the first relating to the management of an acute episode of schizophrenia and the second to the subsequent stabilisation/ maintenance period of treatment	1 year	Acute exacerbation of chronic schizophrenia and the subsequent maintenance phase of treatment Patients presenting with an acute episode of chronic schizophrenia	Olanzaine, risperidone, zotepine	Not stated	UK NHS	UK
Davies 2000[208]	Decision-analytical model. Probabilistic simulations were used to estimate the expected costs and outcomes	3 years	Patients with first episode of schizophrenia	Chlorpromazine, haloperidol, risperidone, clozapine, olanzapine	CHE discussion paper	UK NHS	UK
Davies 1998[209]	Decision tree model	2 years	Chronic schizophrenia	Risperidone, haloperidol	Janssen (Risperidone)	Australian health-care system	UK
De Graeve 2005[210]	Decision tree model	2 years	Young schizophrenics who had been diagnosed for less than 5 years and treated for less than 1 year	Risperidone depot, haloperidol depot, olanzapine oral	Janssen	Belgian health-care system	Belgium
Duggan 2003[237]	Unclear	40 years	All those with treatment-resistant schizophrenia who were willing to take clozapine and were compliant with therapy	Clozapine vs conventional neuroleptic therapy	Project sponsored by Novartis Pharmaceuticals UK	UK NHS	UK
Glazer 1996[211] (related to Edwards 2005,[212] Obradovic 2007[213] and Ganguly 2003[214])	Decision tree	1 year	Outpatient schizophrenic patients with a history of relapse and rehospitalisation. The model follows them for the first postdischarge year	Traditional oral neuroleptic (haloperidol), depot neuroleptic (haloperidol depot), atypical neuroleptic (risperidone)	McNeil Pharmaceutical?	US health-care system	USA

continued

TABLE 47 *Study characteristics (continued)*

Author, year	Type of model	Time period of study	Population characteristics	Drugs studied	Funding/affiliation	Analytical perspective	Where model developed
Glennie 1997[215]	Decision-analytical models	Lifetime	Clozapine analyses – hospitalised treatment-resistant schizophrenic patients with moderate symptoms; risperidone analyses – previously treated hospitalised chronic schizophrenic patients with moderate symptoms	Clozapine, haloperidol, chlorpromazine, risperidone, haloperidol decanoate, fluphenazine decanoate	Canadian Co-ordinating Office for HTA	Canadian health-care system	Not stated
Gutierrez-Recacha 2006[216]	State-transition population model	Lifetime	Spanish-level population?	Conventional antipsychotic (unclear which one), risperidone generic, risperidone patented (plus the above with psychosocial support and with psychosocial support and case management)	None declared	Spanish health-care system	Spain
Hansen 2002[217]	Markov model	5 years	Schizophrenic patients	Zucolopenthixol, haloperidol, risperidone	Lunbeck (zuclopenthixol)	French health-care system	Inspired by Launois, which was developed in France
Heeg 2005[218]	Discrete event simulation model	5 years	Patients with multiple psychotic episodes. First-episode patients are excluded. The model starts with patients experiencing their second or third episode	A distinction is made between: (1) conventional drugs (e.g. haloperidol); (2) atypical antipsychotic agents (e.g. risperidone and olanzapine); and (3) clozapine (treated separately from other atypical drugs because of its distinct side-effect profile)	Development of model financed by Janssen Pharmaceutica, NV, Belgium	UK NHS	The Netherlands
Kongsakon 2005[219]	Cost-analysis model	1 year	Thai schizophrenic patients	Haloperidol, quetiapine, ziprasidone, risperidone, olanzapine	None declared	Societal (Thailand)	Thailand

DOI: 10.3310/hta14030

Author, year	Type of model	Time period of study	Population characteristics	Drugs studied	Funding/affiliation	Analytical perspective	Where model developed
Launois 1998[220]	6-month Markov cycle tree	10 years	The model spans from start of treatment. Three cohorts of patients were evaluated, each receiving a different treatment schedule: (1) sertindole 12–24 mg/day as a single dose; (2) haloperidol 10–20 mg/day in two divided doses; and (3) olanzapine 10–20 mg/day in two divided doses	Sertindole, haloperidol, olanzapine.	Not stated	French health-care system	France (this model has been used to generate cost-effectiveness results for Germany and the UK although only incremental cost-effectiveness ratios for these countries are shown in this paper)
Laurier 1997[221]	Decision tree	9 days	Patients with schizophrenia who experience an acute episode and require a neuroleptic	Zuclopenthixol, haloperidol	Hospital funded	Quebec health-care system	Canada
Lecomte 2000[222]	Markov model	1 year	Chronic schizophrenia patients hospitalised for an acute episode	Haloperidol, olanzapine, risperidone	Janssen (manufacturer of risperidone)	Belgium health-care system	Belgium
Magnus 2005[223]	Markov model	Lifetime	Patients with schizophrenia	Risperidone, olanzapine, typicals (mix), clozapine	None declared	Australian health-care system	Australia
Mortimer 2003[224]	State transition model	1 year	Patients enter the model following recovery from an episode of schizophrenia	Not explicit (clinical data for olanzapine, quetiapine, ziprasidone and risperidone)	Astra Zeneca	UK NHS	UK
Oh 2001[225]	Decision-analytical model	1 year	Hospitalised patients with treatment-resistant schizophrenia and moderate symptomatology	Clozapine, haloperidol, chlorpromazine	Canadian Co-ordinating Office for HTA	Canadian health-care system	Canada
Oh 2001[226]	Decision-analytical model	1 year	Hospitalised chronic schizophrenia patients with moderate symptomatology	Risperidone, haloperidol, haloperidol depot, fluphenazine depot	Janssen funded	Canadian health-care system	Related to Oh 2001[225] (Canada)
Palmer 1998[227] (and 2002,[228] and Sacristan 1997[229])	Decision tree with Markov process	5 years	Patients with schizophrenia who have experienced multiple episodes	Risperidone, olanzapine, haloperidol	Eli Lilly funded	US health-care system	De novo but had input from Glazer 1996[211]

continued

TABLE 47 *Study characteristics (continued)*

Author, year	Type of model	Time period of study	Population characteristics	Drugs studied	Funding/affiliation	Analytical perspective	Where model developed
Perlis 2005[230]	Decision-analytical model (cycle length 3 months)	Lifetime horizon	Schizophrenia patients in an acute psychotic episode	Clozapine	Not stated	US health-care system	Related to Wang 2004[234] (USA)
Tilden 2002[231]	Markov model	5 years	Patients with partial response to conventional antipsychotics	Quetiapine haloperidol	One author appears to be employed by Astra Zeneca	UK NHS	UK
Vera-Llonch 2004[232] (and 2005[233])	Markov	1 year	Chronic schizophrenia or schizoaffective disorder	Risperidone, olanzapine	Janssen funded	US health-care system	USA
Wang 2004[234]	Markov	Lifetime	30-year-old schizophrenia patient hospitalised for an acute episode	Clozapine (first line or third line)	No pharmaceutical funding	US health-care system	USA
Yang 2005[235]	Decision tree	2 years	Stable schizophrenia patients aged less than 35 years, treated for at least 1 year and diagnosed for under 5 years	Risperidone, olanzapine, haloperidol	Janssen part funded	Taiwan health-care system	Taiwan

DOI: 10.3310/hta14030

TABLE 48 *Description of clinical outcomes included in the economic models*

Author, year	Treatment pathways	Data sources	Clinical outcomes included	Side effects included	Definitions and patterns of relapse
Almond 2000[200] (and 1998[201])	Patients go through 20 3-month cycles. In the first cycle there is a probability of suicide; those that do not commit suicide have the option to stay on medication or switch if there is a lack of efficacy, non-compliance or adverse event. The remaining cycles take account of further risk of suicide, switching, relapse, four symptom states and dropout	Parameter values were taken from an RCT or were taken from the original US model	Suicide, dropout rate, relapse. Effectiveness used to support rather than drive model	Unclear	Relapse assumed to entail hospitalisation. Rates taken from clinical trial and assumption (risperidone)
Bagnall 2003[47]	Patients appear to enter model at an acute event and are treated. The treatment can be acceptable or not. The patients then follow the same pathways (different probabilities) of EPS or no EPS and relapse or no relapse	Data on control of symptoms, adverse events and relapse taken from clinical review, patient-specific outcomes taken from literature	Main outcome was QALYs. Symptom control and relapse included. Suicide does not appear to be in the model	EPS, agranulocytosis, hepatic dysfunction	Not very clear but if they relapse they get the same medication treatment
Beard 2006[202]	Patients enter model at acute episode and are given either olanzapine or risperidone. They then either fail and go onto second-line treatment (olanzapine or risperidone) or respond and go onto maintenance. If they fail second-line treatment they are defined as treatment-resistant schizophrenia (TRS) and go onto clozapine; if they respond to second-line treatment they go onto maintenance. Maintenance phase can be stable or acute relapse. During acute relapse there is a risk of suicide (thus death) and patients are either hospital or community managed before returning to stable maintenance (assuming no death)	Parameter values taken from RCT and literature	QALYs, relapse rate	No side effects included. Instead, anticholinergic therapy was included to prevent people getting EPS side effects. Rates differed between treatments and once again were biased against risperidone	Unclear, does not necessarily entail hospitalisation though. Also rates for olanzapine and risperidone seem biased against risperidone in year 1
Bernardo 2006[203] (and 2007[204])	Linked to Zeus trial. Unclear exactly what the clinical pathway was	Parameters taken from ZEUS RCT	Relapse rate and time to relapse	Side-effect rates from ZEUS RCT included	Relapses assumed to require hospitalisation

continued

TABLE 48 *Description of clinical outcomes included in the economic models (continued)*

Author, year	Treatment pathways	Data sources	Clinical outcomes included	Side effects included	Definitions and patterns of relapse
Bobes 2004[205]	Two different treatment pathways are modelled. The first one assumes that patients are outpatients: patients can have an adverse event (AE) or not; if not, symptoms can be controlled or not; if not, continue hospitalisation; if so, discharge. For patients with an AE, the AE treatment that ensues can resolve the issue; if so, they follow the same pathway as no AE; if the symptom is not resolved they switch and then follow the same pathway. Inpatients can have an AE or not; either way they follow the same pathway of compliant or not, followed by relapse or not; if not, they remain as outpatients, if they do relapse they are hospitalised	Parameter values take from the literature	Symptom control	Akathisia, other EPS, weight gain and AEs related to prolactin increase	Relapse requires hospitalisation and only occurs on an outpatient basis
Bounthavong 2007[206]	Patients are given one of three drugs and can either respond or not; non-responders are assumed to switch therapy to clozapine to which they either respond or not; the non-responders are given electroconvulsive therapy (ECT). Patients who respond to the treatment drug have EPS, are rehospitalised or are stable. For EPS they are treated and either it is controlled or not; if not controlled they switch to clozapine and either respond or not. For patients who are rehospitalised they are also switched to clozapine and can respond or not respond and require ECT	Parameter values taken from the literature	Efficacy rate and rehospitalisation rate	EPS	Relapse requires a visit to ER, treatment with haloperidol intramuscularly followed by hospitalisation for 14 days
Byrom 1998[207]	Patients enter model at an acute event. Treatment is then efficacious or non-efficacious. If efficacious it may be tolerated [discharge to family home (GP)/family home (specialist)/sheltered accommodation/remain inpatient], tolerated with EPS (add anticholinergic) or not tolerated (switch medication) In the maintenance module patients are compliant or non-compliant and in either case may or may not experience a relapse	Default values for probabilities and resource use were obtained from a literature search	Treatment responder defined by reduction in BPRS score. Suicide not included in model	EPS	Using a BPRS 0–6 score, response rates defined by a 40% reduction in BPRS

DOI: 10.3310/hta14030

Author, year	Treatment pathways	Data sources	Clinical outcomes included	Side effects included	Definitions and patterns of relapse
Davies 2000[208]	Patients are prescribed antipsychotic medication for first episode. Therapy may be acceptable or not. If acceptable there may be treatable adverse events (in which case treat). Patient will then either continue maintenance therapy (treating adverse events if applicable) or relapse (in which case switch antipsychotic). If therapy not acceptable this may be due to intolerance (in which case switch antipsychotic), inadequate response (in which case switch antipsychotic) or non-compliance [(no relapse (mild/moderate symptoms) or relapse (in which case switch antipsychotic)]	The principle source of data was a review of the published clinical and economic literature	(1) The proportion of people who require one or more changes in therapy; (2) expected total direct costs of the resources used to provide health and social care services; (3) the benefits to patients in terms of expected QALYs	Adverse events were restricted to those for which data were available for all comparators, or which were irreversible or life-threatening. These were EPS (excluding tardive dyskinesia), tardive dyskinesia, neuroleptic malignant syndrome, hepatic dysfunction and agranulocytosis	The definition of inadequate response was taken as that used by the systematic review or trial investigator
Davies 1998[209]	Following treatment patients can either respond with EPS, respond with no EPS or not respond (3 months). Non-responders are either hospitalised or managed in the community; responders with EPS can be non-compliant requiring either community or inpatient care; responders without EPS can have a full or partial response (period up to 12 months). The second part of the model is very divergent and follows patients from 12 to 24 months taking account of further risk of EPS, increased dose for partial responders, non-compliance (hospital or community) and treatment resistance	Parameter values taken from literature and opinion	Favourable outcome, which was defined as full or partial response with or without EPS and increased dose response	EPS	Relapse is captured in hospitalisation. These patients are hospitalised and when discharged some require hospital accommodation. All patients require monitoring by a psychiatrist and GP and counselling from a social worker. This period lasts for 9 months (mean)
De Graeve 2005[210]	Following treatment patients can either respond or not; if they respond the response can be maintained or it can deteriorate, which can require switching. If patients do not respond (relapse or EPS) they can begin to respond or they can switch	Parameter values taken from the literature and opinion	'Effectiveness'	EPS captured in non-response	Relapse in which patients are hospitalised
Duggan 2003[237]	The annual incidence of suicide in people with schizophrenia was combined with published findings to calculate suicide rates for patients prescribed clozapine and those treated with other drugs	Published literature	Life-years saved	Suicide	Not considered

continued

TABLE 48 *Description of clinical outcomes included in the economic models (continued)*

Author, year	Treatment pathways	Data sources	Clinical outcomes included	Side effects included	Definitions and patterns of relapse
Glazer 1996[211] (related to Edwards 2005,[212] Obradovic 2007[213] and Ganguly 2003[214])	Patients are treated with one of the three drugs and are either compliant or not (this is the only difference between treatment strategies), both of which lead on to three health states (different probabilities): stable, exacerbations, rehospitalisations	Parameter values taken from the literature and clinical opinion	Model presents results in terms of cost only	EPS included but not clear where	Patients can suffer relapses that do not require hospitalisation (exacerbations) or ones that do (rehospitalisation)
Glennie 1997[215]	After choosing an initial drug, possible downstream events included tolerability, 'success' vs 'failure', discharge from hospital and relapse. The risperidone decision tree also incorporated EPS into its design	Literature data and expert panel input	Efficacy rate; dropout rate due to side effects; dropout rate due to lack of efficacy; the risperidone model also included the emergence of EPS (the use of concomitant antiparkinsonian medication precluded the assessment of this outcome in the clozapine trials reviewed); QALYs	Risperidone model includes EPS	A 'relapse' occurred if symptoms of schizophrenia developed with sufficient severity to warrant rehospitalisation for intensive therapy
Gutierrez-Recacha 2006[216]	Unclear	Parameter values appear to be taken from the literature but do not really know what the parameters are	Disability-adjusted life-years (DALYs)	Unclear	Unclear
Hansen 2002[217]	Patients are treated with one of the three agents following which they have a risk of death, dropout, switch, outpatient treatment (relapse or no relapse), hospitalisation (relapse or no relapse)	Meta-analysis, literature and expert opinion	Time without relapse	EPS	Relapse not clearly defined but in model can be handled in community and hospital
Heeg 2005[218]	In the basic scenario treatment is started with a conventional antipsychotic. If the drug is ineffective or side effects are intolerable, patients are switched to an atypical, and in cases of a second unsatisfactory outcome the patient is switched to clozapine. Patients remain on this drug indefinitely, except when they develop agranulocytosis, in which case they are switched back to an atypical	Published literature; report; expert opinion	1. Cumulative direct costs over a 5-year period; (2) cumulative number of relapses; (3) cumulative time spent in a psychotic health state; (4) duration of time on first-line treatment after entering the model	EPS, agranulocytosis, sedation, weight gain	Not explicitly defined. Time between relapses estimated from information in published literature

DOI: 10.3310/hta14030

Author, year	Treatment pathways	Data sources	Clinical outcomes included	Side effects included	Definitions and patterns of relapse
Kongsakon 2005[219]	Unclear	Parameter values taken from reviews of trial data, medical literature and clinical judgement	PANSS, BPRS, but cost-effectiveness results not presented	EPS	Unclear
Launois 1998[220]	15 health states – three care groups (hospitalisation, intensive management and mild care) and five patient treatment groups (high-dependency hospital management, intensive home or residential care and mild home or residential care). Likelihood of entering a state is governed by side effects, compliance and relapse	Adverse event rates – registration dossiers for the three compounds studied. Rates of relapse were derived from a survey of published meta-analyses. Transitions of patients from one care group to another were calculated from published literature	Time spent without relapse	Four main adverse events, EPS, sedation, weight gain (defined as ≥ 7% increase from baseline) and sexual dysfunction, were considered	Criteria used to define relapse vary, depending on author. Published comparative rates were used to calculate the probabilities of relapse in different settings
Laurier 1997[221]	Patients enter model at acute episode and are treated with a neuroleptic. Patients can either be controlled or not. If not, can give another five injections max. or not	Parameter values taken from hospital records and literature	Number of injections	Not included	Not applicable
Lecomte 2000[222]	Patients enter model at acute episode and can either commit suicide leading to death or not commit suicide. For those not suiciding they can respond or not, followed by an adverse event or not, which can affect whether or not they are compliant and whether they switch therapy	Parameter values taken from the literature and Delphi panel opinion	Time without symptoms and toxicity (TwiST)	Numerous including tardive dyskinesia, sexual dysfunction, weight gain and sedation	Unclear
Magnus 2005[223]	Unclear	Parameter values taken from literature	DALY	Side effects captured in disability weights, which takes into account how side effects impact on life	Unclear
Mortimer 2003[224]	Relationship between compliance and relapse following recovery from an episode of schizophrenia. The three states are 'well, compliant' (starting state); 'well, not compliant'; and 'relapsed'. The model was updated monthly	Appropriate values for entry into the model were obtained from a review of relevant literature, augmented where necessary by an iterative process of consultation with experts	The output from the model was the cumulated proportion of patients relapsing over 12 1-month cycles	Weight change, EPS and prolactic elevation were considered by the Delphi panel when estimating non-compliance rates	Not defined clearly but probability of relapse varied over time and was affected by compliance

continued

TABLE 48 *Description of clinical outcomes included in the economic models (continued)*

Author, year	Treatment pathways	Data sources	Clinical outcomes included	Side effects included	Definitions and patterns of relapse
Oh 2001[225]	After starting therapy downstream events include tolerability (defined as the presence of treatment-limiting side effects), success or failure, discharge from hospital and relapse	Parameter values taken from literature	QALYs	Side effects as a composite not including EPS (as anticholinergic meds given in trials)	Unclear
Oh 2001[226]	Same as above but appears to also include EPS specifically	Parameter values taken from literature and expert panel	QALYs	EPS and other adverse events	Unclear
Palmer 1998[227] (and 2002,[228] and Sacristan 1997[229])	Following treatment there is a risk of suicide. All those suiciding die; those not suiciding have the following downstream events (cyclical): continue or switch, relapse or no relapse, suicide or not, dropout or continue	Parameter values based on literature and assumption	QALYs	EPS	Relapse appears to include risk of suicide
Perlis 2005[230]	No test strategy examined predicted outcome of patient who is treated with a conventional antipsychotic (CAP). If the patient fails to recover to the point of being discharged from hospital, relapses after recovery, or develops serious tardive dyskinesia with initial CAP he switches to a second CAP. If the patient again fails for one of the above reasons he is switched to clozapine. If he fails to respond to clozapine or develops agranulocytosis he is switched to a CAP. In the 'test' strategy the patient is tested at the outset. Subjects who test negative follow the pathway outlined above. Those who test positive receive clozapine as first-line treatment. If the patient fails to recover to the point of being discharged from hospital, relapses after recovery, or develops agranulocytosis he is switched to a CAP	Published record-linkage data – rate of death by suicide on CAPs. Registry data – rate of death by suicide during clozapine treatment. Clozapine National Registry data (1990–4) – rate of death from agranulocytosis while taking clozapine. Meta-analysis of RCT data – effectiveness of CAPs and clozapine and short-term effectiveness of CAPs and clozapine in prevention of relapse	Quality-adjusted life expectancy	Death due to suicide or agranulocytosis; tardive dyskinesia	Not defined

