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The clinical effectiveness and cost-effectiveness of genotyping for *CYP2D6* for the management of women with breast cancer treated with tamoxifen: a systematic review

N Fleeman,[1]* C Martin Saborido,[2] K Payne,[3] A Boland,[1] R Dickson,[1] Y Dundar,[1] A Fernández Santander,[4] S Howell,[5] W Newman,[6] J Oyee[1] and T Walley[7]

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The research reported in this issue of the journal was commissioned by the HTA programme as project number 08/83/01. The contractual start date was in August 2009. The draft report began editorial review in August 2010 and was accepted for publication in December 2010. As the funder, by devising a commissioning brief, the HTA programme specified the research question and study design. 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.

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Abstract

The clinical effectiveness and cost-effectiveness of genotyping for *CYP2D6* for the management of women with breast cancer treated with tamoxifen: a systematic review

N Fleeman,[1]* C Martin Saborido,[2] K Payne,[3] A Boland,[1] R Dickson,[1] Y Dundar,[1] A Fernández Santander,[4] S Howell,[5] W Newman,[6] J Oyee[1] and T Walley[7]

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Background: Breast cancer is the most common cancer affecting women in the UK. Tamoxifen (TAM) is considered as the standard of care for many women with oestrogen receptor positive breast cancer. However, wide variability in the response of individuals to drugs at the same doses may occur, which may be a result of interindividual genetic differences (pharmacogenetics). TAM is known to be metabolised to its active metabolites *N*-desmethyl TAM and 4-hydroxytamoxifen by a number of CYP450 enzymes, including CYP2D6, CYP3A4, CYP2C9, CYP2C19 and CYP2B6. *N*-desmethyl TAM is further metabolised to endoxifen by CYP2D6. Endoxifen, which is also formed via the action of CYP2D6, is 30- to 100-fold more potent than TAM in suppressing oestrogen-dependent cell proliferation, and is considered an entity responsible for significant pharmacological effects of TAM. Thus, an association between the cytochrome P450 2D6 (*CYP2D6*) genotype and phenotype (expected drug effects) is believed to exist and it has been postulated that *CYP2D6* testing may play a role in optimising an individual's adjuvant hormonal treatment.

Objectives: To determine whether or not testing for cytochrome P450 2D6 (*CYP2D6*) polymorphisms in women with early hormone receptor positive breast cancer leads to improvement in outcomes, is useful for health decision-making and is a cost-effective use of health-care resources.

Data sources: Relevant electronic databases and websites including MEDLINE, EMBASE and HuGENet™ [Centers for Disease Control and Prevention (Office of Public Health Genomics), Human Genome Epidemiology Network] were searched until July 2009. Further studies that became known to the authors via relevant conferences or e-mail alerts from an automatically updated search of the Scopus database were also included as the review progressed, up to March 2010.

Review methods: A systematic review of the clinical effectiveness and cost-effectiveness of *CYP2D6* testing was undertaken. As it was not possible to conduct meta-analyses, data

were extracted into structured tables and narratively discussed. An exploratory analysis of sensitivity and specificity was undertaken. A review of economic evaluations and models of *CYP2D6* testing for patients treated with TAM was also carried out.

Results: A total of 25 cohorts were identified which examined clinical efficacy (overall survival and relapse/recurrence), adverse events and endoxifen plasma concentrations by genotype/phenotype. Significantly, six cohorts suggest extensive metabolisers (Ems) appear to have better outcomes than either poor metabolisers (PMs) or PMs + intermediate metabolisers in terms of relapse/recurrence; however, three cohorts report apparently poorer outcomes for EMs (albeit not statistically significant). There was heterogeneity across the studies in terms of the patient population, alleles tested and outcomes used and defined. One decision model proposing a strategy for *CYP2D6* testing for TAM was identified, but this was not suitable for developing a model to examine the cost-effectiveness of *CYP2D6* testing. It was not possible to produce a de novo model because of a lack of data to populate it.

Conclusion: This is a relatively new area of research that is evolving rapidly and, although international consortia are collaborating, the data are limited and conflicting. Therefore, it is not possible to recommend pharmacogenetic testing in this patient population. Future research needs to focus on which alleles (including, or in addition to, those related to *CYP2D6*) reflect patient response, the link between endoxifen levels and clinical outcomes, and the appropriate pathways for implementation of such pharmacogenetic testing in patient care pathways.