DOI: 10.3310/hta14030

Author, year	Treatment pathways	Data sources	Clinical outcomes included	Side effects included	Definitions and patterns of relapse
Tilden 2002[231]	Patients entering the model are assigned to one of five health states [PANSS improvement ≥ 30% (no EPS), PANSS improvement ≥ 30% (EPS), ≥ 20% but < 30% PANSS improvement (no EPS), ≥ 20% but < 30% PANSS improvement (EPS), no response (< 20% PANSS improvement)]. In each of the first four states patients may be compliant or non-compliant and, furthermore, may or may not experience a relapse. Non-responders may or may not experience a relapse. On relapse some patients may commit suicide, the remainder go into hospital or community care where they are assigned to treatment with either quetiapine or haloperidol. If patients do not respond to treatment they switch to treatment with another atypical antipsychotic. In the next cycle the patients may or may not relapse. If they do relapse then they may commit suicide or go into hospital or community care. All patients receive quetiapine after the second relapse	Published literature and expert opinion. The key source was the PRIZE study	Relapse, suicide	Suicide (no costs included), EPS	Authors unable to identify a study of the relapse rate in patients who do not respond to treatment and therefore it was assumed that the relapse rate would be the same as in patients who failed to comply with treatment. This assumption was supported by a panel of UK experts
Vera-Llonch 2004[232] (and 2005[233])	The Markov model has six health states (four live, two capture). Live states defined according to side effects (none, diabetes, prolactin, both); capture states defined as discontinued or dead. All side effects were assumed reversible following discontinuation	Parameter values based on literature, expert opinion and unpublished trials	Cost of care; clinical outcomes including weight gain, EPS and discontinuation	EPS, weight gain, diabetes, prolactin disorders	Relapse appears to require hospitalisation
Wang 2004[234]	The Markov model has seven health states: recovered from psychosis (with clozapine and with conventional antipsychotic); psychosis (with clozapine and with conventional antipsychotic); tardive dyskinesia (conventional antipsychotic only); agranulocytosis (clozapine only); and dead	Parameter values based on literature	QALYs	Tardive dyskinesia and agranulocytosis	Unclear
Yang 2005[235]	Model structure not presented or clearly described. It appears that patients initiate therapy with one of three drugs and then switch according to their response status (response, clinical deterioration, inadequate response)	Executive committee	Response rates	EPS	Unclear

TABLE 49 *Description of costs and resource use included in the economic models*

Author, year	Currency and year	Discount rate	Data sources	Costs and resource use
Almond 2000[200] (and 1998[201])	UK£, price year 1998	6%	Costs based on published literature and confined to direct medical costs	The following resource items are costed, split into initial treatment, relapse, maintenance and switching: inpatient care; psychiatrist visits; inpatient care/long stay; supported accommodation; outpatient visits; day care; community psychiatric nurse visits; GP visits; cost of antipsychotic drugs
Bagnall 2003[47]	UK£, price year not given	NA	Costs and resources based on UK national statistics and databases, also supplemented with literature when necessary	The following resource items are costed: inpatient care; outpatient visits; day care; community services; cost of antipsychotic drugs, costs of other drugs
Beard 2006[202]	Euro, price year not given	Unclear but NA for 1-year results	Resource use based on German data and literature. Costs based on German schedule	The following resource items were costed: hospital care; community care; cost of antipsychotic drugs; cost of suicide; cost of anticholinergic drugs
Bernardo 2006[203] (and 2007[204])	Euro, price year 2005	NA	Resource use based on trial data and published Spanish literature. Costs based on Spanish Board of Pharmacy and a Spanish health costs database	The following resource items were costed: costs of antipsychotics; costs of concomitant medications; costs of treating side effects; costs of relapse requiring hospitalisation
Bobes 2004[205]	Euro, price year 2002	NA	Resource use based on literature, costs based on Nomenclator of the Official Physicians' Association of Barcelona	The following resource items were costed: antipsychotic medications; hospital stay, concomitant medication; outpatient care; refractory care
Bounthavong 2007[206]	US$, price year 2003	NA	Resource use based on literature, costs based on drug *Red Book* average wholesale price (AWP) data	The following resource items were costed: antipsychotic medications; hospital stay; doctor visits; ER visits; pharmacy dispensing fees; adjunct treatment options; side effects of treatment of EPS
Byrom 1998[207]	Cost data are given in US$ (assume £1 = US$1.60) Care costs 1992–3, drug costs 1992 (when possible)	NA	Default values for probabilities, resource use and costs were obtained from a literature search	The unit costs included costs incurred by the NHS, local authority, education services, criminal justice, and voluntary sector services, and housing and living expenses. The cost of treatment with a typical antipsychotic drug was assumed to be US$0.53 per day, based on 20 mg/day haloperidol. Anticholinergic treatment was assumed to cost US$0.23 per day, based on 6 mg/day biperiden. Switch medication was assumed to be an atypical antipsychotic at a cost of US$6.64 per day, based on 1997 figures for 6 mg/day risperidone.

DOI: 10.3310/hta14030

Author, year	Currency and year	Discount rate	Data sources	Costs and resource use
Davies 2000[208]	UK£, price year 1997	Not stated	Inpatient, outpatient and day case – CIPFA 1998; community services – Netten 1998; drug costs – BNF 1998. Whenever possible, resource use was estimated from clinical guidelines or best practice	The following resource items were costed: inpatient stay (per day); outpatient visits (per visit); day patient (per day); community services (per day); drugs (per patient day)
Davies 1998[209]	Australian$, price year not given	Not stated	Resource use based on literature and opinion, costs based on manual of resource items and their associated costs for use in submissions to the pharmaceutical benefits advisory committee	The following resource items were costed: GP visits; psychiatrist visits; social worker consultations; hospital; hostel; haematological tests; antipsychotic medication; benztropine; dothiepin
De Graeve 2005[210]	Euro, price year 2003	3%	Resource use based on literature, costs based on Belgian ministry of health and Institut national d'assurance maladie-invalidité	The following resource items were costed: psychiatric hospital; general/university hospital; sheltered housing; psychiatric care homes; psychiatric consultation; GP consultation; injection; antipsychotic medication; EPS
Duggan 2003[237]	UK£, price year appears to be 1995	Outcomes were discounted at 1.5% and costs at 6%	Published literature, including guidance; Netten 1996	Patient support and suicide costs
Glazer 1996[211] (related to Edwards 2005,[212] Obradovic 2007[213] and Ganguly 2003[214])	US$, price year not given	NA	Resource use appears to be based on hospital and community data, costs were also based on this source	The following resource items were costed: rehospitalisation; clinic visits; case management; assessing/managing EPS; antipsychotics
Glennie 1997[215]	Canadian$, price year not stated	Future costs and outcomes were discounted at a rate of 5%	1995 Ontario Drug Benefit Formulary and the 1996 RAMQ (Quebec) Drug Benefit Formulary (mediation costs); 1992 Ontario Ministry of Health (OHIP) Schedule of Benefits (physician visit and laboratory test costs); Alberta Standard Cost List (community care costs, including nursing, social work, case manager and residential care); Sunnybrook Health Sciences Centre case costing system (hospitalisation costs); 1992–3 Statistics Canada Hospital Statistics (long-term hospitalisation costs); the Clozaril Guarantee Program (rebate of drug acquisition cost for discontinuation within the first 6 months due to adverse reactions) was factored into the clozapine analysis	Medication costs; physician visit and laboratory test costs; community care costs including nursing, social work, case manager and residential care; hospitalisation costs

continued

TABLE 49 *Description of costs and resource use included in the economic models (continued)*

Author, year	Currency and year	Discount rate	Data sources	Costs and resource use
Gutierrez-Recacha 2006[216]	US$, price year 2000	NA	Resource use and costs based on Spanish data and converted to US$	The following resource items were costed: hospitalisation inpatient; outpatient; laboratory tests; physician visit; antipsychotics; programme costs
Hansen 2002[217]	Euro, price year appears to be 1999	Unclear	Costs and resource use based on Lundbeck studies, expert opinion and Mediavidal	The following resource items were costed: hospital stay; psychiatrist visits; nursing care; psychologist consultations; social worker care; EPS treatment; cost of antipsychotic drugs
Heeg 2005[218]	UK£, 2002	Outcomes were discounted at 1.5% and costs at 6%	Medication costs – Drug Tariff 2002; location costs – Personal Social Services Research Unit (PSSRU) (costs in 2002)	These are limited to costs of medication, visits to the psychiatrist and costs associated with residing in specific treatment locations.
Kongsakon 2005[219]	Thai Baht, price year not given	NA	Costs based on local unit costs, resource use based on published literature	The following resource items were costed: hospital stay; relapse costs; cost of antipsychotic drugs; cost of anticholinergics; together with productivity losses due to unemployment and losses due to suicide gestures or attempts
Launois 1998[220]	US$, price year 1996	Details not provided	Two French databases were used to estimate the range and amount of resources consumed by care group per 6-month period Cost sources: daily tariff charges (inpatient, partial hospitalisation, day hospitalisation and overnight hospitalisation); financial accounting systems (actual costs of professional procedures performed within the community); public prices (antipsychotic drugs used)	The following resource items were costed: hospital stay (inpatient, day and overnight); medical procedure (all combined); nursing procedure; consultation with a psychologist; consultation with a social worker; outpatient antipsychotic treatment; drug costs
Laurier 1997[221]	Canadian$, price year 1995?	NA	Costs based on hospital costs and Quebec fee schedule as required	The following resource items were costed: hospital stay; physician visits; nursing care; laboratory tests; antipsychotic drugs; other drugs
Lecomte 2000[222]	Euro, price year 1998	NA	Costs based on tariff lists, resource use based on Delphi panel opinion	The following resource items were costed for both sheltered and normal housing: hospital stay; physician, psychiatrist, psychotherapist, other visits; antipsychotic drugs; blood tests
Magnus 2005[223]	Australian$, price year 2000	3%	Costs based on Pharmaceutical Benefits Agency, Repatriation Pharmaceutical Benefits Scheme; resource use taken from low prevalence psychotic disorders study and literature	The following resource items were costed: blood tests for clozapine; antipsychotic drugs
Mortimer 2003[224]	Not stated	NA	US and UK literature	Hospital and drug costs

DOI: 10.3310/hta14030

Author, year	Currency and year	Discount rate	Data sources	Costs and resource use
Oh 2001[225]	Canadian$, price year 1995	NA	Costs and resource use based on Ontario Drug Benefit Formulary, Ontario Health Insurance Plan, Alberta Standard Cost List, Sunnybrook Transition Systems, hospital statistics	The following resource items were costed: antipsychotic medications; dispensing fees; visits with health professionals; residential care; hospital care (including relapse)
Oh 2001[226]	Canadian$, price year 1997	NA	Costs and resource use based on Ontario Drug Benefit Formulary and Ontario Health Insurance Plan	The following resource items were costed: antipsychotic medications; dispensing fees; visits with health professionals; residential care; hospital care
Palmer 1998[227] (and 2002,[228] and Sacristan 1997[229])	US$, price year 1995 (original US publication)	5%	Resource use based on expert opinion and literature, costs based on literature, health-care financing administration and National Association of Psychiatric Health Systems	The following resource items were costed: antipsychotic medications; inpatient services; outpatient services; EPS treatment; laboratory tests
Perlis 2005[230]	US$, price year 1999	3% for costs and effects	Drug costs were calculated based on the average wholesale generic price; cost of inpatient stays taken from the Inventory of Mental Health Organizations and General Hospital Mental Health Services (average cost); outpatient and residential treatment costs estimated from Medicaid data; costs of white blood cell (WBC) count weekly monitoring and treatment of agranulocytosis were drawn from published estimates; median of the range of costs for commercially available pharmacogenetic tests used	The following resource items were costed: hospitalisation for acute psychosis; outpatient treatment; residential treatment; antipsychotic medication All clozapine users were also assigned a cost for weekly WBC count monitoring. In addition, clozapine users with agranulocytosis were assigned the cost of hospitalisation for management of this condition, whereas conventional antipsychotic users who developed serious TD were assigned the cost of pharmacological treatment for this side effect (3 months)
Tilden 2002[231]	UK£, price year not stated but appears to be1999	Outcomes were discounted at 1.5% and costs at 6%	Drug costs – BNF 1999; medical service costs – Netten 2000 and CIPFA 2000	The following resource items were costed: study medication; medical services
Vera-Llonch 2004[232] (and 2005[233])	US$, price year 2003	NA	Resource use based on expert opinion and literature, costs based on literature, *Red Book* and Medicare	The following resource items were costed: antipsychotic medications; inpatient services; outpatient services; EPS treatment; laboratory tests
Wang 2004[234]	US$, price year 1999	3%	Resource use based on assumption and literature, costs based on *Red Book*, Inventory of Mental Health Organizations and General Hospital Mental Health Services, and Medicaid	The following resource items were costed: antipsychotic medications; hospitalisation for psychotic episode; outpatient care; residential treatment; EPS treatment; blood tests
Yang 2005[235]	New Taiwanese$, price year 2001	Unclear	Resource use based on executive committee, costs based on Bureau of National Health Insurance	The following resource items were costed: antipsychotic medications; outpatient clinic; day hospital; subacute ward; home car services; community rehabilitation programmes

NA, .

Health Technology Assessment reports published to date

Volume 1, 1997

No. 1
Home parenteral nutrition: a systematic review.
By Richards DM, Deeks JJ, Sheldon TA, Shaffer JL.

No. 2
Diagnosis, management and screening of early localised prostate cancer.
A review by Selley S, Donovan J, Faulkner A, Coast J, Gillatt D.

No. 3
The diagnosis, management, treatment and costs of prostate cancer in England and Wales.
A review by Chamberlain J, Melia J, Moss S, Brown J.

No. 4
Screening for fragile X syndrome.
A review by Murray J, Cuckle H, Taylor G, Hewison J.

No. 5
A review of near patient testing in primary care.
By Hobbs FDR, Delaney BC, Fitzmaurice DA, Wilson S, Hyde CJ, Thorpe GH, *et al*.

No. 6
Systematic review of outpatient services for chronic pain control.
By McQuay HJ, Moore RA, Eccleston C, Morley S, de C Williams AC.

No. 7
Neonatal screening for inborn errors of metabolism: cost, yield and outcome.
A review by Pollitt RJ, Green A, McCabe CJ, Booth A, Cooper NJ, Leonard JV, *et al*.

No. 8
Preschool vision screening.
A review by Snowdon SK, Stewart-Brown SL.

No. 9
Implications of socio-cultural contexts for the ethics of clinical trials.
A review by Ashcroft RE, Chadwick DW, Clark SRL, Edwards RHT, Frith L, Hutton JL.

No. 10
A critical review of the role of neonatal hearing screening in the detection of congenital hearing impairment.
By Davis A, Bamford J, Wilson I, Ramkalawan T, Forshaw M, Wright S.

No. 11
Newborn screening for inborn errors of metabolism: a systematic review.
By Seymour CA, Thomason MJ, Chalmers RA, Addison GM, Bain MD, Cockburn F, *et al*.

No. 12
Routine preoperative testing: a systematic review of the evidence.
By Munro J, Booth A, Nicholl J.

No. 13
Systematic review of the effectiveness of laxatives in the elderly.
By Petticrew M, Watt I, Sheldon T.

No. 14
When and how to assess fast-changing technologies: a comparative study of medical applications of four generic technologies.
A review by Mowatt G, Bower DJ, Brebner JA, Cairns JA, Grant AM, McKee L.

Volume 2, 1998

No. 1
Antenatal screening for Down's syndrome.
A review by Wald NJ, Kennard A, Hackshaw A, McGuire A.

No. 2
Screening for ovarian cancer: a systematic review.
By Bell R, Petticrew M, Luengo S, Sheldon TA.

No. 3
Consensus development methods, and their use in clinical guideline development.
A review by Murphy MK, Black NA, Lamping DL, McKee CM, Sanderson CFB, Askham J, *et al*.

No. 4
A cost–utility analysis of interferon beta for multiple sclerosis.
By Parkin D, McNamee P, Jacoby A, Miller P, Thomas S, Bates D.

No. 5
Effectiveness and efficiency of methods of dialysis therapy for end-stage renal disease: systematic reviews.
By MacLeod A, Grant A, Donaldson C, Khan I, Campbell M, Daly C, *et al*.

No. 6
Effectiveness of hip prostheses in primary total hip replacement: a critical review of evidence and an economic model.
By Faulkner A, Kennedy LG, Baxter K, Donovan J, Wilkinson M, Bevan G.

No. 7
Antimicrobial prophylaxis in colorectal surgery: a systematic review of randomised controlled trials.
By Song F, Glenny AM.

No. 8
Bone marrow and peripheral blood stem cell transplantation for malignancy.
A review by Johnson PWM, Simnett SJ, Sweetenham JW, Morgan GJ, Stewart LA.

No. 9
Screening for speech and language delay: a systematic review of the literature.
By Law J, Boyle J, Harris F, Harkness A, Nye C.

No. 10
Resource allocation for chronic stable angina: a systematic review of effectiveness, costs and cost-effectiveness of alternative interventions.
By Sculpher MJ, Petticrew M, Kelland JL, Elliott RA, Holdright DR, Buxton MJ.

No. 11
Detection, adherence and control of hypertension for the prevention of stroke: a systematic review.
By Ebrahim S.

No. 12
Postoperative analgesia and vomiting, with special reference to day-case surgery: a systematic review.
By McQuay HJ, Moore RA.

No. 13
Choosing between randomised and nonrandomised studies: a systematic review.
By Britton A, McKee M, Black N, McPherson K, Sanderson C, Bain C.

No. 14
Evaluating patient-based outcome measures for use in clinical trials.
A review by Fitzpatrick R, Davey C, Buxton MJ, Jones DR.

No. 15
Ethical issues in the design and conduct of randomised controlled trials.
A review by Edwards SJL, Lilford RJ, Braunholtz DA, Jackson JC, Hewison J, Thornton J.

No. 16
Qualitative research methods in health technology assessment: a review of the literature.
By Murphy E, Dingwall R, Greatbatch D, Parker S, Watson P.

No. 17
The costs and benefits of paramedic skills in pre-hospital trauma care.
By Nicholl J, Hughes S, Dixon S, Turner J, Yates D.

No. 18
Systematic review of endoscopic ultrasound in gastro-oesophageal cancer.
By Harris KM, Kelly S, Berry E, Hutton J, Roderick P, Cullingworth J, *et al*.

No. 19
Systematic reviews of trials and other studies.
By Sutton AJ, Abrams KR, Jones DR, Sheldon TA, Song F.

No. 20
Primary total hip replacement surgery: a systematic review of outcomes and modelling of cost-effectiveness associated with different prostheses.
A review by Fitzpatrick R, Shortall E, Sculpher M, Murray D, Morris R, Lodge M, *et al*.

Volume 3, 1999

No. 1
Informed decision making: an annotated bibliography and systematic review.
By Bekker H, Thornton JG, Airey CM, Connelly JB, Hewison J, Robinson MB, *et al*.

No. 2
Handling uncertainty when performing economic evaluation of healthcare interventions.
A review by Briggs AH, Gray AM.

No. 3
The role of expectancies in the placebo effect and their use in the delivery of health care: a systematic review.
By Crow R, Gage H, Hampson S, Hart J, Kimber A, Thomas H.

No. 4
A randomised controlled trial of different approaches to universal antenatal HIV testing: uptake and acceptability. Annex: Antenatal HIV testing – assessment of a routine voluntary approach.
By Simpson WM, Johnstone FD, Boyd FM, Goldberg DJ, Hart GJ, Gormley SM, *et al*.

No. 5
Methods for evaluating area-wide and organisation-based interventions in health and health care: a systematic review.
By Ukoumunne OC, Gulliford MC, Chinn S, Sterne JAC, Burney PGJ.

No. 6
Assessing the costs of healthcare technologies in clinical trials.
A review by Johnston K, Buxton MJ, Jones DR, Fitzpatrick R.

No. 7
Cooperatives and their primary care emergency centres: organisation and impact.
By Hallam L, Henthorne K.

No. 8
Screening for cystic fibrosis.
A review by Murray J, Cuckle H, Taylor G, Littlewood J, Hewison J.

No. 9
A review of the use of health status measures in economic evaluation.
By Brazier J, Deverill M, Green C, Harper R, Booth A.