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Contents

List of abbreviations

AE	adverse event
AJCC	American Joint Committee on Cancer
ANA	anastrozole
ATAC	Arimidex, Tamoxifen, Alone or in Combination
BIG 1-98	Breast International Group 1-98
BMD	bone mineral density
BRCA1	breast cancer 1
BRCA2	breast cancer 2
CI	confidence interval
CYP2D6	cytochrome P450 2D6
CYP450	cytochrome P450
DFS	disease-free survival
EFS	event-free survival
EM	extensive metaboliser
ER	oestrogen receptor
ER–	oestrogen receptor negative
ER+	oestrogen receptor positive
FDA	Food and Drug Administration
HER2	human epidermal growth factor receptor 2
hetEM	heterozygous extensive metaboliser
HR	hazard ratio
IES	Intergroup Exemestane Study
IM	intermediate metaboliser
ITA	Italian tamoxifen anastrozole
ITPC	International Tamoxifen Pharmacogenomics Consortium
LN+	lymph node positive
NICE	National Institute for Health and Clinical Excellence
NPI	Nottingham Prognostic Index
OS	overall survival
PM	poor metaboliser
QALY	quality-adjusted life-year
RCT	randomised controlled trial
RFS	recurrence-free survival
RFT	recurrence-free time
SSRI	selective serotonin reuptake inhibitor
TAM	tamoxifen
TNM	tumour/nodes/metastasis
TTR	time to recurrence
UICC	Union Internationale Contre le Cancer
UM	ultrarapid metaboliser
vt	variant type
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 been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.

Glossary

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

AmpliChip® A type of assay used to detect *CYP2D6* variants.

Anti-oestrogen therapy Treatment that blocks the binding and actions of oestrogen.

ARMS Genotyping method that uses two pairs of primers to amplify two alleles in one polymerase chain reaction.

Biological therapy Treatments that use natural substances from the body, or drugs made from these substances, to fight cancer or to lessen the side effects that may be caused by some cancer treatments. An example includes trastuzumab (Herceptin®, Roche).

Chemotherapy Treatment with drugs that kill cancer cells.

Coronary arteries The arteries that supply the heart muscle with blood.

Cost–benefit analysis A method of economic evaluation. An attempt to give the consequences of the alternative interventions a monetary value. In this way, the consequences can be more easily compared with the costs of the intervention. This involves measuring individuals' 'willingness to pay' for given outcomes.

Cost-effectiveness analysis A method of economic evaluation. The consequences of the alternatives are measured in natural units, such as years of life gained. The consequences are not given a monetary value.

CYP2D6 The enzyme belonging to the CYP450 enzyme system, also known as cytochrome P450 2D6. This is one of the most important enzymes involved in the metabolism of substances in the human body, mostly in the liver.

CYP2D6 The gene that encodes the CYP2D6 enzyme.

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

Debrisoquine A derivative of guanidine found in urine as a normal product of protein metabolism. It is frequently used for phenotyping the CYP2D6 enzyme (from the molar urinary metabolic ratio of debrisoquine to its metabolite, 4-hydroxydebrisoquine).

Dextromethorphan A drug that is frequently used for phenotyping the CYP2D6 enzyme (from the molar urinary metabolic ratio of dextromethorphan to its metabolite, dextrorphan).

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

Extensive metaboliser Somebody who metabolises tamoxifen normally at the normal therapeutic dose.

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

Genotype The genetic constitution of an individual, i.e. the specific allelic make-up of an individual.

Heterogeneity In statistics this means that there is between-study variation. If heterogeneity exists, the pooled effect size in a meta-analysis has no meaning, as the presence of heterogeneity indicates that there is more than one true effect size in the studies being combined.

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.

Intermediate metaboliser Somebody whose metabolism of tamoxifen lies somewhere between that of extensive metabolisers and poor metabolisers.

Luminex A type of assay used to detect *CYP2D6* variants.

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 constituent of DNA.

Oestrogen receptor negative Cancer cells that are oestrogen receptor negative do not need oestrogen to grow.

Oestrogen receptor positive Cancer cells that may need oestrogen to grow (and can thus be treated with anti-oestrogen therapy).

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.

Polymerase chain reaction A genotyping technique to amplify DNA for sequencing.

Poor metaboliser Somebody with impaired metabolism of tamoxifen at the normal dose.

Protein A complete biological molecule made 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.

Quality-adjusted life-year An index of survival that is weighted or adjusted by a patient's quality of life during the survival period. Quality-adjusted life-years are calculated by multiplying the number of life-years by an appropriate utility or preference score.

Radiotherapy The use of high-energy radiation from X-rays, gamma rays, neutrons, protons and other sources to kill cancer cells and shrink tumours.

Receptor protein 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.

Sequencing Method for determining the order of the nucleotide bases – adenine, guanine, cytosine and thymine – in a molecule of DNA.

Single-nucleotide polymorphism The most common types of genetic variations in human beings that occur when a single nucleotide (adenosine, guanine, cytosine and thymine) in the genome sequence is changed.

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

TaqMan® A type of assay used to detect *CYP2D6* variants.

Ultrarapid metaboliser Somebody who metabolises tamoxifen more rapidly than extensive metabolisers at the normal dose.

Executive summary

Background

Breast cancer is the most common cancer affecting women in the UK. Tamoxifen (TAM) is considered the standard of care for premenopausal women with oestrogen receptor positive (ER+) breast cancer and for postmenopausal women with ER+ early breast cancer considered to be at low risk of disease recurrence.

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 cytochrome P450 (CYP450) enzyme system, which has been identified as a major metabolic pathway for many drugs and a source of interindividual variability in patient response. In particular, TAM is metabolised to its active metabolites *N*-desmethyl TAM and 4-hydroxytamoxifen by a number of CYP450 enzymes, including CYP2D6, CYP3A4, CYP2C9, CYP2C19, and CYP2B6. *N*-desmethyl TAM is further metabolised to endoxifen by CYP2D6. Endoxifen, which is also formed via the action of CYP2D6 is 30- to 100-fold more potent than TAM in suppressing oestrogen-dependent cell proliferation, and is considered an entity responsible for significant pharmacologic effects of TAM.

Wide variability in the response of individuals to drugs at the same doses may occur as a result of interindividual differences which may be inherited (pharmacogenetics). Genes are instructions that produce enzymes. The CYP2D6 enzyme is highly polymorphic: there are more than 60 different alleles of the *CYP2D6* gene which may be deficient or overactive in enzyme activity. It is the alleles that determine an individual's genotype and there is believed to be an association between genotype and the expected drug effects (i.e. the phenotype). For patients with normal enzyme activity [extensive metabolisers (EMs)], usual doses of a drug should result in expected drug concentrations and normal therapeutic response. Patients with deficient alleles [poor metabolisers (PMs) or intermediate metabolisers (IMs)] are likely to have lower exposure to endoxifen and may have compromised clinical effects, whereas patients with multiple alleles [ultra-rapid metabolisers (UMs)] will have increased metabolism.

CYP2D6 activity may be affected not only by an individual's genotype but also by co-administration of drugs that inhibit the metabolic activity of CYP2D6. For example, patients treated with TAM are commonly also prescribed selective serotonin reuptake inhibitors to treat adverse events (AEs) such as hot flushes, but it has been reported that fluoxetine or paroxetine effectively changes the phenotype from EM to PM in some individuals. Co-administration of such substances therefore needs to be taken into consideration.

Objectives

Clinical validity

In patients treated with TAM:

- Do women with breast cancer, identified as EMs for *CYP2D6*, have similar or different clinical outcomes to those identified as PMs, IMs or UMs?
- Is there a relationship between *CYP2D6* status and endoxifen concentrations?
- Are endoxifen concentrations related to clinical outcomes?

Clinical utility

- Do women with breast cancer who are identified as EMs for *CYP2D6* have similar or different clinical outcomes with TAM compared with aromatase inhibitors?

Cost-effectiveness

- What is the relative cost-effectiveness of *CYP2D6* testing as a management option for women with breast cancer?

Methods

Two systematic reviews related to genotyping for *CYP2D6* in the management of women with breast cancer were conducted. The first reviewed the clinical effectiveness, while the second considered economic evaluations related to *CYP2D6* testing.