No. 10
Methods for the analysis of quality-of-life and survival data in health technology assessment.
A review by Billingham LJ, Abrams KR, Jones DR.

No. 11
Antenatal and neonatal haemoglobinopathy screening in the UK: review and economic analysis.
By Zeuner D, Ades AE, Karnon J, Brown J, Dezateux C, Anionwu EN.

No. 12
Assessing the quality of reports of randomised trials: implications for the conduct of meta-analyses.
A review by Moher D, Cook DJ, Jadad AR, Tugwell P, Moher M, Jones A, *et al*.

No. 13
'Early warning systems' for identifying new healthcare technologies.
By Robert G, Stevens A, Gabbay J.

No. 14
A systematic review of the role of human papillomavirus testing within a cervical screening programme.
By Cuzick J, Sasieni P, Davies P, Adams J, Normand C, Frater A, *et al*.

No. 15
Near patient testing in diabetes clinics: appraising the costs and outcomes.
By Grieve R, Beech R, Vincent J, Mazurkiewicz J.

No. 16
Positron emission tomography: establishing priorities for health technology assessment.
A review by Robert G, Milne R.

No. 17 (Pt 1)
The debridement of chronic wounds: a systematic review.
By Bradley M, Cullum N, Sheldon T.

No. 17 (Pt 2)
Systematic reviews of wound care management: (2) Dressings and topical agents used in the healing of chronic wounds.
By Bradley M, Cullum N, Nelson EA, Petticrew M, Sheldon T, Torgerson D.

No. 18
A systematic literature review of spiral and electron beam computed tomography: with particular reference to clinical applications in hepatic lesions, pulmonary embolus and coronary artery disease.
By Berry E, Kelly S, Hutton J, Harris KM, Roderick P, Boyce JC, *et al*.

No. 19
What role for statins? A review and economic model.
By Ebrahim S, Davey Smith G, McCabe C, Payne N, Pickin M, Sheldon TA, *et al*.

No. 20
Factors that limit the quality, number and progress of randomised controlled trials.
A review by Prescott RJ, Counsell CE, Gillespie WJ, Grant AM, Russell IT, Kiauka S, *et al*.

No. 21
Antimicrobial prophylaxis in total hip replacement: a systematic review.
By Glenny AM, Song F.

No. 22
Health promoting schools and health promotion in schools: two systematic reviews.
By Lister-Sharp D, Chapman S, Stewart-Brown S, Sowden A.

No. 23
Economic evaluation of a primary care-based education programme for patients with osteoarthritis of the knee.
A review by Lord J, Victor C, Littlejohns P, Ross FM, Axford JS.

Volume 4, 2000

No. 1
The estimation of marginal time preference in a UK-wide sample (TEMPUS) project.
A review by Cairns JA, van der Pol MM.

No. 2
Geriatric rehabilitation following fractures in older people: a systematic review.
By Cameron I, Crotty M, Currie C, Finnegan T, Gillespie L, Gillespie W, *et al*.

No. 3
Screening for sickle cell disease and thalassaemia: a systematic review with supplementary research.
By Davies SC, Cronin E, Gill M, Greengross P, Hickman M, Normand C.

No. 4
Community provision of hearing aids and related audiology services.
A review by Reeves DJ, Alborz A, Hickson FS, Bamford JM.

No. 5
False-negative results in screening programmes: systematic review of impact and implications.
By Petticrew MP, Sowden AJ, Lister-Sharp D, Wright K.

No. 6
Costs and benefits of community postnatal support workers: a randomised controlled trial.
By Morrell CJ, Spiby H, Stewart P, Walters S, Morgan A.

No. 7
Implantable contraceptives (subdermal implants and hormonally impregnated intrauterine systems) versus other forms of reversible contraceptives: two systematic reviews to assess relative effectiveness, acceptability, tolerability and cost-effectiveness.
By French RS, Cowan FM, Mansour DJA, Morris S, Procter T, Hughes D, *et al*.

No. 8
An introduction to statistical methods for health technology assessment.
A review by White SJ, Ashby D, Brown PJ.

No. 9
Disease-modifying drugs for multiple sclerosis: a rapid and systematic review.
By Clegg A, Bryant J, Milne R.

No. 10
Publication and related biases.
A review by Song F, Eastwood AJ, Gilbody S, Duley L, Sutton AJ.

No. 11
Cost and outcome implications of the organisation of vascular services.
By Michaels J, Brazier J, Palfreyman S, Shackley P, Slack R.

No. 12
Monitoring blood glucose control in diabetes mellitus: a systematic review.
By Coster S, Gulliford MC, Seed PT, Powrie JK, Swaminathan R.

No. 13
The effectiveness of domiciliary health visiting: a systematic review of international studies and a selective review of the British literature.
By Elkan R, Kendrick D, Hewitt M, Robinson JJA, Tolley K, Blair M, *et al*.

No. 14
The determinants of screening uptake and interventions for increasing uptake: a systematic review.
By Jepson R, Clegg A, Forbes C, Lewis R, Sowden A, Kleijnen J.

No. 15
The effectiveness and cost-effectiveness of prophylactic removal of wisdom teeth.
A rapid review by Song F, O'Meara S, Wilson P, Golder S, Kleijnen J.

No. 16
Ultrasound screening in pregnancy: a systematic review of the clinical effectiveness, cost-effectiveness and women's views.
By Bricker L, Garcia J, Henderson J, Mugford M, Neilson J, Roberts T, *et al*.

No. 17
A rapid and systematic review of the effectiveness and cost-effectiveness of the taxanes used in the treatment of advanced breast and ovarian cancer.
By Lister-Sharp D, McDonagh MS, Khan KS, Kleijnen J.

No. 18
Liquid-based cytology in cervical screening: a rapid and systematic review.
By Payne N, Chilcott J, McGoogan E.

No. 19
Randomised controlled trial of non-directive counselling, cognitive–behaviour therapy and usual general practitioner care in the management of depression as well as mixed anxiety and depression in primary care.
By King M, Sibbald B, Ward E, Bower P, Lloyd M, Gabbay M, *et al*.

No. 20
Routine referral for radiography of patients presenting with low back pain: is patients' outcome influenced by GPs' referral for plain radiography?
By Kerry S, Hilton S, Patel S, Dundas D, Rink E, Lord J.

No. 21
Systematic reviews of wound care management: (3) antimicrobial agents for chronic wounds; (4) diabetic foot ulceration.
By O'Meara S, Cullum N, Majid M, Sheldon T.

No. 22
Using routine data to complement and enhance the results of randomised controlled trials.
By Lewsey JD, Leyland AH, Murray GD, Boddy FA.

No. 23
Coronary artery stents in the treatment of ischaemic heart disease: a rapid and systematic review.
By Meads C, Cummins C, Jolly K, Stevens A, Burls A, Hyde C.

No. 24
Outcome measures for adult critical care: a systematic review.
By Hayes JA, Black NA, Jenkinson C, Young JD, Rowan KM, Daly K, *et al*.

No. 25
A systematic review to evaluate the effectiveness of interventions to promote the initiation of breastfeeding.
By Fairbank L, O'Meara S, Renfrew MJ, Woolridge M, Sowden AJ, Lister-Sharp D.

No. 26
Implantable cardioverter defibrillators: arrhythmias. A rapid and systematic review.
By Parkes J, Bryant J, Milne R.

No. 27
Treatments for fatigue in multiple sclerosis: a rapid and systematic review.
By Brañas P, Jordan R, Fry-Smith A, Burls A, Hyde C.

No. 28
Early asthma prophylaxis, natural history, skeletal development and economy (EASE): a pilot randomised controlled trial.
By Baxter-Jones ADG, Helms PJ, Russell G, Grant A, Ross S, Cairns JA, *et al*.

No. 29
Screening for hypercholesterolaemia versus case finding for familial hypercholesterolaemia: a systematic review and cost-effectiveness analysis.
By Marks D, Wonderling D, Thorogood M, Lambert H, Humphries SE, Neil HAW.

No. 30
A rapid and systematic review of the clinical effectiveness and cost-effectiveness of glycoprotein IIb/IIIa antagonists in the medical management of unstable angina.
By McDonagh MS, Bachmann LM, Golder S, Kleijnen J, ter Riet G.

No. 31
A randomised controlled trial of prehospital intravenous fluid replacement therapy in serious trauma.
By Turner J, Nicholl J, Webber L, Cox H, Dixon S, Yates D.

No. 32
Intrathecal pumps for giving opioids in chronic pain: a systematic review.
By Williams JE, Louw G, Towlerton G.

No. 33
Combination therapy (interferon alfa and ribavirin) in the treatment of chronic hepatitis C: a rapid and systematic review.
By Shepherd J, Waugh N, Hewitson P.

No. 34
A systematic review of comparisons of effect sizes derived from randomised and non-randomised studies.
By MacLehose RR, Reeves BC, Harvey IM, Sheldon TA, Russell IT, Black AMS.

No. 35
Intravascular ultrasound-guided interventions in coronary artery disease: a systematic literature review, with decision-analytic modelling, of outcomes and cost-effectiveness.
By Berry E, Kelly S, Hutton J, Lindsay HSJ, Blaxill JM, Evans JA, *et al*.

No. 36
A randomised controlled trial to evaluate the effectiveness and cost-effectiveness of counselling patients with chronic depression.
By Simpson S, Corney R, Fitzgerald P, Beecham J.

No. 37
Systematic review of treatments for atopic eczema.
By Hoare C, Li Wan Po A, Williams H.

No. 38
Bayesian methods in health technology assessment: a review.
By Spiegelhalter DJ, Myles JP, Jones DR, Abrams KR.

No. 39
The management of dyspepsia: a systematic review.
By Delaney B, Moayyedi P, Deeks J, Innes M, Soo S, Barton P, *et al*.

No. 40
A systematic review of treatments for severe psoriasis.
By Griffiths CEM, Clark CM, Chalmers RJG, Li Wan Po A, Williams HC.

Volume 5, 2001

No. 1
Clinical and cost-effectiveness of donepezil, rivastigmine and galantamine for Alzheimer's disease: a rapid and systematic review.
By Clegg A, Bryant J, Nicholson T, McIntyre L, De Broe S, Gerard K, *et al*.

No. 2
The clinical effectiveness and cost-effectiveness of riluzole for motor neurone disease: a rapid and systematic review.
By Stewart A, Sandercock J, Bryan S, Hyde C, Barton PM, Fry-Smith A, *et al*.

No. 3
Equity and the economic evaluation of healthcare.
By Sassi F, Archard L, Le Grand J.

No. 4
Quality-of-life measures in chronic diseases of childhood.
By Eiser C, Morse R.

No. 5
Eliciting public preferences for healthcare: a systematic review of techniques.
By Ryan M, Scott DA, Reeves C, Bate A, van Teijlingen ER, Russell EM, *et al*.

No. 6
General health status measures for people with cognitive impairment: learning disability and acquired brain injury.
By Riemsma RP, Forbes CA, Glanville JM, Eastwood AJ, Kleijnen J.

No. 7
An assessment of screening strategies for fragile X syndrome in the UK.
By Pembrey ME, Barnicoat AJ, Carmichael B, Bobrow M, Turner G.

No. 8
Issues in methodological research: perspectives from researchers and commissioners.
By Lilford RJ, Richardson A, Stevens A, Fitzpatrick R, Edwards S, Rock F, *et al*.

No. 9
Systematic reviews of wound care management: (5) beds; (6) compression; (7) laser therapy, therapeutic ultrasound, electrotherapy and electromagnetic therapy.
By Cullum N, Nelson EA, Flemming K, Sheldon T.

No. 10
Effects of educational and psychosocial interventions for adolescents with diabetes mellitus: a systematic review.
By Hampson SE, Skinner TC, Hart J, Storey L, Gage H, Foxcroft D, *et al*.

No. 11
Effectiveness of autologous chondrocyte transplantation for hyaline cartilage defects in knees: a rapid and systematic review.
By Jobanputra P, Parry D, Fry-Smith A, Burls A.

No. 12
Statistical assessment of the learning curves of health technologies.
By Ramsay CR, Grant AM, Wallace SA, Garthwaite PH, Monk AF, Russell IT.

No. 13
The effectiveness and cost-effectiveness of temozolomide for the treatment of recurrent malignant glioma: a rapid and systematic review.
By Dinnes J, Cave C, Huang S, Major K, Milne R.

No. 14
A rapid and systematic review of the clinical effectiveness and cost-effectiveness of debriding agents in treating surgical wounds healing by secondary intention.
By Lewis R, Whiting P, ter Riet G, O'Meara S, Glanville J.

No. 15
Home treatment for mental health problems: a systematic review.
By Burns T, Knapp M, Catty J, Healey A, Henderson J, Watt H, *et al*.

No. 16
How to develop cost-conscious guidelines.
By Eccles M, Mason J.

No. 17
The role of specialist nurses in multiple sclerosis: a rapid and systematic review.
By De Broe S, Christopher F, Waugh N.

No. 18
A rapid and systematic review of the clinical effectiveness and cost-effectiveness of orlistat in the management of obesity.
By O'Meara S, Riemsma R, Shirran L, Mather L, ter Riet G.

No. 19
The clinical effectiveness and cost-effectiveness of pioglitazone for type 2 diabetes mellitus: a rapid and systematic review.
By Chilcott J, Wight J, Lloyd Jones M, Tappenden P.

No. 20
Extended scope of nursing practice: a multicentre randomised controlled trial of appropriately trained nurses and preregistration house officers in preoperative assessment in elective general surgery.
By Kinley H, Czoski-Murray C, George S, McCabe C, Primrose J, Reilly C, *et al*.

No. 21
Systematic reviews of the effectiveness of day care for people with severe mental disorders: (1) Acute day hospital versus admission; (2) Vocational rehabilitation; (3) Day hospital versus outpatient care.
By Marshall M, Crowther R, Almaraz- Serrano A, Creed F, Sledge W, Kluiter H, *et al*.

No. 22
The measurement and monitoring of surgical adverse events.
By Bruce J, Russell EM, Mollison J, Krukowski ZH.

No. 23
Action research: a systematic review and guidance for assessment.
By Waterman H, Tillen D, Dickson R, de Koning K.

No. 24
A rapid and systematic review of the clinical effectiveness and cost-effectiveness of gemcitabine for the treatment of pancreatic cancer.
By Ward S, Morris E, Bansback N, Calvert N, Crellin A, Forman D, *et al*.

No. 25
A rapid and systematic review of the evidence for the clinical effectiveness and cost-effectiveness of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer.
By Lloyd Jones M, Hummel S, Bansback N, Orr B, Seymour M.

No. 26
Comparison of the effectiveness of inhaler devices in asthma and chronic obstructive airways disease: a systematic review of the literature.
By Brocklebank D, Ram F, Wright J, Barry P, Cates C, Davies L, *et al*.

No. 27
The cost-effectiveness of magnetic resonance imaging for investigation of the knee joint.
By Bryan S, Weatherburn G, Bungay H, Hatrick C, Salas C, Parry D, *et al*.

No. 28
A rapid and systematic review of the clinical effectiveness and cost-effectiveness of topotecan for ovarian cancer.
By Forbes C, Shirran L, Bagnall A-M, Duffy S, ter Riet G.

No. 29
Superseded by a report published in a later volume.

No. 30
The role of radiography in primary care patients with low back pain of at least 6 weeks duration: a randomised (unblinded) controlled trial.
By Kendrick D, Fielding K, Bentley E, Miller P, Kerslake R, Pringle M.

No. 31
Design and use of questionnaires: a review of best practice applicable to surveys of health service staff and patients.
By McColl E, Jacoby A, Thomas L, Soutter J, Bamford C, Steen N, *et al*.

No. 32
A rapid and systematic review of the clinical effectiveness and cost-effectiveness of paclitaxel, docetaxel, gemcitabine and vinorelbine in non-small-cell lung cancer.
By Clegg A, Scott DA, Sidhu M, Hewitson P, Waugh N.

No. 33
Subgroup analyses in randomised controlled trials: quantifying the risks of false-positives and false-negatives.
By Brookes ST, Whitley E, Peters TJ, Mulheran PA, Egger M, Davey Smith G.

No. 34
Depot antipsychotic medication in the treatment of patients with schizophrenia: (1) Meta-review; (2) Patient and nurse attitudes.
By David AS, Adams C.

No. 35
A systematic review of controlled trials of the effectiveness and cost-effectiveness of brief psychological treatments for depression.
By Churchill R, Hunot V, Corney R, Knapp M, McGuire H, Tylee A, *et al*.

No. 36
Cost analysis of child health surveillance.
By Sanderson D, Wright D, Acton C, Duree D.

Volume 6, 2002

No. 1
A study of the methods used to select review criteria for clinical audit.
By Hearnshaw H, Harker R, Cheater F, Baker R, Grimshaw G.

No. 2
Fludarabine as second-line therapy for B cell chronic lymphocytic leukaemia: a technology assessment.
By Hyde C, Wake B, Bryan S, Barton P, Fry-Smith A, Davenport C, *et al*.

No. 3
Rituximab as third-line treatment for refractory or recurrent Stage III or IV follicular non-Hodgkin's lymphoma: a systematic review and economic evaluation.
By Wake B, Hyde C, Bryan S, Barton P, Song F, Fry-Smith A, *et al*.

No. 4
A systematic review of discharge arrangements for older people.
By Parker SG, Peet SM, McPherson A, Cannaby AM, Baker R, Wilson A, *et al*.

No. 5
The clinical effectiveness and cost-effectiveness of inhaler devices used in the routine management of chronic asthma in older children: a systematic review and economic evaluation.
By Peters J, Stevenson M, Beverley C, Lim J, Smith S.

No. 6
The clinical effectiveness and cost-effectiveness of sibutramine in the management of obesity: a technology assessment.
By O'Meara S, Riemsma R, Shirran L, Mather L, ter Riet G.

No. 7
The cost-effectiveness of magnetic resonance angiography for carotid artery stenosis and peripheral vascular disease: a systematic review.
By Berry E, Kelly S, Westwood ME, Davies LM, Gough MJ, Bamford JM, *et al*.

No. 8
Promoting physical activity in South Asian Muslim women through 'exercise on prescription'.
By Carroll B, Ali N, Azam N.

No. 9
Zanamivir for the treatment of influenza in adults: a systematic review and economic evaluation.
By Burls A, Clark W, Stewart T, Preston C, Bryan S, Jefferson T, *et al*.

No. 10
A review of the natural history and epidemiology of multiple sclerosis: implications for resource allocation and health economic models.
By Richards RG, Sampson FC, Beard SM, Tappenden P.

No. 11
Screening for gestational diabetes: a systematic review and economic evaluation.
By Scott DA, Loveman E, McIntyre L, Waugh N.

No. 12
The clinical effectiveness and cost-effectiveness of surgery for people with morbid obesity: a systematic review and economic evaluation.
By Clegg AJ, Colquitt J, Sidhu MK, Royle P, Loveman E, Walker A.

No. 13
The clinical effectiveness of trastuzumab for breast cancer: a systematic review.
By Lewis R, Bagnall A-M, Forbes C, Shirran E, Duffy S, Kleijnen J, *et al*.

No. 14
The clinical effectiveness and cost-effectiveness of vinorelbine for breast cancer: a systematic review and economic evaluation.
By Lewis R, Bagnall A-M, King S, Woolacott N, Forbes C, Shirran L, *et al*.

No. 15
A systematic review of the effectiveness and cost-effectiveness of metal-on-metal hip resurfacing arthroplasty for treatment of hip disease.
By Vale L, Wyness L, McCormack K, McKenzie L, Brazzelli M, Stearns SC.

No. 16
The clinical effectiveness and cost-effectiveness of bupropion and nicotine replacement therapy for smoking cessation: a systematic review and economic evaluation.
By Woolacott NF, Jones L, Forbes CA, Mather LC, Sowden AJ, Song FJ, *et al*.

No. 17
A systematic review of effectiveness and economic evaluation of new drug treatments for juvenile idiopathic arthritis: etanercept.
By Cummins C, Connock M, Fry-Smith A, Burls A.

No. 18
Clinical effectiveness and cost-effectiveness of growth hormone in children: a systematic review and economic evaluation.
By Bryant J, Cave C, Mihaylova B, Chase D, McIntyre L, Gerard K, *et al*.

No. 19
Clinical effectiveness and cost-effectiveness of growth hormone in adults in relation to impact on quality of life: a systematic review and economic evaluation.
By Bryant J, Loveman E, Chase D, Mihaylova B, Cave C, Gerard K, *et al*.

No. 20
Clinical medication review by a pharmacist of patients on repeat prescriptions in general practice: a randomised controlled trial.
By Zermansky AG, Petty DR, Raynor DK, Lowe CJ, Freementle N, Vail A.