Several search strategies of bibliographic databases were undertaken of various databases including MEDLINE, EMBASE, The Cochrane Library (Cochrane Database of Systematic Reviews and Cochrane Controlled Trials Register), Web of Science (for the Science Citation Index and Conference Proceedings Citation Index) and the Centre for Reviews and Dissemination databases (Database of Abstracts of Reviews of Effects, NHS Economic Evaluation Database, Health Technology Assessment), the Human Genome Epidemiology Network Published Literature database, Proceedings of the American Society of Clinical Oncology, the San Antonio Breast Cancer Symposium and the European Society for Medical Oncology. Current research was identified from database citations through searching the National Research Register, the Current Controlled Trials register, the Medical Research Council Clinical Trials Register and the US National Institutes of Health website (ClinicalTrials.gov). Relevant reviews were hand searched in order to identify any further studies. Searches were completed by 21 July 2009. However, further studies that became known to the authors via relevant conferences or e-mail alerts from an automatically updated search of the Scopus database were also included as the review progressed, up to, and including, 17 March 2010.

Data were extracted into structured tables and narratively discussed in the relevant sections of the report. In the absence of clinical utility studies and owing to heterogeneity of the alleles genotyped, phenotypes derived, patients included and outcomes measured, meta-analyses of the clinical validity data could not be performed; exploratory analysis of clinical sensitivity and specificity was therefore conducted to supplement the narrative. Data extracted from the clinical and economic reviews were intended to inform the future development of an economic model.

Inclusion criteria

For the clinical review, any study design except single-case studies was included. The patient population was women with ER+ breast cancer treated with TAM and genotyped for *CYP2D6*. Relevant outcome measures included efficacy end points, AEs and measures of endoxifen concentrations. For the economics literature review, economic evaluations that considered both the costs and benefits of *CYP2D6* genotyping and strategies comparing aromatase inhibitors with TAM were included.

Results

Clinical evaluation

Number and quality of studies

The literature search yielded 1186 citations, of which 39 were included in the review. These citations reported on 34 separate studies, but it was apparent that many of the studies reported on the same cohort of patients although with a few subtle differences, such as using only a specific subgroup of patients, considering different genotypes, taking into account concomitant medication that inhibits CYP2D6 or analysing different outcomes. Thus, in total, 25 cohorts were included in the review.

While the majority of the studies included in these cohorts were published as full papers in peer-reviewed journals, six cohorts were reported only as findings in conference proceedings. The majority of cohorts ($n = 18$) were explicit about both the source population from which the study population was derived and the definition of the study population itself. While 5 out of 12 cohorts with missing genotype data failed to state why there were missing data, all but four of the cohorts (which were published only as abstracts) presented the number of patients contributing to each analysis.

Cohort characteristics

The size of the cohorts varied, with the smallest containing 12 subjects and the largest containing 2880 (which also included patients from three published studies). However, the majority ($n = 19$) of cohorts included between 60 and 300 patients. The seven cohorts that measured endoxifen plasma concentrations were conducted prospectively, with all other studies being analysed retrospectively, using archived samples.

Cohorts included patients from the USA and/or Europe ($n = 18$) or the Asian countries of China, Japan and South Korea ($n = 6$) or from all continents ($n = 1$). In all but four studies, the TAM dose was either stated to be 20 mg/day or believed to be this in the absence of these data being provided. The majority of included patients were postmenopausal with early ER+ breast cancer. Adequate data on adjuvant chemotherapy and CYP2D6 inhibitor use were often missing (in 14 and 13 cohorts, respectively). There was wide variety in a number of other patient characteristics, such as tumour size and nodal status, across the studies.

Fifteen cohorts measured efficacy, six cohorts reported on AEs and seven cohorts measured endoxifen concentrations in relation to CYP2D6 status.

Derivation and classification of phenotypes

An important finding from our review was that there is no consensus about how *CYP2D6* phenotypes should be derived from their genotypes and how they should thus be compared, which has made the conduct of this review particularly problematic. Thus, for the purpose of this review, the following 'standardised comparisons' were used to analyse the efficacy data:

- PM versus EM
- IM versus EM
- PM + IM versus EM
- PM versus EM + IM
- Asian patients genotyped **10* allele (i.e. a common allele found in these populations)
- other.

It should be noted that, for the purposes of these comparisons, UMs are likely to be classified as EMs. This is because not all genotyping methods are able to detect UMs, and where cohorts have used methods that did, UMs appear to be classified with EMs.

Differences in cohort characteristics by genotype or phenotype

As well as differences in cohort characteristics, such as tumour size, across studies, it was evident that there were also differences within individual studies by genotype or phenotype. While eight cohorts provided these data in their publications, five of these and three others adjusted for such variables in their analyses.