No. 21
The effectiveness of infliximab and etanercept for the treatment of rheumatoid arthritis: a systematic review and economic evaluation.
By Jobanputra P, Barton P, Bryan S, Burls A.

No. 22
A systematic review and economic evaluation of computerised cognitive behaviour therapy for depression and anxiety.
By Kaltenthaler E, Shackley P, Stevens K, Beverley C, Parry G, Chilcott J.

No. 23
A systematic review and economic evaluation of pegylated liposomal doxorubicin hydrochloride for ovarian cancer.
By Forbes C, Wilby J, Richardson G, Sculpher M, Mather L, Reimsma R.

No. 24
A systematic review of the effectiveness of interventions based on a stages-of-change approach to promote individual behaviour change.
By Riemsma RP, Pattenden J, Bridle C, Sowden AJ, Mather L, Watt IS, *et al*.

No. 25
A systematic review update of the clinical effectiveness and cost-effectiveness of glycoprotein IIb/IIIa antagonists.
By Robinson M, Ginnelly L, Sculpher M, Jones L, Riemsma R, Palmer S, *et al*.

No. 26
A systematic review of the effectiveness, cost-effectiveness and barriers to implementation of thrombolytic and neuroprotective therapy for acute ischaemic stroke in the NHS.
By Sandercock P, Berge E, Dennis M, Forbes J, Hand P, Kwan J, *et al*.

No. 27
A randomised controlled crossover trial of nurse practitioner versus doctor-led outpatient care in a bronchiectasis clinic.
By Caine N, Sharples LD, Hollingworth W, French J, Keogan M, Exley A, *et al*.

No. 28
Clinical effectiveness and cost – consequences of selective serotonin reuptake inhibitors in the treatment of sex offenders.
By Adi Y, Ashcroft D, Browne K, Beech A, Fry-Smith A, Hyde C.

No. 29
Treatment of established osteoporosis: a systematic review and cost–utility analysis.
By Kanis JA, Brazier JE, Stevenson M, Calvert NW, Lloyd Jones M.

No. 30
Which anaesthetic agents are cost-effective in day surgery? Literature review, national survey of practice and randomised controlled trial.
By Elliott RA Payne K, Moore JK, Davies LM, Harper NJN, St Leger AS, *et al*.

No. 31
Screening for hepatitis C among injecting drug users and in genitourinary medicine clinics: systematic reviews of effectiveness, modelling study and national survey of current practice.
By Stein K, Dalziel K, Walker A, McIntyre L, Jenkins B, Horne J, *et al*.

No. 32
The measurement of satisfaction with healthcare: implications for practice from a systematic review of the literature.
By Crow R, Gage H, Hampson S, Hart J, Kimber A, Storey L, *et al*.

No. 33
The effectiveness and cost-effectiveness of imatinib in chronic myeloid leukaemia: a systematic review.
By Garside R, Round A, Dalziel K, Stein K, Royle R.

No. 34
A comparative study of hypertonic saline, daily and alternate-day rhDNase in children with cystic fibrosis.
By Suri R, Wallis C, Bush A, Thompson S, Normand C, Flather M, *et al*.

No. 35
A systematic review of the costs and effectiveness of different models of paediatric home care.
By Parker G, Bhakta P, Lovett CA, Paisley S, Olsen R, Turner D, *et al*.

Volume 7, 2003

No. 1
How important are comprehensive literature searches and the assessment of trial quality in systematic reviews? Empirical study.
By Egger M, Jüni P, Bartlett C, Holenstein F, Sterne J.

No. 2
Systematic review of the effectiveness and cost-effectiveness, and economic evaluation, of home versus hospital or satellite unit haemodialysis for people with end-stage renal failure.
By Mowatt G, Vale L, Perez J, Wyness L, Fraser C, MacLeod A, *et al*.

No. 3
Systematic review and economic evaluation of the effectiveness of infliximab for the treatment of Crohn's disease.
By Clark W, Raftery J, Barton P, Song F, Fry-Smith A, Burls A.

No. 4
A review of the clinical effectiveness and cost-effectiveness of routine anti-D prophylaxis for pregnant women who are rhesus negative.
By Chilcott J, Lloyd Jones M, Wight J, Forman K, Wray J, Beverley C, *et al*.

No. 5
Systematic review and evaluation of the use of tumour markers in paediatric oncology: Ewing's sarcoma and neuroblastoma.
By Riley RD, Burchill SA, Abrams KR, Heney D, Lambert PC, Jones DR, *et al*.

No. 6
The cost-effectiveness of screening for *Helicobacter pylori* to reduce mortality and morbidity from gastric cancer and peptic ulcer disease: a discrete-event simulation model.
By Roderick P, Davies R, Raftery J, Crabbe D, Pearce R, Bhandari P, *et al*.

No. 7
The clinical effectiveness and cost-effectiveness of routine dental checks: a systematic review and economic evaluation.
By Davenport C, Elley K, Salas C, Taylor-Weetman CL, Fry-Smith A, Bryan S, *et al*.

No. 8
A multicentre randomised controlled trial assessing the costs and benefits of using structured information and analysis of women's preferences in the management of menorrhagia.
By Kennedy ADM, Sculpher MJ, Coulter A, Dwyer N, Rees M, Horsley S, *et al*.

No. 9
Clinical effectiveness and cost–utility of photodynamic therapy for wet age-related macular degeneration: a systematic review and economic evaluation.
By Meads C, Salas C, Roberts T, Moore D, Fry-Smith A, Hyde C.

No. 10
Evaluation of molecular tests for prenatal diagnosis of chromosome abnormalities.
By Grimshaw GM, Szczepura A, Hultén M, MacDonald F, Nevin NC, Sutton F, *et al*.

No. 11
First and second trimester antenatal screening for Down's syndrome: the results of the Serum, Urine and Ultrasound Screening Study (SURUSS).
By Wald NJ, Rodeck C, Hackshaw AK, Walters J, Chitty L, Mackinson AM.

No. 12
The effectiveness and cost-effectiveness of ultrasound locating devices for central venous access: a systematic review and economic evaluation.
By Calvert N, Hind D, McWilliams RG, Thomas SM, Beverley C, Davidson A.

No. 13
A systematic review of atypical antipsychotics in schizophrenia.
By Bagnall A-M, Jones L, Lewis R, Ginnelly L, Glanville J, Torgerson D, *et al.*

No. 14
Prostate Testing for Cancer and Treatment (ProtecT) feasibility study.
By Donovan J, Hamdy F, Neal D, Peters T, Oliver S, Brindle L, *et al*.

No. 15
Early thrombolysis for the treatment of acute myocardial infarction: a systematic review and economic evaluation.
By Boland A, Dundar Y, Bagust A, Haycox A, Hill R, Mujica Mota R, *et al*.

No. 16
Screening for fragile X syndrome: a literature review and modelling.
By Song FJ, Barton P, Sleightholme V, Yao GL, Fry-Smith A.

No. 17
Systematic review of endoscopic sinus surgery for nasal polyps.
By Dalziel K, Stein K, Round A, Garside R, Royle P.

No. 18
Towards efficient guidelines: how to monitor guideline use in primary care.
By Hutchinson A, McIntosh A, Cox S, Gilbert C.

No. 19
Effectiveness and cost-effectiveness of acute hospital-based spinal cord injuries services: systematic review.
By Bagnall A-M, Jones L, Richardson G, Duffy S, Riemsma R.

No. 20
Prioritisation of health technology assessment. The PATHS model: methods and case studies.
By Townsend J, Buxton M, Harper G.

No. 21
Systematic review of the clinical effectiveness and cost-effectiveness of tension-free vaginal tape for treatment of urinary stress incontinence.
By Cody J, Wyness L, Wallace S, Glazener C, Kilonzo M, Stearns S, *et al*.

No. 22
The clinical and cost-effectiveness of patient education models for diabetes: a systematic review and economic evaluation.
By Loveman E, Cave C, Green C, Royle P, Dunn N, Waugh N.

No. 23
The role of modelling in prioritising and planning clinical trials.
By Chilcott J, Brennan A, Booth A, Karnon J, Tappenden P.

No. 24
Cost–benefit evaluation of routine influenza immunisation in people 65–74 years of age.
By Allsup S, Gosney M, Haycox A, Regan M.

No. 25
The clinical and cost-effectiveness of pulsatile machine perfusion versus cold storage of kidneys for transplantation retrieved from heart-beating and non-heart-beating donors.
By Wight J, Chilcott J, Holmes M, Brewer N.

No. 26
Can randomised trials rely on existing electronic data? A feasibility study to explore the value of routine data in health technology assessment.
By Williams JG, Cheung WY, Cohen DR, Hutchings HA, Longo MF, Russell IT.

No. 27
Evaluating non-randomised intervention studies.
By Deeks JJ, Dinnes J, D'Amico R, Sowden AJ, Sakarovitch C, Song F, *et al*.

No. 28
A randomised controlled trial to assess the impact of a package comprising a patient-orientated, evidence-based self-help guidebook and patient-centred consultations on disease management and satisfaction in inflammatory bowel disease.
By Kennedy A, Nelson E, Reeves D, Richardson G, Roberts C, Robinson A, *et al*.

No. 29
The effectiveness of diagnostic tests for the assessment of shoulder pain due to soft tissue disorders: a systematic review.
By Dinnes J, Loveman E, McIntyre L, Waugh N.

No. 30
The value of digital imaging in diabetic retinopathy.
By Sharp PF, Olson J, Strachan F, Hipwell J, Ludbrook A, O'Donnell M, *et al*.

No. 31
Lowering blood pressure to prevent myocardial infarction and stroke: a new preventive strategy.
By Law M, Wald N, Morris J.

No. 32
Clinical and cost-effectiveness of capecitabine and tegafur with uracil for the treatment of metastatic colorectal cancer: systematic review and economic evaluation.
By Ward S, Kaltenthaler E, Cowan J, Brewer N.

No. 33
Clinical and cost-effectiveness of new and emerging technologies for early localised prostate cancer: a systematic review.
By Hummel S, Paisley S, Morgan A, Currie E, Brewer N.

No. 34
Literature searching for clinical and cost-effectiveness studies used in health technology assessment reports carried out for the National Institute for Clinical Excellence appraisal system.
By Royle P, Waugh N.

No. 35
Systematic review and economic decision modelling for the prevention and treatment of influenza A and B.
By Turner D, Wailoo A, Nicholson K, Cooper N, Sutton A, Abrams K.

No. 36
A randomised controlled trial to evaluate the clinical and cost-effectiveness of Hickman line insertions in adult cancer patients by nurses.
By Boland A, Haycox A, Bagust A, Fitzsimmons L.

No. 37
Redesigning postnatal care: a randomised controlled trial of protocol-based midwifery-led care focused on individual women's physical and psychological health needs.
By MacArthur C, Winter HR, Bick DE, Lilford RJ, Lancashire RJ, Knowles H, *et al*.

No. 38
Estimating implied rates of discount in healthcare decision-making.
By West RR, McNabb R, Thompson AGH, Sheldon TA, Grimley Evans J.

No. 39
Systematic review of isolation policies in the hospital management of methicillin-resistant *Staphylococcus aureus*: a review of the literature with epidemiological and economic modelling.
By Cooper BS, Stone SP, Kibbler CC, Cookson BD, Roberts JA, Medley GF, *et al*.

No. 40
Treatments for spasticity and pain in multiple sclerosis: a systematic review.
By Beard S, Hunn A, Wight J.

No. 41
The inclusion of reports of randomised trials published in languages other than English in systematic reviews.
By Moher D, Pham B, Lawson ML, Klassen TP.

No. 42
The impact of screening on future health-promoting behaviours and health beliefs: a systematic review.
By Bankhead CR, Brett J, Bukach C, Webster P, Stewart-Brown S, Munafo M, *et al*.

Volume 8, 2004

No. 1
What is the best imaging strategy for acute stroke?
By Wardlaw JM, Keir SL, Seymour J, Lewis S, Sandercock PAG, Dennis MS, *et al*.

No. 2
Systematic review and modelling of the investigation of acute and chronic chest pain presenting in primary care.
By Mant J, McManus RJ, Oakes RAL, Delaney BC, Barton PM, Deeks JJ, *et al*.

No. 3
The effectiveness and cost-effectiveness of microwave and thermal balloon endometrial ablation for heavy menstrual bleeding: a systematic review and economic modelling.
By Garside R, Stein K, Wyatt K, Round A, Price A.

No. 4
A systematic review of the role of bisphosphonates in metastatic disease.
By Ross JR, Saunders Y, Edmonds PM, Patel S, Wonderling D, Normand C, *et al*.

No. 5
Systematic review of the clinical effectiveness and cost-effectiveness of capecitabine (Xeloda®) for locally advanced and/or metastatic breast cancer.
By Jones L, Hawkins N, Westwood M, Wright K, Richardson G, Riemsma R.

No. 6
Effectiveness and efficiency of guideline dissemination and implementation strategies.
By Grimshaw JM, Thomas RE, MacLennan G, Fraser C, Ramsay CR, Vale L, *et al*.

No. 7
Clinical effectiveness and costs of the Sugarbaker procedure for the treatment of pseudomyxoma peritonei.
By Bryant J, Clegg AJ, Sidhu MK, Brodin H, Royle P, Davidson P.

No. 8
Psychological treatment for insomnia in the regulation of long-term hypnotic drug use.
By Morgan K, Dixon S, Mathers N, Thompson J, Tomeny M.

No. 9
Improving the evaluation of therapeutic interventions in multiple sclerosis: development of a patient-based measure of outcome.
By Hobart JC, Riazi A, Lamping DL, Fitzpatrick R, Thompson AJ.

No. 10
A systematic review and economic evaluation of magnetic resonance cholangiopancreatography compared with diagnostic endoscopic retrograde cholangiopancreatography.
By Kaltenthaler E, Bravo Vergel Y, Chilcott J, Thomas S, Blakeborough T, Walters SJ, *et al*.

No. 11
The use of modelling to evaluate new drugs for patients with a chronic condition: the case of antibodies against tumour necrosis factor in rheumatoid arthritis.
By Barton P, Jobanputra P, Wilson J, Bryan S, Burls A.

No. 12
Clinical effectiveness and cost-effectiveness of neonatal screening for inborn errors of metabolism using tandem mass spectrometry: a systematic review.
By Pandor A, Eastham J, Beverley C, Chilcott J, Paisley S.

No. 13
Clinical effectiveness and cost-effectiveness of pioglitazone and rosiglitazone in the treatment of type 2 diabetes: a systematic review and economic evaluation.
By Czoski-Murray C, Warren E, Chilcott J, Beverley C, Psyllaki MA, Cowan J.

No. 14
Routine examination of the newborn: the EMREN study. Evaluation of an extension of the midwife role including a randomised controlled trial of appropriately trained midwives and paediatric senior house officers.
By Townsend J, Wolke D, Hayes J, Davé S, Rogers C, Bloomfield L, *et al*.

No. 15
Involving consumers in research and development agenda setting for the NHS: developing an evidence-based approach.
By Oliver S, Clarke-Jones L, Rees R, Milne R, Buchanan P, Gabbay J, *et al*.

No. 16
A multi-centre randomised controlled trial of minimally invasive direct coronary bypass grafting versus percutaneous transluminal coronary angioplasty with stenting for proximal stenosis of the left anterior descending coronary artery.
By Reeves BC, Angelini GD, Bryan AJ, Taylor FC, Cripps T, Spyt TJ, *et al*.

No. 17
Does early magnetic resonance imaging influence management or improve outcome in patients referred to secondary care with low back pain? A pragmatic randomised controlled trial.
By Gilbert FJ, Grant AM, Gillan MGC, Vale L, Scott NW, Campbell MK, *et al*.

No. 18
The clinical and cost-effectiveness of anakinra for the treatment of rheumatoid arthritis in adults: a systematic review and economic analysis.
By Clark W, Jobanputra P, Barton P, Burls A.

No. 19
A rapid and systematic review and economic evaluation of the clinical and cost-effectiveness of newer drugs for treatment of mania associated with bipolar affective disorder.
By Bridle C, Palmer S, Bagnall A-M, Darba J, Duffy S, Sculpher M, *et al*.

No. 20
Liquid-based cytology in cervical screening: an updated rapid and systematic review and economic analysis.
By Karnon J, Peters J, Platt J, Chilcott J, McGoogan E, Brewer N.

No. 21
Systematic review of the long-term effects and economic consequences of treatments for obesity and implications for health improvement.
By Avenell A, Broom J, Brown TJ, Poobalan A, Aucott L, Stearns SC, *et al*.

No. 22
Autoantibody testing in children with newly diagnosed type 1 diabetes mellitus.
By Dretzke J, Cummins C, Sandercock J, Fry-Smith A, Barrett T, Burls A.

No. 23
Clinical effectiveness and cost-effectiveness of prehospital intravenous fluids in trauma patients.
By Dretzke J, Sandercock J, Bayliss S, Burls A.

No. 24
Newer hypnotic drugs for the short-term management of insomnia: a systematic review and economic evaluation.
By Dündar Y, Boland A, Strobl J, Dodd S, Haycox A, Bagust A, *et al*.

No. 25
Development and validation of methods for assessing the quality of diagnostic accuracy studies.
By Whiting P, Rutjes AWS, Dinnes J, Reitsma JB, Bossuyt PMM, Kleijnen J.

No. 26
EVALUATE hysterectomy trial: a multicentre randomised trial comparing abdominal, vaginal and laparoscopic methods of hysterectomy.
By Garry R, Fountain J, Brown J, Manca A, Mason S, Sculpher M, *et al*.

No. 27
Methods for expected value of information analysis in complex health economic models: developments on the health economics of interferon-β and glatiramer acetate for multiple sclerosis.
By Tappenden P, Chilcott JB, Eggington S, Oakley J, McCabe C.

No. 28
Effectiveness and cost-effectiveness of imatinib for first-line treatment of chronic myeloid leukaemia in chronic phase: a systematic review and economic analysis.
By Dalziel K, Round A, Stein K, Garside R, Price A.

No. 29
VenUS I: a randomised controlled trial of two types of bandage for treating venous leg ulcers.
By Iglesias C, Nelson EA, Cullum NA, Torgerson DJ, on behalf of the VenUS Team.

No. 30
Systematic review of the effectiveness and cost-effectiveness, and economic evaluation, of myocardial perfusion scintigraphy for the diagnosis and management of angina and myocardial infarction.
By Mowatt G, Vale L, Brazzelli M, Hernandez R, Murray A, Scott N, *et al*.

No. 31
A pilot study on the use of decision theory and value of information analysis as part of the NHS Health Technology Assessment programme.
By Claxton K, Ginnelly L, Sculpher M, Philips Z, Palmer S.

No. 32
The Social Support and Family Health Study: a randomised controlled trial and economic evaluation of two alternative forms of postnatal support for mothers living in disadvantaged inner-city areas.
By Wiggins M, Oakley A, Roberts I, Turner H, Rajan L, Austerberry H, *et al*.

No. 33
Psychosocial aspects of genetic screening of pregnant women and newborns: a systematic review.
By Green JM, Hewison J, Bekker HL, Bryant, Cuckle HS.

No. 34
Evaluation of abnormal uterine bleeding: comparison of three outpatient procedures within cohorts defined by age and menopausal status.
By Critchley HOD, Warner P, Lee AJ, Brechin S, Guise J, Graham B.

No. 35
Coronary artery stents: a rapid systematic review and economic evaluation.
By Hill R, Bagust A, Bakhai A, Dickson R, Dündar Y, Haycox A, *et al*.

No. 36
Review of guidelines for good practice in decision-analytic modelling in health technology assessment.
By Philips Z, Ginnelly L, Sculpher M, Claxton K, Golder S, Riemsma R, *et al*.

No. 37
Rituximab (MabThera®) for aggressive non-Hodgkin's lymphoma: systematic review and economic evaluation.
By Knight C, Hind D, Brewer N, Abbott V.

No. 38
Clinical effectiveness and cost-effectiveness of clopidogrel and modified-release dipyridamole in the secondary prevention of occlusive vascular events: a systematic review and economic evaluation.
By Jones L, Griffin S, Palmer S, Main C, Orton V, Sculpher M, *et al.*

No. 39
Pegylated interferon α-2a and -2b in combination with ribavirin in the treatment of chronic hepatitis C: a systematic review and economic evaluation.
By Shepherd J, Brodin H, Cave C, Waugh N, Price A, Gabbay J.