Efficacy by genotype or phenotype

Not all clinical end points measured by the cohorts were clearly defined. Where end points were defined, it was apparent that different definitions were commonly used, for example DFS. Crucially, not all cohorts genotyped for the same alleles. Thus, comparisons across studies should be treated with a degree of caution.

Poor metaboliser versus extensive metaboliser

From two cohorts, no evidence of a difference in overall survival (OS) between PMs and EMs was reported. However, there was evidence of improved outcomes in terms of relapse/recurrence (disease-free survival, recurrence-free survival or time to recurrence) in the three cohorts that compared these outcomes.

Intermediate metaboliser versus extensive metaboliser

There was no evidence of a difference in OS or relapse/recurrence between IMs and EMs from the only cohort that compared outcomes for these two phenotypes.

Poor metaboliser plus intermediate metaboliser versus extensive metaboliser

In the four cohorts that explored OS between these groups of patients, there was no evidence of a difference between PMs + IMs and EMs. However, five out of eight cohorts reported significantly improved outcomes for relapse/recurrence in EMs. Interestingly, in one of these cohorts, reported only as an abstract, the significant differences were found only when using the AmpliChip® (Roche Molecular Systems) to genotype for an extensive number of alleles and not when four common alleles were tested for.

Poor metaboliser versus extensive metaboliser plus intermediate metaboliser

There was no evidence of a difference in OS or of relapse/recurrence between PMs and EMs + IMs from any of the three cohorts that compared these outcomes in these groups of patients.

Asian patients genotyped for the **10* allele

No cohorts reported convincing evidence of differences by genotype for OS (one cohort), breast cancer mortality (two cohorts) or relapse/recurrence (four cohorts).

Other

Summarising the data from the three cohorts that reported outcomes by phenotypes that do not fit the 'standard comparisons' explored above is problematic owing to the different genotype/phenotype/functional classifications used. However, in each of the cohorts there was some suggestive evidence that EMs have better relapse/recurrence outcomes than patients with other phenotypes.

Adverse events by genotype or phenotype

Three cohorts reported that EMs and IMs were more likely than PMs to experience hot flushes. One cohort also suggested that EMs were more likely to develop severe or very severe hot flushes, and also reported that, of those patients who discontinued treatment because of TAM side effects, just under half did so as a result of hot flushes. None of these patients was found to be a PM. In fact, this cohort reported that EMs were at greatest risk of discontinuing treatment as a result of TAM side effects.

Endoxifen concentrations by genotype or phenotype

Seven cohorts examined endoxifen concentrations in relation to *CYP2D6*; five included patients from the USA or Europe and two included patients from Asia. All seven cohorts reported lower endoxifen concentrations in PMs or those with the **10/*10* genotypes than in those with the *wt/wt* genotype (EM); pronounced decreases in mean endoxifen plasma concentrations were also evident in patients taking potent CYP2D6 inhibitors in two of these cohorts. Two cohorts of Caucasian patients reported conflicting findings with regard to concentrations for IMs, one reporting these to be closer to EMs and the other reporting them to be closer to PMs. Finally, one of the cohorts that also included patients taking an aromatase inhibitor [anastrozole (ANA)] reported that ANA concentrations were not affected by the combination with TAM but endoxifen levels were lower. Furthermore, the differences for endoxifen were no longer significant after excluding PMs.

Exploratory analysis

Because of the lack of convincing data for clinical validity, comparing EMs with other genotypes, an exploratory analysis for sensitivity and specificity was undertaken based on the limited number of studies ($n = 9$) that presented these data. Data suggested that the sensitivity of testing simply for the **4* allele in the adjuvant setting was 15% for OS and between 21% and 37% for relapse/recurrence. Specificity was calculated to be between 15% and 73% for OS and between 52% and 86% for relapse/recurrence. Utilising data from the only cohort to test simply for **10* suggested a sensitivity of 50% and specificity of 95% for recurrence/relapse. When a more comprehensive genotyping strategy was used, a sensitivity of 18% and specificity of 83% were calculated for OS, and, from two cohorts, sensitivity of between 18% and 30% and specificity between 86% and 88% for relapse/recurrence. It should be noted, however, that the exact same alleles were not genotyped in each of these two cohorts.