No. 40
Clopidogrel used in combination with aspirin compared with aspirin alone in the treatment of non-ST-segment-elevation acute coronary syndromes: a systematic review and economic evaluation.
By Main C, Palmer S, Griffin S, Jones L, Orton V, Sculpher M, *et al.*

No. 41
Provision, uptake and cost of cardiac rehabilitation programmes: improving services to under-represented groups.
By Beswick AD, Rees K, Griebsch I, Taylor FC, Burke M, West RR, *et al.*

No. 42
Involving South Asian patients in clinical trials.
By Hussain-Gambles M, Leese B, Atkin K, Brown J, Mason S, Tovey P.

No. 43
Clinical and cost-effectiveness of continuous subcutaneous insulin infusion for diabetes.
By Colquitt JL, Green C, Sidhu MK, Hartwell D, Waugh N.

No. 44
Identification and assessment of ongoing trials in health technology assessment reviews.
By Song FJ, Fry-Smith A, Davenport C, Bayliss S, Adi Y, Wilson JS, *et al*.

No. 45
Systematic review and economic evaluation of a long-acting insulin analogue, insulin glargine
By Warren E, Weatherley-Jones E, Chilcott J, Beverley C.

No. 46
Supplementation of a home-based exercise programme with a class-based programme for people with osteoarthritis of the knees: a randomised controlled trial and health economic analysis.
By McCarthy CJ, Mills PM, Pullen R, Richardson G, Hawkins N, Roberts CR, *et al*.

No. 47
Clinical and cost-effectiveness of once-daily versus more frequent use of same potency topical corticosteroids for atopic eczema: a systematic review and economic evaluation.
By Green C, Colquitt JL, Kirby J, Davidson P, Payne E.

No. 48
Acupuncture of chronic headache disorders in primary care: randomised controlled trial and economic analysis.
By Vickers AJ, Rees RW, Zollman CE, McCarney R, Smith CM, Ellis N, *et al*.

No. 49
Generalisability in economic evaluation studies in healthcare: a review and case studies.
By Sculpher MJ, Pang FS, Manca A, Drummond MF, Golder S, Urdahl H, *et al*.

No. 50
Virtual outreach: a randomised controlled trial and economic evaluation of joint teleconferenced medical consultations.
By Wallace P, Barber J, Clayton W, Currell R, Fleming K, Garner P, *et al*.

Volume 9, 2005

No. 1
Randomised controlled multiple treatment comparison to provide a cost-effectiveness rationale for the selection of antimicrobial therapy in acne.
By Ozolins M, Eady EA, Avery A, Cunliffe WJ, O'Neill C, Simpson NB, *et al*.

No. 2
Do the findings of case series studies vary significantly according to methodological characteristics?
By Dalziel K, Round A, Stein K, Garside R, Castelnuovo E, Payne L.

No. 3
Improving the referral process for familial breast cancer genetic counselling: findings of three randomised controlled trials of two interventions.
By Wilson BJ, Torrance N, Mollison J, Wordsworth S, Gray JR, Haites NE, *et al*.

No. 4
Randomised evaluation of alternative electrosurgical modalities to treat bladder outflow obstruction in men with benign prostatic hyperplasia.
By Fowler C, McAllister W, Plail R, Karim O, Yang Q.

No. 5
A pragmatic randomised controlled trial of the cost-effectiveness of palliative therapies for patients with inoperable oesophageal cancer.
By Shenfine J, McNamee P, Steen N, Bond J, Griffin SM.

No. 6
Impact of computer-aided detection prompts on the sensitivity and specificity of screening mammography.
By Taylor P, Champness J, Given-Wilson R, Johnston K, Potts H.

No. 7
Issues in data monitoring and interim analysis of trials.
By Grant AM, Altman DG, Babiker AB, Campbell MK, Clemens FJ, Darbyshire JH, *et al*.

No. 8
Lay public's understanding of equipoise and randomisation in randomised controlled trials.
By Robinson EJ, Kerr CEP, Stevens AJ, Lilford RJ, Braunholtz DA, Edwards SJ, *et al*.

No. 9
Clinical and cost-effectiveness of electroconvulsive therapy for depressive illness, schizophrenia, catatonia and mania: systematic reviews and economic modelling studies.
By Greenhalgh J, Knight C, Hind D, Beverley C, Walters S.

No. 10
Measurement of health-related quality of life for people with dementia: development of a new instrument (DEMQOL) and an evaluation of current methodology.
By Smith SC, Lamping DL, Banerjee S, Harwood R, Foley B, Smith P, *et al*.

No. 11
Clinical effectiveness and cost-effectiveness of drotrecogin alfa (activated) (Xigris®) for the treatment of severe sepsis in adults: a systematic review and economic evaluation.
By Green C, Dinnes J, Takeda A, Shepherd J, Hartwell D, Cave C, *et al*.

No. 12
A methodological review of how heterogeneity has been examined in systematic reviews of diagnostic test accuracy.
By Dinnes J, Deeks J, Kirby J, Roderick P.

No. 13
Cervical screening programmes: can automation help? Evidence from systematic reviews, an economic analysis and a simulation modelling exercise applied to the UK.
By Willis BH, Barton P, Pearmain P, Bryan S, Hyde C.

No. 14
Laparoscopic surgery for inguinal hernia repair: systematic review of effectiveness and economic evaluation.
By McCormack K, Wake B, Perez J, Fraser C, Cook J, McIntosh E, *et al*.

No. 15
Clinical effectiveness, tolerability and cost-effectiveness of newer drugs for epilepsy in adults: a systematic review and economic evaluation.
By Wilby J, Kainth A, Hawkins N, Epstein D, McIntosh H, McDaid C, *et al*.

No. 16
A randomised controlled trial to compare the cost-effectiveness of tricyclic antidepressants, selective serotonin reuptake inhibitors and lofepramine.
By Peveler R, Kendrick T, Buxton M, Longworth L, Baldwin D, Moore M, *et al*.

No. 17
Clinical effectiveness and cost-effectiveness of immediate angioplasty for acute myocardial infarction: systematic review and economic evaluation.
By Hartwell D, Colquitt J, Loveman E, Clegg AJ, Brodin H, Waugh N, *et al*.

No. 18
A randomised controlled comparison of alternative strategies in stroke care.
By Kalra L, Evans A, Perez I, Knapp M, Swift C, Donaldson N.

No. 19
The investigation and analysis of critical incidents and adverse events in healthcare.
By Woloshynowych M, Rogers S, Taylor-Adams S, Vincent C.

No. 20
Potential use of routine databases in health technology assessment.
By Raftery J, Roderick P, Stevens A.

No. 21
Clinical and cost-effectiveness of newer immunosuppressive regimens in renal transplantation: a systematic review and modelling study.
By Woodroffe R, Yao GL, Meads C, Bayliss S, Ready A, Raftery J, *et al*.

No. 22
A systematic review and economic evaluation of alendronate, etidronate, risedronate, raloxifene and teriparatide for the prevention and treatment of postmenopausal osteoporosis.
By Stevenson M, Lloyd Jones M, De Nigris E, Brewer N, Davis S, Oakley J.

No. 23
A systematic review to examine the impact of psycho-educational interventions on health outcomes and costs in adults and children with difficult asthma.
By Smith JR, Mugford M, Holland R, Candy B, Noble MJ, Harrison BDW, *et al*.

No. 24
An evaluation of the costs, effectiveness and quality of renal replacement therapy provision in renal satellite units in England and Wales.
By Roderick P, Nicholson T, Armitage A, Mehta R, Mullee M, Gerard K, *et al*.

No. 25
Imatinib for the treatment of patients with unresectable and/or metastatic gastrointestinal stromal tumours: systematic review and economic evaluation.
By Wilson J, Connock M, Song F, Yao G, Fry-Smith A, Raftery J, *et al*.

No. 26
Indirect comparisons of competing interventions.
By Glenny AM, Altman DG, Song F, Sakarovitch C, Deeks JJ, D'Amico R, *et al*.

No. 27
Cost-effectiveness of alternative strategies for the initial medical management of non-ST elevation acute coronary syndrome: systematic review and decision-analytical modelling.
By Robinson M, Palmer S, Sculpher M, Philips Z, Ginnelly L, Bowens A, *et al*.

No. 28
Outcomes of electrically stimulated gracilis neosphincter surgery.
By Tillin T, Chambers M, Feldman R.

No. 29
The effectiveness and cost-effectiveness of pimecrolimus and tacrolimus for atopic eczema: a systematic review and economic evaluation.
By Garside R, Stein K, Castelnuovo E, Pitt M, Ashcroft D, Dimmock P, *et al*.

No. 30
Systematic review on urine albumin testing for early detection of diabetic complications.
By Newman DJ, Mattock MB, Dawnay ABS, Kerry S, McGuire A, Yaqoob M, *et al*.

No. 31
Randomised controlled trial of the cost-effectiveness of water-based therapy for lower limb osteoarthritis.
By Cochrane T, Davey RC, Matthes Edwards SM.

No. 32
Longer term clinical and economic benefits of offering acupuncture care to patients with chronic low back pain.
By Thomas KJ, MacPherson H, Ratcliffe J, Thorpe L, Brazier J, Campbell M, *et al*.

No. 33
Cost-effectiveness and safety of epidural steroids in the management of sciatica.
By Price C, Arden N, Coglan L, Rogers P.

No. 34
The British Rheumatoid Outcome Study Group (BROSG) randomised controlled trial to compare the effectiveness and cost-effectiveness of aggressive versus symptomatic therapy in established rheumatoid arthritis.
By Symmons D, Tricker K, Roberts C, Davies L, Dawes P, Scott DL.

No. 35
Conceptual framework and systematic review of the effects of participants' and professionals' preferences in randomised controlled trials.
By King M, Nazareth I, Lampe F, Bower P, Chandler M, Morou M, *et al*.

No. 36
The clinical and cost-effectiveness of implantable cardioverter defibrillators: a systematic review.
By Bryant J, Brodin H, Loveman E, Payne E, Clegg A.

No. 37
A trial of problem-solving by community mental health nurses for anxiety, depression and life difficulties among general practice patients. The CPN-GP study.
By Kendrick T, Simons L, Mynors-Wallis L, Gray A, Lathlean J, Pickering R, *et al*.

No. 38
The causes and effects of socio-demographic exclusions from clinical trials.
By Bartlett C, Doyal L, Ebrahim S, Davey P, Bachmann M, Egger M, *et al*.

No. 39
Is hydrotherapy cost-effective? A randomised controlled trial of combined hydrotherapy programmes compared with physiotherapy land techniques in children with juvenile idiopathic arthritis.
By Epps H, Ginnelly L, Utley M, Southwood T, Gallivan S, Sculpher M, *et al*.

No. 40
A randomised controlled trial and cost-effectiveness study of systematic screening (targeted and total population screening) versus routine practice for the detection of atrial fibrillation in people aged 65 and over. The SAFE study.
By Hobbs FDR, Fitzmaurice DA, Mant J, Murray E, Jowett S, Bryan S, *et al*.

No. 41
Displaced intracapsular hip fractures in fit, older people: a randomised comparison of reduction and fixation, bipolar hemiarthroplasty and total hip arthroplasty.
By Keating JF, Grant A, Masson M, Scott NW, Forbes JF.

No. 42
Long-term outcome of cognitive behaviour therapy clinical trials in central Scotland.
By Durham RC, Chambers JA, Power KG, Sharp DM, Macdonald RR, Major KA, *et al*.

No. 43
The effectiveness and cost-effectiveness of dual-chamber pacemakers compared with single-chamber pacemakers for bradycardia due to atrioventricular block or sick sinus syndrome: systematic review and economic evaluation.
By Castelnuovo E, Stein K, Pitt M, Garside R, Payne E.

No. 44
Newborn screening for congenital heart defects: a systematic review and cost-effectiveness analysis.
By Knowles R, Griebsch I, Dezateux C, Brown J, Bull C, Wren C.

No. 45
The clinical and cost-effectiveness of left ventricular assist devices for end-stage heart failure: a systematic review and economic evaluation.
By Clegg AJ, Scott DA, Loveman E, Colquitt J, Hutchinson J, Royle P, *et al*.

No. 46
The effectiveness of the Heidelberg Retina Tomograph and laser diagnostic glaucoma scanning system (GDx) in detecting and monitoring glaucoma.
By Kwartz AJ, Henson DB, Harper RA, Spencer AF, McLeod D.

No. 47
Clinical and cost-effectiveness of autologous chondrocyte implantation for cartilage defects in knee joints: systematic review and economic evaluation.
By Clar C, Cummins E, McIntyre L, Thomas S, Lamb J, Bain L, *et al*.

No. 48
Systematic review of effectiveness of different treatments for childhood retinoblastoma.
By McDaid C, Hartley S, Bagnall A-M, Ritchie G, Light K, Riemsma R.

No. 49
Towards evidence-based guidelines for the prevention of venous thromboembolism: systematic reviews of mechanical methods, oral anticoagulation, dextran and regional anaesthesia as thromboprophylaxis.
By Roderick P, Ferris G, Wilson K, Halls H, Jackson D, Collins R, *et al*.

No. 50
The effectiveness and cost-effectiveness of parent training/education programmes for the treatment of conduct disorder, including oppositional defiant disorder, in children.
By Dretzke J, Frew E, Davenport C, Barlow J, Stewart-Brown S, Sandercock J, *et al*.

Volume 10, 2006

No. 1
The clinical and cost-effectiveness of donepezil, rivastigmine, galantamine and memantine for Alzheimer's disease.
By Loveman E, Green C, Kirby J, Takeda A, Picot J, Payne E, *et al*.

No. 2
FOOD: a multicentre randomised trial evaluating feeding policies in patients admitted to hospital with a recent stroke.
By Dennis M, Lewis S, Cranswick G, Forbes J.

No. 3
The clinical effectiveness and cost-effectiveness of computed tomography screening for lung cancer: systematic reviews.
By Black C, Bagust A, Boland A, Walker S, McLeod C, De Verteuil R, *et al*.

No. 4
A systematic review of the effectiveness and cost-effectiveness of neuroimaging assessments used to visualise the seizure focus in people with refractory epilepsy being considered for surgery.
By Whiting P, Gupta R, Burch J, Mujica Mota RE, Wright K, Marson A, *et al*.

No. 5
Comparison of conference abstracts and presentations with full-text articles in the health technology assessments of rapidly evolving technologies.
By Dundar Y, Dodd S, Dickson R, Walley T, Haycox A, Williamson PR.

No. 6
Systematic review and evaluation of methods of assessing urinary incontinence.
By Martin JL, Williams KS, Abrams KR, Turner DA, Sutton AJ, Chapple C, *et al*.

No. 7
The clinical effectiveness and cost-effectiveness of newer drugs for children with epilepsy. A systematic review.
By Connock M, Frew E, Evans B-W, Bryan S, Cummins C, Fry-Smith A, *et al*.

No. 8
Surveillance of Barrett's oesophagus: exploring the uncertainty through systematic review, expert workshop and economic modelling.
By Garside R, Pitt M, Somerville M, Stein K, Price A, Gilbert N.

No. 9
Topotecan, pegylated liposomal doxorubicin hydrochloride and paclitaxel for second-line or subsequent treatment of advanced ovarian cancer: a systematic review and economic evaluation.
By Main C, Bojke L, Griffin S, Norman G, Barbieri M, Mather L, *et al*.

No. 10
Evaluation of molecular techniques in prediction and diagnosis of cytomegalovirus disease in immunocompromised patients.
By Szczepura A, Westmoreland D, Vinogradova Y, Fox J, Clark M.

No. 11
Screening for thrombophilia in high-risk situations: systematic review and cost-effectiveness analysis. The Thrombosis: Risk and Economic Assessment of Thrombophilia Screening (TREATS) study.
By Wu O, Robertson L, Twaddle S, Lowe GDO, Clark P, Greaves M, *et al*.

No. 12
A series of systematic reviews to inform a decision analysis for sampling and treating infected diabetic foot ulcers.
By Nelson EA, O'Meara S, Craig D, Iglesias C, Golder S, Dalton J, *et al*.

No. 13
Randomised clinical trial, observational study and assessment of cost-effectiveness of the treatment of varicose veins (REACTIV trial).
By Michaels JA, Campbell WB, Brazier JE, MacIntyre JB, Palfreyman SJ, Ratcliffe J, *et al*.

No. 14
The cost-effectiveness of screening for oral cancer in primary care.
By Speight PM, Palmer S, Moles DR, Downer MC, Smith DH, Henriksson M, *et al*.

No. 15
Measurement of the clinical and cost-effectiveness of non-invasive diagnostic testing strategies for deep vein thrombosis.
By Goodacre S, Sampson F, Stevenson M, Wailoo A, Sutton A, Thomas S, *et al*.

No. 16
Systematic review of the effectiveness and cost-effectiveness of HealOzone® for the treatment of occlusal pit/fissure caries and root caries.
By Brazzelli M, McKenzie L, Fielding S, Fraser C, Clarkson J, Kilonzo M, *et al*.

No. 17
Randomised controlled trials of conventional antipsychotic versus new atypical drugs, and new atypical drugs versus clozapine, in people with schizophrenia responding poorly to, or intolerant of, current drug treatment.
By Lewis SW, Davies L, Jones PB, Barnes TRE, Murray RM, Kerwin R, *et al*.

No. 18
Diagnostic tests and algorithms used in the investigation of haematuria: systematic reviews and economic evaluation.
By Rodgers M, Nixon J, Hempel S, Aho T, Kelly J, Neal D, *et al*.

No. 19
Cognitive behavioural therapy in addition to antispasmodic therapy for irritable bowel syndrome in primary care: randomised controlled trial.
By Kennedy TM, Chalder T, McCrone P, Darnley S, Knapp M, Jones RH, *et al*.

No. 20
A systematic review of the clinical effectiveness and cost-effectiveness of enzyme replacement therapies for Fabry's disease and mucopolysaccharidosis type 1.
By Connock M, Juarez-Garcia A, Frew E, Mans A, Dretzke J, Fry-Smith A, *et al*.

No. 21
Health benefits of antiviral therapy for mild chronic hepatitis C: randomised controlled trial and economic evaluation.
By Wright M, Grieve R, Roberts J, Main J, Thomas HC, on behalf of the UK Mild Hepatitis C Trial Investigators.

No. 22
Pressure relieving support surfaces: a randomised evaluation.
By Nixon J, Nelson EA, Cranny G, Iglesias CP, Hawkins K, Cullum NA, *et al*.

No. 23
A systematic review and economic model of the effectiveness and cost-effectiveness of methylphenidate, dexamfetamine and atomoxetine for the treatment of attention deficit hyperactivity disorder in children and adolescents.
By King S, Griffin S, Hodges Z, Weatherly H, Asseburg C, Richardson G, *et al.*

No. 24
The clinical effectiveness and cost-effectiveness of enzyme replacement therapy for Gaucher's disease: a systematic review.
By Connock M, Burls A, Frew E, Fry-Smith A, Juarez-Garcia A, McCabe C, *et al*.

No. 25
Effectiveness and cost-effectiveness of salicylic acid and cryotherapy for cutaneous warts. An economic decision model.
By Thomas KS, Keogh-Brown MR, Chalmers JR, Fordham RJ, Holland RC, Armstrong SJ, *et al*.

No. 26
A systematic literature review of the effectiveness of non-pharmacological interventions to prevent wandering in dementia and evaluation of the ethical implications and acceptability of their use.
By Robinson L, Hutchings D, Corner L, Beyer F, Dickinson H, Vanoli A, *et al*.

No. 27
A review of the evidence on the effects and costs of implantable cardioverter defibrillator therapy in different patient groups, and modelling of cost-effectiveness and cost–utility for these groups in a UK context.
By Buxton M, Caine N, Chase D, Connelly D, Grace A, Jackson C, *et al*.

No. 28
Adefovir dipivoxil and pegylated interferon alfa-2a for the treatment of chronic hepatitis B: a systematic review and economic evaluation.
By Shepherd J, Jones J, Takeda A, Davidson P, Price A.

No. 29
An evaluation of the clinical and cost-effectiveness of pulmonary artery catheters in patient management in intensive care: a systematic review and a randomised controlled trial.
By Harvey S, Stevens K, Harrison D, Young D, Brampton W, McCabe C, *et al*.

No. 30
Accurate, practical and cost-effective assessment of carotid stenosis in the UK.
By Wardlaw JM, Chappell FM, Stevenson M, De Nigris E, Thomas S, Gillard J, *et al*.

No. 31
Etanercept and infliximab for the treatment of psoriatic arthritis: a systematic review and economic evaluation.
By Woolacott N, Bravo Vergel Y, Hawkins N, Kainth A, Khadjesari Z, Misso K, *et al*.

No. 32
The cost-effectiveness of testing for hepatitis C in former injecting drug users.
By Castelnuovo E, Thompson-Coon J, Pitt M, Cramp M, Siebert U, Price A, *et al*.

No. 33
Computerised cognitive behaviour therapy for depression and anxiety update: a systematic review and economic evaluation.
By Kaltenthaler E, Brazier J, De Nigris E, Tumur I, Ferriter M, Beverley C, *et al*.

No. 34
Cost-effectiveness of using prognostic information to select women with breast cancer for adjuvant systemic therapy.
By Williams C, Brunskill S, Altman D, Briggs A, Campbell H, Clarke M, *et al*.

No. 35
Psychological therapies including dialectical behaviour therapy for borderline personality disorder: a systematic review and preliminary economic evaluation.
By Brazier J, Tumur I, Holmes M, Ferriter M, Parry G, Dent-Brown K, *et al*.

No. 36
Clinical effectiveness and cost-effectiveness of tests for the diagnosis and investigation of urinary tract infection in children: a systematic review and economic model.
By Whiting P, Westwood M, Bojke L, Palmer S, Richardson G, Cooper J, *et al*.

No. 37
Cognitive behavioural therapy in chronic fatigue syndrome: a randomised controlled trial of an outpatient group programme.
By O'Dowd H, Gladwell P, Rogers CA, Hollinghurst S, Gregory A.

No. 38
A comparison of the cost-effectiveness of five strategies for the prevention of nonsteroidal anti-inflammatory drug-induced gastrointestinal toxicity: a systematic review with economic modelling.
By Brown TJ, Hooper L, Elliott RA, Payne K, Webb R, Roberts C, et al.

No. 39
The effectiveness and cost-effectiveness of computed tomography screening for coronary artery disease: systematic review.
By Waugh N, Black C, Walker S, McIntyre L, Cummins E, Hillis G.

No. 40
What are the clinical outcome and cost-effectiveness of endoscopy undertaken by nurses when compared with doctors? A Multi-Institution Nurse Endoscopy Trial (MINuET).
By Williams J, Russell I, Durai D, Cheung W-Y, Farrin A, Bloor K, *et al*.

No. 41
The clinical and cost-effectiveness of oxaliplatin and capecitabine for the adjuvant treatment of colon cancer: systematic review and economic evaluation.
By Pandor A, Eggington S, Paisley S, Tappenden P, Sutcliffe P.

No. 42
A systematic review of the effectiveness of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis in adults and an economic evaluation of their cost-effectiveness.
By Chen Y-F, Jobanputra P, Barton P, Jowett S, Bryan S, Clark W, *et al*.

No. 43
Telemedicine in dermatology: a randomised controlled trial.
By Bowns IR, Collins K, Walters SJ, McDonagh AJG.

No. 44
Cost-effectiveness of cell salvage and alternative methods of minimising perioperative allogeneic blood transfusion: a systematic review and economic model.
By Davies L, Brown TJ, Haynes S, Payne K, Elliott RA, McCollum C.

No. 45
Clinical effectiveness and cost-effectiveness of laparoscopic surgery for colorectal cancer: systematic reviews and economic evaluation.
By Murray A, Lourenco T, de Verteuil R, Hernandez R, Fraser C, McKinley A, *et al*.

No. 46
Etanercept and efalizumab for the treatment of psoriasis: a systematic review.
By Woolacott N, Hawkins N, Mason A, Kainth A, Khadjesari Z, Bravo Vergel Y, *et al*.

No. 47
Systematic reviews of clinical decision tools for acute abdominal pain.
By Liu JLY, Wyatt JC, Deeks JJ, Clamp S, Keen J, Verde P, *et al*.

No. 48
Evaluation of the ventricular assist device programme in the UK.
By Sharples L, Buxton M, Caine N, Cafferty F, Demiris N, Dyer M, *et al*.

No. 49
A systematic review and economic model of the clinical and cost-effectiveness of immunosuppressive therapy for renal transplantation in children.
By Yao G, Albon E, Adi Y, Milford D, Bayliss S, Ready A, *et al*.

No. 50
Amniocentesis results: investigation of anxiety. The ARIA trial.
By Hewison J, Nixon J, Fountain J, Cocks K, Jones C, Mason G, *et al*.

Volume 11, 2007

No. 1
Pemetrexed disodium for the treatment of malignant pleural mesothelioma: a systematic review and economic evaluation.
By Dundar Y, Bagust A, Dickson R, Dodd S, Green J, Haycox A, *et al*.

No. 2
A systematic review and economic model of the clinical effectiveness and cost-effectiveness of docetaxel in combination with prednisone or prednisolone for the treatment of hormone-refractory metastatic prostate cancer.
By Collins R, Fenwick E, Trowman R, Perard R, Norman G, Light K, *et al*.

No. 3
A systematic review of rapid diagnostic tests for the detection of tuberculosis infection.
By Dinnes J, Deeks J, Kunst H, Gibson A, Cummins E, Waugh N, *et al*.

No. 4
The clinical effectiveness and cost-effectiveness of strontium ranelate for the prevention of osteoporotic fragility fractures in postmenopausal women.
By Stevenson M, Davis S, Lloyd-Jones M, Beverley C.

No. 5
A systematic review of quantitative and qualitative research on the role and effectiveness of written information available to patients about individual medicines.
By Raynor DK, Blenkinsopp A, Knapp P, Grime J, Nicolson DJ, Pollock K, *et al*.

No. 6
Oral naltrexone as a treatment for relapse prevention in formerly opioid-dependent drug users: a systematic review and economic evaluation.
By Adi Y, Juarez-Garcia A, Wang D, Jowett S, Frew E, Day E, *et al*.

No. 7
Glucocorticoid-induced osteoporosis: a systematic review and cost–utility analysis.
By Kanis JA, Stevenson M, McCloskey EV, Davis S, Lloyd-Jones M.

No. 8
Epidemiological, social, diagnostic and economic evaluation of population screening for genital chlamydial infection.
By Low N, McCarthy A, Macleod J, Salisbury C, Campbell R, Roberts TE, *et al*.

No. 9
Methadone and buprenorphine for the management of opioid dependence: a systematic review and economic evaluation.
By Connock M, Juarez-Garcia A, Jowett S, Frew E, Liu Z, Taylor RJ, *et al*.

No. 10
Exercise Evaluation Randomised Trial (EXERT): a randomised trial comparing GP referral for leisure centre-based exercise, community-based walking and advice only.
By Isaacs AJ, Critchley JA, See Tai S, Buckingham K, Westley D, Harridge SDR, *et al*.

No. 11
Interferon alfa (pegylated and non-pegylated) and ribavirin for the treatment of mild chronic hepatitis C: a systematic review and economic evaluation.
By Shepherd J, Jones J, Hartwell D, Davidson P, Price A, Waugh N.

No. 12
Systematic review and economic evaluation of bevacizumab and cetuximab for the treatment of metastatic colorectal cancer.
By Tappenden P, Jones R, Paisley S, Carroll C.

No. 13
A systematic review and economic evaluation of epoetin alfa, epoetin beta and darbepoetin alfa in anaemia associated with cancer, especially that attributable to cancer treatment.
By Wilson J, Yao GL, Raftery J, Bohlius J, Brunskill S, Sandercock J, *et al*.

No. 14
A systematic review and economic evaluation of statins for the prevention of coronary events.
By Ward S, Lloyd Jones M, Pandor A, Holmes M, Ara R, Ryan A, *et al*.

No. 15
A systematic review of the effectiveness and cost-effectiveness of different models of community-based respite care for frail older people and their carers.
By Mason A, Weatherly H, Spilsbury K, Arksey H, Golder S, Adamson J, *et al*.

No. 16
Additional therapy for young children with spastic cerebral palsy: a randomised controlled trial.
By Weindling AM, Cunningham CC, Glenn SM, Edwards RT, Reeves DJ.

No. 17
Screening for type 2 diabetes: literature review and economic modelling.
By Waugh N, Scotland G, McNamee P, Gillett M, Brennan A, Goyder E, *et al*.

No. 18
The effectiveness and cost-effectiveness of cinacalcet for secondary hyperparathyroidism in end-stage renal disease patients on dialysis: a systematic review and economic evaluation.
By Garside R, Pitt M, Anderson R, Mealing S, Roome C, Snaith A, *et al*.

No. 19
The clinical effectiveness and cost-effectiveness of gemcitabine for metastatic breast cancer: a systematic review and economic evaluation.
By Takeda AL, Jones J, Loveman E, Tan SC, Clegg AJ.

No. 20
A systematic review of duplex ultrasound, magnetic resonance angiography and computed tomography angiography for the diagnosis and assessment of symptomatic, lower limb peripheral arterial disease.
By Collins R, Cranny G, Burch J, Aguiar-Ibáñez R, Craig D, Wright K, *et al*.

No. 21
The clinical effectiveness and cost-effectiveness of treatments for children with idiopathic steroid-resistant nephrotic syndrome: a systematic review.
By Colquitt JL, Kirby J, Green C, Cooper K, Trompeter RS.

No. 22
A systematic review of the routine monitoring of growth in children of primary school age to identify growth-related conditions.
By Fayter D, Nixon J, Hartley S, Rithalia A, Butler G, Rudolf M, *et al*.

No. 23
Systematic review of the effectiveness of preventing and treating *Staphylococcus aureus* carriage in reducing peritoneal catheter-related infections.
By McCormack K, Rabindranath K, Kilonzo M, Vale L, Fraser C, McIntyre L, *et al*.

No. 24
The clinical effectiveness and cost of repetitive transcranial magnetic stimulation versus electroconvulsive therapy in severe depression: a multicentre pragmatic randomised controlled trial and economic analysis.
By McLoughlin DM, Mogg A, Eranti S, Pluck G, Purvis R, Edwards D, *et al*.

No. 25
A randomised controlled trial and economic evaluation of direct versus indirect and individual versus group modes of speech and language therapy for children with primary language impairment.
By Boyle J, McCartney E, Forbes J, O'Hare A.

No. 26
Hormonal therapies for early breast cancer: systematic review and economic evaluation.
By Hind D, Ward S, De Nigris E, Simpson E, Carroll C, Wyld L.

No. 27
Cardioprotection against the toxic effects of anthracyclines given to children with cancer: a systematic review.
By Bryant J, Picot J, Levitt G, Sullivan I, Baxter L, Clegg A.

No. 28
Adalimumab, etanercept and infliximab for the treatment of ankylosing spondylitis: a systematic review and economic evaluation.
By McLeod C, Bagust A, Boland A, Dagenais P, Dickson R, Dundar Y, *et al*.

No. 29
Prenatal screening and treatment strategies to prevent group B streptococcal and other bacterial infections in early infancy: cost-effectiveness and expected value of information analyses.
By Colbourn T, Asseburg C, Bojke L, Philips Z, Claxton K, Ades AE, *et al*.

No. 30
Clinical effectiveness and cost-effectiveness of bone morphogenetic proteins in the non-healing of fractures and spinal fusion: a systematic review.
By Garrison KR, Donell S, Ryder J, Shemilt I, Mugford M, Harvey I, *et al*.

No. 31
A randomised controlled trial of postoperative radiotherapy following breast-conserving surgery in a minimum-risk older population. The PRIME trial.
By Prescott RJ, Kunkler IH, Williams LJ, King CC, Jack W, van der Pol M, *et al*.

No. 32
Current practice, accuracy, effectiveness and cost-effectiveness of the school entry hearing screen.
By Bamford J, Fortnum H, Bristow K, Smith J, Vamvakas G, Davies L, *et al*.

No. 33
The clinical effectiveness and cost-effectiveness of inhaled insulin in diabetes mellitus: a systematic review and economic evaluation.
By Black C, Cummins E, Royle P, Philip S, Waugh N.

No. 34
Surveillance of cirrhosis for hepatocellular carcinoma: systematic review and economic analysis.
By Thompson Coon J, Rogers G, Hewson P, Wright D, Anderson R, Cramp M, *et al*.

No. 35
The Birmingham Rehabilitation Uptake Maximisation Study (BRUM). Homebased compared with hospital-based cardiac rehabilitation in a multi-ethnic population: cost-effectiveness and patient adherence.
By Jolly K, Taylor R, Lip GYH, Greenfield S, Raftery J, Mant J, *et al*.

No. 36
A systematic review of the clinical, public health and cost-effectiveness of rapid diagnostic tests for the detection and identification of bacterial intestinal pathogens in faeces and food.
By Abubakar I, Irvine L, Aldus CF, Wyatt GM, Fordham R, Schelenz S, *et al*.

No. 37
A randomised controlled trial examining the longer-term outcomes of standard versus new antiepileptic drugs. The SANAD trial.
By Marson AG, Appleton R, Baker GA, Chadwick DW, Doughty J, Eaton B, *et al*.

No. 38
Clinical effectiveness and cost-effectiveness of different models of managing long-term oral anti-coagulation therapy: a systematic review and economic modelling.
By Connock M, Stevens C, Fry-Smith A, Jowett S, Fitzmaurice D, Moore D, *et al*.

No. 39
A systematic review and economic model of the clinical effectiveness and cost-effectiveness of interventions for preventing relapse in people with bipolar disorder.
By Soares-Weiser K, Bravo Vergel Y, Beynon S, Dunn G, Barbieri M, Duffy S, *et al*.

No. 40
Taxanes for the adjuvant treatment of early breast cancer: systematic review and economic evaluation.
By Ward S, Simpson E, Davis S, Hind D, Rees A, Wilkinson A.

No. 41
The clinical effectiveness and cost-effectiveness of screening for open angle glaucoma: a systematic review and economic evaluation.
By Burr JM, Mowatt G, Hernández R, Siddiqui MAR, Cook J, Lourenco T, *et al*.

No. 42
Acceptability, benefit and costs of early screening for hearing disability: a study of potential screening tests and models.
By Davis A, Smith P, Ferguson M, Stephens D, Gianopoulos I.

No. 43
Contamination in trials of educational interventions.
By Keogh-Brown MR, Bachmann MO, Shepstone L, Hewitt C, Howe A, Ramsay CR, *et al*.

No. 44
Overview of the clinical effectiveness of positron emission tomography imaging in selected cancers.
By Facey K, Bradbury I, Laking G, Payne E.

No. 45
The effectiveness and cost-effectiveness of carmustine implants and temozolomide for the treatment of newly diagnosed high-grade glioma: a systematic review and economic evaluation.
By Garside R, Pitt M, Anderson R, Rogers G, Dyer M, Mealing S, *et al*.

No. 46
Drug-eluting stents: a systematic review and economic evaluation.
By Hill RA, Boland A, Dickson R, Dündar Y, Haycox A, McLeod C, *et al*.

No. 47
The clinical effectiveness and cost-effectiveness of cardiac resynchronisation (biventricular pacing) for heart failure: systematic review and economic model.
By Fox M, Mealing S, Anderson R, Dean J, Stein K, Price A, *et al*.

No. 48
Recruitment to randomised trials: strategies for trial enrolment and participation study. The STEPS study.
By Campbell MK, Snowdon C, Francis D, Elbourne D, McDonald AM, Knight R, *et al*.

No. 49
Cost-effectiveness of functional cardiac testing in the diagnosis and management of coronary artery disease: a randomised controlled trial. The CECaT trial.
By Sharples L, Hughes V, Crean A, Dyer M, Buxton M, Goldsmith K, *et al*.

No. 50
Evaluation of diagnostic tests when there is no gold standard. A review of methods.
By Rutjes AWS, Reitsma JB, Coomarasamy A, Khan KS, Bossuyt PMM.

No. 51
Systematic reviews of the clinical effectiveness and cost-effectiveness of proton pump inhibitors in acute upper gastrointestinal bleeding.
By Leontiadis GI, Sreedharan A, Dorward S, Barton P, Delaney B, Howden CW, *et al*.

No. 52
A review and critique of modelling in prioritising and designing screening programmes.
By Karnon J, Goyder E, Tappenden P, McPhie S, Towers I, Brazier J, *et al*.

No. 53
An assessment of the impact of the NHS Health Technology Assessment Programme.
By Hanney S, Buxton M, Green C, Coulson D, Raftery J.

Volume 12, 2008

No. 1
A systematic review and economic model of switching from nonglycopeptide to glycopeptide antibiotic prophylaxis for surgery.
By Cranny G, Elliott R, Weatherly H, Chambers D, Hawkins N, Myers L, *et al*.

No. 2
'Cut down to quit' with nicotine replacement therapies in smoking cessation: a systematic review of effectiveness and economic analysis.
By Wang D, Connock M, Barton P, Fry-Smith A, Aveyard P, Moore D.

No. 3
A systematic review of the effectiveness of strategies for reducing fracture risk in children with juvenile idiopathic arthritis with additional data on long-term risk of fracture and cost of disease management.
By Thornton J, Ashcroft D, O'Neill T, Elliott R, Adams J, Roberts C, *et al*.

No. 4
Does befriending by trained lay workers improve psychological well-being and quality of life for carers of people with dementia, and at what cost? A randomised controlled trial.
By Charlesworth G, Shepstone L, Wilson E, Thalanany M, Mugford M, Poland F.

No. 5
A multi-centre retrospective cohort study comparing the efficacy, safety and cost-effectiveness of hysterectomy and uterine artery embolisation for the treatment of symptomatic uterine fibroids. The HOPEFUL study.
By Hirst A, Dutton S, Wu O, Briggs A, Edwards C, Waldenmaier L, *et al*.

No. 6
Methods of prediction and prevention of pre-eclampsia: systematic reviews of accuracy and effectiveness literature with economic modelling.
By Meads CA, Cnossen JS, Meher S, Juarez-Garcia A, ter Riet G, Duley L, *et al*.

No. 7
The use of economic evaluations in NHS decision-making: a review and empirical investigation.
By Williams I, McIver S, Moore D, Bryan S.

No. 8
Stapled haemorrhoidectomy (haemorrhoidopexy) for the treatment of haemorrhoids: a systematic review and economic evaluation.
By Burch J, Epstein D, Baba-Akbari A, Weatherly H, Fox D, Golder S, *et al*.

No. 9
The clinical effectiveness of diabetes education models for Type 2 diabetes: a systematic review.
By Loveman E, Frampton GK, Clegg AJ.

No. 10
Payment to healthcare professionals for patient recruitment to trials: systematic review and qualitative study.
By Raftery J, Bryant J, Powell J, Kerr C, Hawker S.

No. 11
Cyclooxygenase-2 selective non-steroidal anti-inflammatory drugs (etodolac, meloxicam, celecoxib, rofecoxib, etoricoxib, valdecoxib and lumiracoxib) for osteoarthritis and rheumatoid arthritis: a systematic review and economic evaluation.
By Chen Y-F, Jobanputra P, Barton P, Bryan S, Fry-Smith A, Harris G, *et al*.

No. 12
The clinical effectiveness and cost-effectiveness of central venous catheters treated with anti-infective agents in preventing bloodstream infections: a systematic review and economic evaluation.
By Hockenhull JC, Dwan K, Boland A, Smith G, Bagust A, Dundar Y, *et al*.

No. 13
Stepped treatment of older adults on laxatives. The STOOL trial.
By Mihaylov S, Stark C, McColl E, Steen N, Vanoli A, Rubin G, *et al*.

No. 14
A randomised controlled trial of cognitive behaviour therapy in adolescents with major depression treated by selective serotonin reuptake inhibitors. The ADAPT trial.
By Goodyer IM, Dubicka B, Wilkinson P, Kelvin R, Roberts C, Byford S, *et al*.

No. 15
The use of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer: systematic review and economic evaluation.
By Hind D, Tappenden P, Tumur I, Eggington E, Sutcliffe P, Ryan A.

No. 16
Ranibizumab and pegaptanib for the treatment of age-related macular degeneration: a systematic review and economic evaluation.
By Colquitt JL, Jones J, Tan SC, Takeda A, Clegg AJ, Price A.

No. 17
Systematic review of the clinical effectiveness and cost-effectiveness of 64-slice or higher computed tomography angiography as an alternative to invasive coronary angiography in the investigation of coronary artery disease.
By Mowatt G, Cummins E, Waugh N, Walker S, Cook J, Jia X, *et al*.

No. 18
Structural neuroimaging in psychosis: a systematic review and economic evaluation.
By Albon E, Tsourapas A, Frew E, Davenport C, Oyebode F, Bayliss S, *et al*.

No. 19
Systematic review and economic analysis of the comparative effectiveness of different inhaled corticosteroids and their usage with long-acting beta$_2$ agonists for the treatment of chronic asthma in adults and children aged 12 years and over.
By Shepherd J, Rogers G, Anderson R, Main C, Thompson-Coon J, Hartwell D, *et al*.

No. 20
Systematic review and economic analysis of the comparative effectiveness of different inhaled corticosteroids and their usage with long-acting beta$_2$ agonists for the treatment of chronic asthma in children under the age of 12 years.
By Main C, Shepherd J, Anderson R, Rogers G, Thompson-Coon J, Liu Z, *et al*.