Economic evaluation

A total of 63 studies were identified from the literature search for evidence relating to the costs and benefits of *CYP2D6* genotyping for the management of women with breast cancer, but none of these papers met the inclusion criteria of being an economic evaluation comparing TAM with any aromatase inhibitors and genotyped for *CYP2D6*. However, two studies identified from the search have been discussed to help inform the development of future economic evaluations.

The lack of convincing data for clinical effectiveness, alongside other important parameter uncertainties, precluded the development of a de novo economic model, although a decision tree and a Markov model structure have been proposed. Crucially, the key points that do not allow us to populate the model are related to the undefined number of alleles to be tested, which alleles to test for, the lack of consensus about which test should be used, the lack of consensus about how to classify phenotypes and the heterogeneity around the results from the evidence found in the clinical review.

Discussion

From a number of individual cohorts, there is some suggestive evidence that genotyping for *CY2D6* may have a role to play in the management of women with ER+ breast cancer treated with TAM. Given six cohorts suggest EMs appear to have better outcomes than either PMs or PMs + IMs in terms of relapse/recurrence, this could translate to EMs being suitable candidates for TAM and PMs (and possibly IMs) being offered aromatase inhibitors instead, assuming the differences in relapse/recurrence outcomes between the two phenotypes are similar in magnitude to the differences found in studies comparing aromatase inhibitors with TAM. However, the suggestive evidence is taken from cohorts which, with two exceptions, are relatively small in number (≤ 500 patients). In addition, three cohorts report contradictory findings (albeit not statistically significant). Thus, the evidence must be treated with caution.

Much of the uncertainty in the clinical evidence is derived from the heterogeneity across the cohorts and around confounding prognostic factors within genotype groups. There are also differences in outcome definitions, alleles tested and the ways in which phenotypes are derived, making comparisons problematic. Additional uncertainties also exist around the role that CYP2D6 enzyme plays in the metabolism of TAM and, in particular, the relationship between endoxifen levels and clinical outcomes; our review failed to identify any studies that addressed this association.

Thus, given the lack of convincing evidence for clinical validity, our review did not identify any clinical utility studies or any full economic evaluations relevant to the UK. Given these deficiencies in the evidence base, we encountered a number of problems in attempting to develop and populate an economic model to address the cost-effectiveness of *CYP2D6* testing. Instead, we have begun the process of identifying the important parameters for which additional data will be needed to populate a model that includes the identification of the alleles to be tested, the available techniques, the sensitivity and specificity of these tests, the true costs of the tests, the provision of care that follows once women have been genotyped and the use of concomitant medication that can change the metabolism of TAM.

It is important to emphasise that the actual cost of pharmacogenetic testing is not known. However, test costs would form only a very small proportion of the overall costs of implementing pharmacogenetic testing into patient care pathways.

Conclusions

It has not been possible for this review to ascertain whether pharmacogenetic testing for *CYP2D6* is clinically effective or cost-effective. Key issues include the fact that it is not clear which alleles should be tested for and how phenotypes should then be derived. Assuming we are able to resolve these issues, there remain the uncertainties of how such testing would be implemented, in and impact on, the future pathways of care for these women.

Future studies will need to determine, as a minimum, the alleles that appear to be related to clinical outcomes and therefore need to be tested for. The link between a genotype and the patient response and ultimate clinical outcomes then needs to be determined in clinical utility studies. The next uncertainty relates to how the pharmacogenetic testing should be carried out. Currently, there is one approved commercially available testing system and a number of bespoke tests being used, but it is not apparent what type of test would be relevant for a UK population. The final issues relate to the lack of evidence of the effectiveness of testing and mechanisms for integrating

such testing into the care pathway for women with breast cancer and whether premenopausal and/or postmenopausal women should be targeted, what would be the likely uptake of pharmacogenetic testing and whether this would be mainly driven by clinicians or by patients.

The remit of this review was narrow and specifically examined the role of CYP2D6. Recent data suggest that the metabolism of TAM is complex and may be related to the effects of more than one genotype. It may be necessary, therefore, for future research to examine other metabolic pathways. In the meantime, further examination of the link between endoxifen levels and clinical outcomes could be of value and could be a mechanism that is easily integrated into existing care pathways.

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Chapter 1

Introduction to CYP2D6 and *CYP2D6* testing

Pharmacogenetic testing and the use of testing in clinical practice is a relatively new, evolving and complex topic. This short summary provides an introduction to the basic concepts that need to be considered in relation to cytochrome P450 2D6 (CYP2D6) and *CYP2D6* testing.