No. 21
Ezetimibe for the treatment of hypercholesterolaemia: a systematic review and economic evaluation.
By Ara R, Tumur I, Pandor A, Duenas A, Williams R, Wilkinson A, *et al*.

No. 22
Topical or oral ibuprofen for chronic knee pain in older people. The TOIB study.
By Underwood M, Ashby D, Carnes D, Castelnuovo E, Cross P, Harding G, *et al*.

No. 23
A prospective randomised comparison of minor surgery in primary and secondary care. The MiSTIC trial.
By George S, Pockney P, Primrose J, Smith H, Little P, Kinley H, *et al*.

No. 24
A review and critical appraisal of measures of therapist–patient interactions in mental health settings.
By Cahill J, Barkham M, Hardy G, Gilbody S, Richards D, Bower P, *et al*.

No. 25
The clinical effectiveness and cost-effectiveness of screening programmes for amblyopia and strabismus in children up to the age of 4–5 years: a systematic review and economic evaluation.
By Carlton J, Karnon J, Czoski-Murray C, Smith KJ, Marr J.

No. 26
A systematic review of the clinical effectiveness and cost-effectiveness and economic modelling of minimal incision total hip replacement approaches in the management of arthritic disease of the hip.
By de Verteuil R, Imamura M, Zhu S, Glazener C, Fraser C, Munro N, *et al*.

No. 27
A preliminary model-based assessment of the cost–utility of a screening programme for early age-related macular degeneration.
By Karnon J, Czoski-Murray C, Smith K, Brand C, Chakravarthy U, Davis S, *et al*.

No. 28
Intravenous magnesium sulphate and sotalol for prevention of atrial fibrillation after coronary artery bypass surgery: a systematic review and economic evaluation.
By Shepherd J, Jones J, Frampton GK, Tanajewski L, Turner D, Price A.

No. 29
Absorbent products for urinary/faecal incontinence: a comparative evaluation of key product categories.
By Fader M, Cottenden A, Getliffe K, Gage H, Clarke-O'Neill S, Jamieson K, *et al*.

No. 30
A systematic review of repetitive functional task practice with modelling of resource use, costs and effectiveness.
By French B, Leathley M, Sutton C, McAdam J, Thomas L, Forster A, *et al*.

No. 31
The effectiveness and cost-effectivness of minimal access surgery amongst people with gastro-oesophageal reflux disease – a UK collaborative study. The REFLUX trial.
By Grant A, Wileman S, Ramsay C, Bojke L, Epstein D, Sculpher M, *et al*.

No. 32
Time to full publication of studies of anti-cancer medicines for breast cancer and the potential for publication bias: a short systematic review.
By Takeda A, Loveman E, Harris P, Hartwell D, Welch K.

No. 33
Performance of screening tests for child physical abuse in accident and emergency departments.
By Woodman J, Pitt M, Wentz R, Taylor B, Hodes D, Gilbert RE.

No. 34
Curative catheter ablation in atrial fibrillation and typical atrial flutter: systematic review and economic evaluation.
By Rodgers M, McKenna C, Palmer S, Chambers D, Van Hout S, Golder S, *et al*.

No. 35
Systematic review and economic modelling of effectiveness and cost utility of surgical treatments for men with benign prostatic enlargement.
By Lourenco T, Armstrong N, N'Dow J, Nabi G, Deverill M, Pickard R, *et al*.

No. 36
Immunoprophylaxis against respiratory syncytial virus (RSV) with palivizumab in children: a systematic review and economic evaluation.
By Wang D, Cummins C, Bayliss S, Sandercock J, Burls A.

Volume 13, 2009

No. 1
Deferasirox for the treatment of iron overload associated with regular blood transfusions (transfusional haemosiderosis) in patients suffering with chronic anaemia: a systematic review and economic evaluation.
By McLeod C, Fleeman N, Kirkham J, Bagust A, Boland A, Chu P, *et al*.

No. 2
Thrombophilia testing in people with venous thromboembolism: systematic review and cost-effectiveness analysis.
By Simpson EL, Stevenson MD, Rawdin A, Papaioannou D.

No. 3
Surgical procedures and non-surgical devices for the management of non-apnoeic snoring: a systematic review of clinical effects and associated treatment costs.
By Main C, Liu Z, Welch K, Weiner G, Quentin Jones S, Stein K.

No. 4
Continuous positive airway pressure devices for the treatment of obstructive sleep apnoea–hypopnoea syndrome: a systematic review and economic analysis.
By McDaid C, Griffin S, Weatherly H, Durée K, van der Burgt M, van Hout S, Akers J, *et al*.

No. 5
Use of classical and novel biomarkers as prognostic risk factors for localised prostate cancer: a systematic review.
By Sutcliffe P, Hummel S, Simpson E, Young T, Rees A, Wilkinson A, *et al*.

No. 6
The harmful health effects of recreational ecstasy: a systematic review of observational evidence.
By Rogers G, Elston J, Garside R, Roome C, Taylor R, Younger P, *et al*.

No. 7
Systematic review of the clinical effectiveness and cost-effectiveness of oesophageal Doppler monitoring in critically ill and high-risk surgical patients.
By Mowatt G, Houston G, Hernández R, de Verteuil R, Fraser C, Cuthbertson B, *et al*.

No. 8
The use of surrogate outcomes in model-based cost-effectiveness analyses: a survey of UK Health Technology Assessment reports.
By Taylor RS, Elston J.

No. 9
Controlling Hypertension and Hypotension Immediately Post Stroke (CHHIPS) – a randomised controlled trial.
By Potter J, Mistri A, Brodie F, Chernova J, Wilson E, Jagger C, *et al*.

No. 10
Routine antenatal anti-D prophylaxis for RhD-negative women: a systematic review and economic evaluation.
By Pilgrim H, Lloyd-Jones M, Rees A.

No. 11
Amantadine, oseltamivir and zanamivir for the prophylaxis of influenza (including a review of existing guidance no. 67): a systematic review and economic evaluation.
By Tappenden P, Jackson R, Cooper K, Rees A, Simpson E, Read R, *et al.*

No. 12
Improving the evaluation of therapeutic interventions in multiple sclerosis: the role of new psychometric methods.
By Hobart J, Cano S.

No. 13
Treatment of severe ankle sprain: a pragmatic randomised controlled trial comparing the clinical effectiveness and cost-effectiveness of three types of mechanical ankle support with tubular bandage. The CAST trial.
By Cooke MW, Marsh JL, Clark M, Nakash R, Jarvis RM, Hutton JL, *et al.*, on behalf of the CAST trial group.

No. 14
Non-occupational postexposure prophylaxis for HIV: a systematic review.
By Bryant J, Baxter L, Hird S.

No. 15
Blood glucose self-monitoring in type 2 diabetes: a randomised controlled trial.
By Farmer AJ, Wade AN, French DP, Simon J, Yudkin P, Gray A, *et al.*

No. 16
How far does screening women for domestic (partner) violence in different health-care settings meet criteria for a screening programme? Systematic reviews of nine UK National Screening Committee criteria.
By Feder G, Ramsay J, Dunne D, Rose M, Arsene C, Norman R, *et al.*

No. 17
Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin: systematic review and economic evaluation.
By Simpson, EL, Duenas A, Holmes MW, Papaioannou D, Chilcott J.

No. 18
The role of magnetic resonance imaging in the identification of suspected acoustic neuroma: a systematic review of clinical and cost-effectiveness and natural history.
By Fortnum H, O'Neill C, Taylor R, Lenthall R, Nikolopoulos T, Lightfoot G, *et al.*

No. 19
Dipsticks and diagnostic algorithms in urinary tract infection: development and validation, randomised trial, economic analysis, observational cohort and qualitative study.
By Little P, Turner S, Rumsby K, Warner G, Moore M, Lowes JA, *et al.*

No. 20
Systematic review of respite care in the frail elderly.
By Shaw C, McNamara R, Abrams K, Cannings-John R, Hood K, Longo M, *et al.*

No. 21
Neuroleptics in the treatment of aggressive challenging behaviour for people with intellectual disabilities: a randomised controlled trial (NACHBID).
By Tyrer P, Oliver-Africano P, Romeo R, Knapp M, Dickens S, Bouras N, *et al.*

No. 22
Randomised controlled trial to determine the clinical effectiveness and cost-effectiveness of selective serotonin reuptake inhibitors plus supportive care, versus supportive care alone, for mild to moderate depression with somatic symptoms in primary care: the THREAD (THREshold for AntiDepressant response) study.
By Kendrick T, Chatwin J, Dowrick C, Tylee A, Morriss R, Peveler R, *et al.*

No. 23
Diagnostic strategies using DNA testing for hereditary haemochromatosis in at-risk populations: a systematic review and economic evaluation.
By Bryant J, Cooper K, Picot J, Clegg A, Roderick P, Rosenberg W, *et al.*

No. 24
Enhanced external counterpulsation for the treatment of stable angina and heart failure: a systematic review and economic analysis.
By McKenna C, McDaid C, Suekarran S, Hawkins N, Claxton K, Light K, *et al.*

No. 25
Development of a decision support tool for primary care management of patients with abnormal liver function tests without clinically apparent liver disease: a record-linkage population cohort study and decision analysis (ALFIE).
By Donnan PT, McLernon D, Dillon JF, Ryder S, Roderick P, Sullivan F, *et al.*

No. 26
A systematic review of presumed consent systems for deceased organ donation.
By Rithalia A, McDaid C, Suekarran S, Norman G, Myers L, Sowden A.

No. 27
Paracetamol and ibuprofen for the treatment of fever in children: the PITCH randomised controlled trial.
By Hay AD, Redmond NM, Costelloe C, Montgomery AA, Fletcher M, Hollinghurst S, *et al.*

No. 28
A randomised controlled trial to compare minimally invasive glucose monitoring devices with conventional monitoring in the management of insulin-treated diabetes mellitus (MITRE).
By Newman SP, Cooke D, Casbard A, Walker S, Meredith S, Nunn A, *et al.*

No. 29
Sensitivity analysis in economic evaluation: an audit of NICE current practice and a review of its use and value in decision-making.
By Andronis L, Barton P, Bryan S.

Suppl. 1
Trastuzumab for the treatment of primary breast cancer in HER2-positive women: a single technology appraisal.
By Ward S, Pilgrim H, Hind D.

Docetaxel for the adjuvant treatment of early node-positive breast cancer: a single technology appraisal.
By Chilcott J, Lloyd Jones M, Wilkinson A.

The use of paclitaxel in the management of early stage breast cancer.
By Griffin S, Dunn G, Palmer S, Macfarlane K, Brent S, Dyker A, *et al.*

Rituximab for the first-line treatment of stage III/IV follicular non-Hodgkin's lymphoma.
By Dundar Y, Bagust A, Hounsome J, McLeod C, Boland A, Davis H, *et al.*

Bortezomib for the treatment of multiple myeloma patients.
By Green C, Bryant J, Takeda A, Cooper K, Clegg A, Smith A, *et al.*

Fludarabine phosphate for the first-line treatment of chronic lymphocytic leukaemia.
By Walker S, Palmer S, Erhorn S, Brent S, Dyker A, Ferrie L, *et al.*

Erlotinib for the treatment of relapsed non-small cell lung cancer.
By McLeod C, Bagust A, Boland A, Hockenhull J, Dundar Y, Proudlove C, *et al.*

Cetuximab plus radiotherapy for the treatment of locally advanced squamous cell carcinoma of the head and neck.
By Griffin S, Walker S, Sculpher M, White S, Erhorn S, Brent S, *et al.*

Infliximab for the treatment of adults with psoriasis.
By Loveman E, Turner D, Hartwell D, Cooper K, Clegg A.

No. 30
Psychological interventions for postnatal depression: cluster randomised trial and economic evaluation. The PoNDER trial.
By Morrell CJ, Warner R, Slade P, Dixon S, Walters S, Paley G, *et al*.

No. 31
The effect of different treatment durations of clopidogrel in patients with non-ST-segment elevation acute coronary syndromes: a systematic review and value of information analysis.
By Rogowski R, Burch J, Palmer S, Craigs C, Golder S, Woolacott N.

No. 32
Systematic review and individual patient data meta-analysis of diagnosis of heart failure, with modelling of implications of different diagnostic strategies in primary care.
By Mant J, Doust J, Roalfe A, Barton P, Cowie MR, Glasziou P, *et al*.

No. 33
A multicentre randomised controlled trial of the use of continuous positive airway pressure and non-invasive positive pressure ventilation in the early treatment of patients presenting to the emergency department with severe acute cardiogenic pulmonary oedema: the 3CPO trial.
By Gray AJ, Goodacre S, Newby DE, Masson MA, Sampson F, Dixon S, *et al*., on behalf of the 3CPO study investigators.

No. 34
Early high-dose lipid-lowering therapy to avoid cardiac events: a systematic review and economic evaluation.
By Ara R, Pandor A, Stevens J, Rees A, Rafia R.

No. 35
Adefovir dipivoxil and pegylated interferon alpha for the treatment of chronic hepatitis B: an updated systematic review and economic evaluation.
By Jones J, Shepherd J, Baxter L, Gospodarevskaya E, Hartwell D, Harris P, *et al*.

No. 36
Methods to identify postnatal depression in primary care: an integrated evidence synthesis and value of information analysis.
By Hewitt CE, Gilbody SM, Brealey S, Paulden M, Palmer S, Mann R, *et al*.

No. 37
A double-blind randomised placebo-controlled trial of topical intranasal corticosteroids in 4- to 11-year-old children with persistent bilateral otitis media with effusion in primary care.
By Williamson I, Benge S, Barton S, Petrou S, Letley L, Fasey N, *et al*.

No. 38
The effectiveness and cost-effectiveness of methods of storing donated kidneys from deceased donors: a systematic review and economic model.
By Bond M, Pitt M, Akoh J, Moxham T, Hoyle M, Anderson R.

No. 39
Rehabilitation of older patients: day hospital compared with rehabilitation at home. A randomised controlled trial.
By Parker SG, Oliver P, Pennington M, Bond J, Jagger C, Enderby PM, *et al*.

No. 40
Breastfeeding promotion for infants in neonatal units: a systematic review and economic analysis
By Renfrew MJ, Craig D, Dyson L, McCormick F, Rice S, King SE, *et al*.

No. 41
The clinical effectiveness and cost-effectiveness of bariatric (weight loss) surgery for obesity: a systematic review and economic evaluation.
By Picot J, Jones J, Colquitt JL, Gospodarevskaya E, Loveman E, Baxter L, *et al*.

No. 42
Rapid testing for group B streptococcus during labour: a test accuracy study with evaluation of acceptability and cost-effectiveness.
By Daniels J, Gray J, Pattison H, Roberts T, Edwards E, Milner P, *et al*.

No. 43
Screening to prevent spontaneous preterm birth: systematic reviews of accuracy and effectiveness literature with economic modelling.
By Honest H, Forbes CA, Durée KH, Norman G, Duffy SB, Tsourapas A, *et al*.

No. 44
The effectiveness and cost-effectiveness of cochlear implants for severe to profound deafness in children and adults: a systematic review and economic model.
By Bond M, Mealing S, Anderson R, Elston J, Weiner G, Taylor RS, *et al*.

Suppl. 2
Gemcitabine for the treatment of metastatic breast cancer.
By Jones J, Takeda A, Tan SC, Cooper K, Loveman E, Clegg A.

Varenicline in the management of smoking cessation: a single technology appraisal.
By Hind D, Tappenden P, Peters J, Kenjegalieva K.

Alteplase for the treatment of acute ischaemic stroke: a single technology appraisal.
By Lloyd Jones M, Holmes M.

Rituximab for the treatment of rheumatoid arthritis.
By Bagust A, Boland A, Hockenhull J, Fleeman N, Greenhalgh J, Dundar Y, *et al*.

Omalizumab for the treatment of severe persistent allergic asthma.
By Jones J, Shepherd J, Hartwell D, Harris P, Cooper K, Takeda A, *et al*.

Rituximab for the treatment of relapsed or refractory stage III or IV follicular non-Hodgkin's lymphoma.
By Boland A, Bagust A, Hockenhull J, Davis H, Chu P, Dickson R.

Adalimumab for the treatment of psoriasis.
By Turner D, Picot J, Cooper K, Loveman E.

Dabigatran etexilate for the prevention of venous thromboembolism in patients undergoing elective hip and knee surgery: a single technology appraisal.
By Holmes M, C Carroll C, Papaioannou D.

Romiplostim for the treatment of chronic immune or idiopathic thrombocytopenic purpura: a single technology appraisal.
By Mowatt G, Boachie C, Crowther M, Fraser C, Hernández R, Jia X, *et al*.

Sunitinib for the treatment of gastrointestinal stromal tumours: a critique of the submission from Pfizer.
By Bond M, Hoyle M, Moxham T, Napier M, Anderson R.

No. 45
Vitamin K to prevent fractures in older women: systematic review and economic evaluation.
By Stevenson M, Lloyd-Jones M, Papaioannou D.

No. 46
The effects of biofeedback for the treatment of essential hypertension: a systematic review.
By Greenhalgh J, Dickson R, Dundar Y.

No. 47
A randomised controlled trial of the use of aciclovir and/or prednisolone for the early treatment of Bell's palsy: the BELLS study.
By Sullivan FM, Swan IRC, Donnan PT, Morrison JM, Smith BH, McKinstry B, *et al*.

Suppl. 3
Lapatinib for the treatment of HER2-overexpressing breast cancer.
By Jones J, Takeda A, Picot J, von Keyserlingk C, Clegg A.

Infliximab for the treatment of ulcerative colitis.
By Hyde C, Bryan S, Juarez-Garcia A, Andronis L, Fry-Smith A.

Rimonabant for the treatment of overweight and obese people.
By Burch J, McKenna C, Palmer S, Norman G, Glanville J, Sculpher M, *et al*.

Telbivudine for the treatment of chronic hepatitis B infection.
By Hartwell D, Jones J, Harris P, Cooper K.

Entecavir for the treatment of chronic hepatitis B infection.
By Shepherd J, Gospodarevskaya E, Frampton G, Cooper, K.

Febuxostat for the treatment of hyperuricaemia in people with gout: a single technology appraisal.
By Stevenson M, Pandor A.

Rivaroxaban for the prevention of venous thromboembolism: a single technology appraisal.
By Stevenson M, Scope A, Holmes M, Rees A, Kaltenthaler E.

Cetuximab for the treatment of recurrent and/or metastatic squamous cell carcinoma of the head and neck.
By Greenhalgh J, Bagust A, Boland A, Fleeman N, McLeod C, Dundar Y, *et al*.

Mifamurtide for the treatment of osteosarcoma: a single technology appraisal.
By Pandor A, Fitzgerald P, Stevenson M, Papaioannou D.

Ustekinumab for the treatment of moderate to severe psoriasis.
By Gospodarevskaya E, Picot J, Cooper K, Loveman E, Takeda A.

No. 48
Endovascular stents for abdominal aortic aneurysms: a systematic review and economic model.
By Chambers D, Epstein D, Walker S, Fayter D, Paton F, Wright K, *et al*.

No. 49
Clinical and cost-effectiveness of epoprostenol, iloprost, bosentan, sitaxentan and sildenafil for pulmonary arterial hypertension within their licensed indications: a systematic review and economic evaluation.
By Chen Y-F, Jowett S, Barton P, Malottki K, Hyde C, Gibbs JSR, *et al*.

No. 50
Cessation of attention deficit hyperactivity disorder drugs in the young (CADDY) – a pharmacoepidemiological and qualitative study.
By Wong ICK, Asherson P, Bilbow A, Clifford S, Coghill D, R DeSoysa R, *et al*.

No. 51
ARTISTIC: a randomised trial of human papillomavirus (HPV) testing in primary cervical screening.
By Kitchener HC, Almonte M, Gilham C, Dowie R, Stoykova B, Sargent A, *et al*.

No. 52
The clinical effectiveness of glucosamine and chondroitin supplements in slowing or arresting progression of osteoarthritis of the knee: a systematic review and economic evaluation.
By Black C, Clar C, Henderson R, MacEachern C, McNamee P, Quayyum Z, *et al*.

No. 53
Randomised preference trial of medical versus surgical termination of pregnancy less than 14 weeks' gestation (TOPS).
By Robson SC, Kelly T, Howel D, Deverill M, Hewison J, Lie MLS, *et al*.

No. 54
Randomised controlled trial of the use of three dressing preparations in the management of chronic ulceration of the foot in diabetes.
By Jeffcoate WJ, Price PE, Phillips CJ, Game FL, Mudge E, Davies S, *et al*.

No. 55
VenUS II: a randomised controlled trial of larval therapy in the management of leg ulcers.
By Dumville JC, Worthy G, Soares MO, Bland JM, Cullum N, Dowson C, *et al*.

No. 56
A prospective randomised controlled trial and economic modelling of antimicrobial silver dressings versus non-adherent control dressings for venous leg ulcers: the VULCAN trial
By Michaels JA, Campbell WB, King BM, MacIntyre J, Palfreyman SJ, Shackley P, *et al*.

No. 57
Communication of carrier status information following universal newborn screening for sickle cell disorders and cystic fibrosis: qualitative study of experience and practice.
By Kai J, Ulph F, Cullinan T, Qureshi N.

No. 58
Antiviral drugs for the treatment of influenza: a systematic review and economic evaluation.
By Burch J, Paulden M, Conti S, Stock C, Corbett M, Welton NJ, *et al*.

No. 59
Development of a toolkit and glossary to aid in the adaptation of health technology assessment (HTA) reports for use in different contexts.
By Chase D, Rosten C, Turner S, Hicks N, Milne R.

No. 60
Colour vision testing for diabetic retinopathy: a systematic review of diagnostic accuracy and economic evaluation.
By Rodgers M, Hodges R, Hawkins J, Hollingworth W, Duffy S, McKibbin M, *et al*.

No. 61
Systematic review of the effectiveness and cost-effectiveness of weight management schemes for the under fives: a short report.
By Bond M, Wyatt K, Lloyd J, Welch K, Taylor R.

No. 62
Are adverse effects incorporated in economic models? An initial review of current practice.
By Craig D, McDaid C, Fonseca T, Stock C, Duffy S, Woolacott N.

Volume 14, 2010

No. 1
Multicentre randomised controlled trial examining the cost-effectiveness of contrast-enhanced high field magnetic resonance imaging in women with primary breast cancer scheduled for wide local excision (COMICE).
By Turnbull LW, Brown SR, Olivier C, Harvey I, Brown J, Drew P, *et al*.

No. 2
Bevacizumab, sorafenib tosylate, sunitinib and temsirolimus for renal cell carcinoma: a systematic review and economic evaluation.
By Thompson Coon J, Hoyle M, Green C, Liu Z, Welch K, Moxham T, *et al*.

Health Technology Assessment programme

Director,
Professor Tom Walley,
Director, NIHR HTA programme, Professor of Clinical Pharmacology, University of Liverpool

Deputy Director,
Professor Jon Nicholl,
Director, Medical Care Research Unit, University of Sheffield

Prioritisation Strategy Group

Members

Chair,
Professor Tom Walley,
Director, NIHR HTA programme, Professor of Clinical Pharmacology, University of Liverpool

Deputy Chair,
Professor Jon Nicholl,
Director, Medical Care Research Unit, University of Sheffield

Dr Bob Coates,
Consultant Advisor, NETSCC, HTA

Dr Andrew Cook,
Consultant Advisor, NETSCC, HTA

Dr Peter Davidson,
Director of Science Support, NETSCC, HTA

Professor Robin E Ferner,
Consultant Physician and Director, West Midlands Centre for Adverse Drug Reactions, City Hospital NHS Trust, Birmingham

Professor Paul Glasziou,
Professor of Evidence-Based Medicine, University of Oxford

Dr Nick Hicks,
Director of NHS Support, NETSCC, HTA

Dr Edmund Jessop,
Medical Adviser, National Specialist, National Commissioning Group (NCG), Department of Health, London

Ms Lynn Kerridge,
Chief Executive Officer, NETSCC and NETSCC, HTA

Dr Ruairidh Milne,
Director of Strategy and Development, NETSCC

Ms Kay Pattison,
Section Head, NHS R&D Programme, Department of Health

Ms Pamela Young,
Specialist Programme Manager, NETSCC, HTA

HTA Commissioning Board

Members

Programme Director,
Professor Tom Walley,
Director, NIHR HTA programme, Professor of Clinical Pharmacology, University of Liverpool

Chair,
Professor Jon Nicholl,
Director, Medical Care Research Unit, University of Sheffield

Deputy Chair,
Dr Andrew Farmer,
Senior Lecturer in General Practice, Department of Primary Health Care, University of Oxford

Professor Ann Ashburn,
Professor of Rehabilitation and Head of Research, Southampton General Hospital

Professor Deborah Ashby,
Professor of Medical Statistics, Queen Mary, University of London

Professor John Cairns,
Professor of Health Economics, London School of Hygiene and Tropical Medicine

Professor Peter Croft,
Director of Primary Care Sciences Research Centre, Keele University

Professor Nicky Cullum,
Director of Centre for Evidence-Based Nursing, University of York

Professor Jenny Donovan,
Professor of Social Medicine, University of Bristol

Professor Steve Halligan,
Professor of Gastrointestinal Radiology, University College Hospital, London

Professor Freddie Hamdy,
Professor of Urology, University of Sheffield

Professor Allan House,
Professor of Liaison Psychiatry, University of Leeds

Dr Martin J Landray,
Reader in Epidemiology, Honorary Consultant Physician, Clinical Trial Service Unit, University of Oxford

Professor Stuart Logan,
Director of Health & Social Care Research, The Peninsula Medical School, Universities of Exeter and Plymouth

Dr Rafael Perera,
Lecturer in Medical Statisitics, Department of Primary Health Care, Univeristy of Oxford

Professor Ian Roberts,
Professor of Epidemiology & Public Health, London School of Hygiene and Tropical Medicine

Professor Mark Sculpher,
Professor of Health Economics, University of York

Professor Helen Smith,
Professor of Primary Care, University of Brighton

Professor Kate Thomas,
Professor of Complementary & Alternative Medicine Research, University of Leeds

Professor David John Torgerson,
Director of York Trials Unit, University of York

Professor Hywel Williams,
Professor of Dermato-Epidemiology, University of Nottingham

Observers

Ms Kay Pattison,
Section Head, NHS R&D Programme, Department of Health

Dr Morven Roberts,
Clinical Trials Manager, Medical Research Council

Diagnostic Technologies & Screening Panel

Members

Chair,
Professor Paul Glasziou,
Professor of Evidence-Based Medicine, University of Oxford

Deputy Chair,
Dr David Elliman,
Consultant Paediatrician and Honorary Senior Lecturer, Great Ormond Street Hospital, London

Professor Judith E Adams, Consultant Radiologist, Manchester Royal Infirmary, Central Manchester & Manchester Children's University Hospitals NHS Trust, and Professor of Diagnostic Radiology, Imaging Science and Biomedical Engineering, Cancer & Imaging Sciences, University of Manchester

Ms Jane Bates, Consultant Ultrasound Practitioner, Ultrasound Department, Leeds Teaching Hospital NHS Trust

Dr Stephanie Dancer, Consultant Microbiologist, Hairmyres Hospital, East Kilbride

Professor Glyn Elwyn, Primary Medical Care Research Group, Swansea Clinical School, University of Wales

Dr Ron Gray, Consultant Clinical Epidemiologist, Department of Public Health, University of Oxford

Professor Paul D Griffiths, Professor of Radiology, University of Sheffield

Dr Jennifer J Kurinczuk, Consultant Clinical Epidemiologist, National Perinatal Epidemiology Unit, Oxford

Dr Susanne M Ludgate, Medical Director, Medicines & Healthcare Products Regulatory Agency, London

Dr Anne Mackie, Director of Programmes, UK National Screening Committee

Dr Michael Millar, Consultant Senior Lecturer in Microbiology, Barts and The London NHS Trust, Royal London Hospital

Mr Stephen Pilling, Director, Centre for Outcomes, Research & Effectiveness, Joint Director, National Collaborating Centre for Mental Health, University College London

Mrs Una Rennard, Service User Representative

Dr Phil Shackley, Senior Lecturer in Health Economics, School of Population and Health Sciences, University of Newcastle upon Tyne

Dr W Stuart A Smellie, Consultant in Chemical Pathology, Bishop Auckland General Hospital

Dr Nicholas Summerton, Consultant Clinical and Public Health Advisor, NICE

Ms Dawn Talbot, Service User Representative

Dr Graham Taylor, Scientific Advisor, Regional DNA Laboratory, St James's University Hospital, Leeds

Professor Lindsay Wilson Turnbull, Scientific Director of the Centre for Magnetic Resonance Investigations and YCR Professor of Radiology, Hull Royal Infirmary

Observers

Dr Tim Elliott, Team Leader, Cancer Screening, Department of Health

Dr Catherine Moody, Programme Manager, Neuroscience and Mental Health Board

Dr Ursula Wells, Principal Research Officer, Department of Health

Pharmaceuticals Panel

Members

Chair,
Professor Robin Ferner,
Consultant Physician and Director, West Midlands Centre for Adverse Drug Reactions, City Hospital NHS Trust, Birmingham

Deputy Chair,
Professor Imti Choonara,
Professor in Child Health, University of Nottingham

Mrs Nicola Carey, Senior Research Fellow, School of Health and Social Care, The University of Reading

Mr John Chapman, Service User Representative

Dr Peter Elton, Director of Public Health, Bury Primary Care Trust

Dr Ben Goldacre, Research Fellow, Division of Psychological Medicine and Psychiatry, King's College London

Mrs Barbara Greggains, Service User Representative

Dr Bill Gutteridge, Medical Adviser, London Strategic Health Authority

Dr Dyfrig Hughes, Reader in Pharmacoeconomics and Deputy Director, Centre for Economics and Policy in Health, IMSCaR, Bangor University

Professor Jonathan Ledermann, Professor of Medical Oncology and Director of the Cancer Research UK and University College London Cancer Trials Centre

Dr Yoon K Loke, Senior Lecturer in Clinical Pharmacology, University of East Anglia

Professor Femi Oyebode, Consultant Psychiatrist and Head of Department, University of Birmingham

Dr Andrew Prentice, Senior Lecturer and Consultant Obstetrician and Gynaecologist, The Rosie Hospital, University of Cambridge

Dr Martin Shelly, General Practitioner, Leeds, and Associate Director, NHS Clinical Governance Support Team, Leicester

Dr Gillian Shepherd, Director, Health and Clinical Excellence, Merck Serono Ltd

Mrs Katrina Simister, Assistant Director New Medicines, National Prescribing Centre, Liverpool

Mr David Symes, Service User Representative

Dr Lesley Wise, Unit Manager, Pharmacoepidemiology Research Unit, VRMM, Medicines & Healthcare Products Regulatory Agency

Observers

Ms Kay Pattison, Section Head, NHS R&D Programme, Department of Health

Mr Simon Reeve, Head of Clinical and Cost-Effectiveness, Medicines, Pharmacy and Industry Group, Department of Health

Dr Heike Weber, Programme Manager, Medical Research Council

Dr Ursula Wells, Principal Research Officer, Department of Health

Current and past membership details of all HTA programme 'committees' are available from the HTA website (www.hta.ac.uk)

Therapeutic Procedures Panel

Members

Chair,
Dr John C Pounsford,
Consultant Physician, North Bristol NHS Trust

Deputy Chair,
Professor Scott Weich,
Professor of Psychiatry, Division of Health in the Community, University of Warwick, Coventry

Professor Jane Barlow,
Professor of Public Health in the Early Years, Health Sciences Research Institute, Warwick Medical School, Coventry

Ms Maree Barnett,
Acting Branch Head of Vascular Programme, Department of Health

Mrs Val Carlill,
Service User Representative

Mrs Anthea De Barton-Watson,
Service User Representative

Mr Mark Emberton,
Senior Lecturer in Oncological Urology, Institute of Urology, University College Hospital, London

Professor Steve Goodacre,
Professor of Emergency Medicine, University of Sheffield

Professor Christopher Griffiths,
Professor of Primary Care, Barts and The London School of Medicine and Dentistry

Mr Paul Hilton,
Consultant Gynaecologist and Urogynaecologist, Royal Victoria Infirmary, Newcastle upon Tyne

Professor Nicholas James,
Professor of Clinical Oncology, University of Birmingham, and Consultant in Clinical Oncology, Queen Elizabeth Hospital

Dr Peter Martin,
Consultant Neurologist, Addenbrooke's Hospital, Cambridge

Dr Kate Radford,
Senior Lecturer (Research), Clinical Practice Research Unit, University of Central Lancashire, Preston

Mr Jim Reece
Service User Representative

Dr Karen Roberts,
Nurse Consultant, Dunston Hill Hospital Cottages

Observers

Dr Phillip Leech,
Principal Medical Officer for Primary Care, Department of Health

Ms Kay Pattison,
Section Head, NHS R&D Programme, Department of Health

Dr Morven Roberts,
Clinical Trials Manager, Medical Research Council

Professor Tom Walley,
Director, NIHR HTA programme, Professor of Clinical Pharmacology, University of Liverpool

Dr Ursula Wells,
Principal Research Officer, Department of Health

Disease Prevention Panel

Members

Chair,
Dr Edmund Jessop,
Medical Adviser, National Specialist, National Commissioning Group (NCG), London

Deputy Chair,
Dr David Pencheon,
Director, NHS Sustainable Development Unit, Cambridge

Dr Elizabeth Fellow-Smith,
Medical Director, West London Mental Health Trust, Middlesex

Dr John Jackson,
General Practitioner, Parkway Medical Centre, Newcastle upon Tyne

Professor Mike Kelly,
Director, Centre for Public Health Excellence, NICE, London

Dr Chris McCall,
General Practitioner, The Hadleigh Practice, Corfe Mullen, Dorset

Ms Jeanett Martin,
Director of Nursing, BarnDoc Limited, Lewisham Primary Care Trust

Dr Julie Mytton,
Locum Consultant in Public Health Medicine, Bristol Primary Care Trust

Miss Nicky Mullany,
Service User Representative

Professor Ian Roberts,
Professor of Epidemiology and Public Health, London School of Hygiene & Tropical Medicine

Professor Ken Stein,
Senior Clinical Lecturer in Public Health, University of Exeter

Dr Kieran Sweeney,
Honorary Clinical Senior Lecturer, Peninsula College of Medicine and Dentistry, Universities of Exeter and Plymouth

Professor Carol Tannahill,
Glasgow Centre for Population Health

Professor Margaret Thorogood,
Professor of Epidemiology, University of Warwick Medical School, Coventry

Observers

Ms Christine McGuire,
Research & Development, Department of Health

Dr Caroline Stone,
Programme Manager, Medical Research Council

Expert Advisory Network

Members

Professor Douglas Altman, Professor of Statistics in Medicine, Centre for Statistics in Medicine, University of Oxford

Professor John Bond, Professor of Social Gerontology & Health Services Research, University of Newcastle upon Tyne

Professor Andrew Bradbury, Professor of Vascular Surgery, Solihull Hospital, Birmingham

Mr Shaun Brogan, Chief Executive, Ridgeway Primary Care Group, Aylesbury

Mrs Stella Burnside OBE, Chief Executive, Regulation and Improvement Authority, Belfast

Ms Tracy Bury, Project Manager, World Confederation for Physical Therapy, London

Professor Iain T Cameron, Professor of Obstetrics and Gynaecology and Head of the School of Medicine, University of Southampton

Dr Christine Clark, Medical Writer and Consultant Pharmacist, Rossendale

Professor Collette Clifford, Professor of Nursing and Head of Research, The Medical School, University of Birmingham

Professor Barry Cookson, Director, Laboratory of Hospital Infection, Public Health Laboratory Service, London

Dr Carl Counsell, Clinical Senior Lecturer in Neurology, University of Aberdeen

Professor Howard Cuckle, Professor of Reproductive Epidemiology, Department of Paediatrics, Obstetrics & Gynaecology, University of Leeds

Dr Katherine Darton, Information Unit, MIND – The Mental Health Charity, London

Professor Carol Dezateux, Professor of Paediatric Epidemiology, Institute of Child Health, London

Mr John Dunning, Consultant Cardiothoracic Surgeon, Papworth Hospital NHS Trust, Cambridge

Mr Jonothan Earnshaw, Consultant Vascular Surgeon, Gloucestershire Royal Hospital, Gloucester

Professor Martin Eccles, Professor of Clinical Effectiveness, Centre for Health Services Research, University of Newcastle upon Tyne

Professor Pam Enderby, Dean of Faculty of Medicine, Institute of General Practice and Primary Care, University of Sheffield

Professor Gene Feder, Professor of Primary Care Research & Development, Centre for Health Sciences, Barts and The London School of Medicine and Dentistry

Mr Leonard R Fenwick, Chief Executive, Freeman Hospital, Newcastle upon Tyne

Mrs Gillian Fletcher, Antenatal Teacher and Tutor and President, National Childbirth Trust, Henfield

Professor Jayne Franklyn, Professor of Medicine, University of Birmingham

Mr Tam Fry, Honorary Chairman, Child Growth Foundation, London

Professor Fiona Gilbert, Consultant Radiologist and NCRN Member, University of Aberdeen

Professor Paul Gregg, Professor of Orthopaedic Surgical Science, South Tees Hospital NHS Trust

Bec Hanley, Co-director, TwoCan Associates, West Sussex

Dr Maryann L Hardy, Senior Lecturer, University of Bradford

Mrs Sharon Hart, Healthcare Management Consultant, Reading

Professor Robert E Hawkins, CRC Professor and Director of Medical Oncology, Christie CRC Research Centre, Christie Hospital NHS Trust, Manchester

Professor Richard Hobbs, Head of Department of Primary Care & General Practice, University of Birmingham

Professor Alan Horwich, Dean and Section Chairman, The Institute of Cancer Research, London

Professor Allen Hutchinson, Director of Public Health and Deputy Dean of ScHARR, University of Sheffield

Professor Peter Jones, Professor of Psychiatry, University of Cambridge, Cambridge

Professor Stan Kaye, Cancer Research UK Professor of Medical Oncology, Royal Marsden Hospital and Institute of Cancer Research, Surrey

Dr Duncan Keeley, General Practitioner (Dr Burch & Ptnrs), The Health Centre, Thame

Dr Donna Lamping, Research Degrees Programme Director and Reader in Psychology, Health Services Research Unit, London School of Hygiene and Tropical Medicine, London

Mr George Levvy, Chief Executive, Motor Neurone Disease Association, Northampton

Professor James Lindesay, Professor of Psychiatry for the Elderly, University of Leicester

Professor Julian Little, Professor of Human Genome Epidemiology, University of Ottawa

Professor Alistaire McGuire, Professor of Health Economics, London School of Economics

Professor Rajan Madhok, Medical Director and Director of Public Health, Directorate of Clinical Strategy & Public Health, North & East Yorkshire & Northern Lincolnshire Health Authority, York

Professor Alexander Markham, Director, Molecular Medicine Unit, St James's University Hospital, Leeds

Dr Peter Moore, Freelance Science Writer, Ashtead

Dr Andrew Mortimore, Public Health Director, Southampton City Primary Care Trust

Dr Sue Moss, Associate Director, Cancer Screening Evaluation Unit, Institute of Cancer Research, Sutton

Professor Miranda Mugford, Professor of Health Economics and Group Co-ordinator, University of East Anglia

Professor Jim Neilson, Head of School of Reproductive & Developmental Medicine and Professor of Obstetrics and Gynaecology, University of Liverpool

Mrs Julietta Patnick, National Co-ordinator, NHS Cancer Screening Programmes, Sheffield

Professor Robert Peveler, Professor of Liaison Psychiatry, Royal South Hants Hospital, Southampton

Professor Chris Price, Director of Clinical Research, Bayer Diagnostics Europe, Stoke Poges

Professor William Rosenberg, Professor of Hepatology and Consultant Physician, University of Southampton

Professor Peter Sandercock, Professor of Medical Neurology, Department of Clinical Neurosciences, University of Edinburgh

Dr Susan Schonfield, Consultant in Public Health, Hillingdon Primary Care Trust, Middlesex

Dr Eamonn Sheridan, Consultant in Clinical Genetics, St James's University Hospital, Leeds

Dr Margaret Somerville, Director of Public Health Learning, Peninsula Medical School, University of Plymouth

Professor Sarah Stewart-Brown, Professor of Public Health, Division of Health in the Community, University of Warwick, Coventry

Professor Ala Szczepura, Professor of Health Service Research, Centre for Health Services Studies, University of Warwick, Coventry

Mrs Joan Webster, Consumer Member, Southern Derbyshire Community Health Council

Professor Martin Whittle, Clinical Co-director, National Co-ordinating Centre for Women's and Children's Health, Lymington

Feedback

The HTA programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (www.hta.ac.uk) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

We look forward to hearing from you.

NETSCC, Health Technology Assessment
Alpha House
University of Southampton Science Park
Southampton SO16 7NS, UK
Email: hta@hta.ac.uk
www.hta.ac.uk

ISSN 1366-5278