Enzymes, genes and pharmacogenetics

Differences in the response of individuals to the same drug at the same dose may occur as a result of interindividual differences in enzymes (e.g. CYP2D6) responsible for metabolising the drug. These differences may be inherited and occur as a result of differences in the genes (e.g. *CYP2D6*) that encode the enzyme.

In humans, each gene is composed of two alleles, one inherited from each parent, and a person may have two copies of the same allele (homozygous) or one copy of two different alleles (heterozygous). Alleles that differ from the normal or common form are known as polymorphisms [variant (*vt*)], while a normal allele is referred to as wild type (*wt*). It is from these differences that an individual's genotype is derived, for example the homozygous *wt* (i.e. *wt*/*wt*) genotype.

A phenotype is the observable physical trait of an organism, which, in pharmacogenetics, relates to an individual's reaction to a drug, usually as a result of the way in which the drug is metabolised. The phenotype is largely determined by the overall genetic make-up of a person, although it may also be influenced by environmental factors (e.g. diet and smoking).

The cytochrome P450 (CYP450) enzyme system, to which CYP2D6 belongs, has been identified as a major metabolic pathway for many drugs and a source of interindividual variability in patient response. It is believed to play a prominent role in the way in which tamoxifen (TAM) is metabolised and thus may explain differences in responses in individual patients to the same dose as it is known that TAM is metabolised to its active metabolites (which are thought to affect patient response, rather than TAM itself) by a number of CYP450 enzymes (including CYP2D6).

Based on studies that have examined the urinary metabolic ratios of drugs such as debrisoquine and/or dextromethorphan to their metabolites (4-hydroxydebrisoquine and dextrorphan, respectively), an association between *CYP2D6* genotypes (genetic make-up) and phenotypes (response to treatment) is believed to exist. It is thus also believed that patients experiencing a normal response at a normal dose of TAM would be *CYP2D6* extensive metabolisers (EMs). These individuals are thought to be homozygous for the *wt* allele. Patients experiencing reduced clinical effects owing to deficient alleles are referred to as poor metabolisers (PMs) and are thought to be homozygous (and possibly heterozygous) for the *vt* allele.

However, there are a number of different *vt* alleles, some which result in decreased enzyme activity and others that result in a complete lack of enzyme activity (i.e. the differing extent to which the drug is metabolised). PMs must possess at least one of these complete lack of function alleles (e.g. **4*; see *Table 1*).

Patients are sometimes also considered to be intermediate metabolisers (IMs) if clinical effects lie somewhere between EMs and PMs. Generally, IMs are thought to possess at least one decreased

TABLE 1 Common *CYP2D6* alleles and associate enzymatic function

CYP2D6 variant	Predicted enzymatic function via enzymes encoded by the gene
wt *alleles*	
**1, *2, *35*	Normal (associated with EMs)
vt *alleles*	
**3, *4, *5, *6, *9*	Loss of function, i.e. a complete lack of enzyme activity (associated with PMs)
**10, *17, *41*	Decreased activity (associated with IMs)
Multiple alleles	
e.g. **1×N, *2×N*	Increased activity (usually associated with UMs, although this is not always the case)

IM, intermediate metaboliser; UM, ultrarapid metaboliser; *N*, number of copies of the allele, e.g. two copies.
There is not universal agreement that **2* is a *wt* allele; most studies report differences in the metabolic ratio between **1* and **2* and, therefore, classify **2* as a *vt* allele. Furthermore, there is not universal agreement whether there should be a distinction among IM and EM or PM status, or between UM and EM status.

activity allele (e.g. **10*). Patients are also sometimes considered to be ultrarapid metabolisers (UMs) when there are multiple copies of an allele (e.g. **2×2*, **2×3*, etc.). However, multiple copies of an allele do not necessarily result in increased activity. Furthermore, for *CYP2D6* there is no uniformly agreed way in which to relate genotype to phenotype. While it is acknowledged by all that a patient with a *wt/wt* genotype would be an EM and a patient with the **4/*4* genotype would be a PM, some would also classify patients heterozygous for these alleles differently, for example a patient with the *wt/*4* genotype could be considered an EM, IM or PM.

Genotyping for CYP2D6

There is growing anticipation that genotyping for *CYP2D6* may be used to assist in treatment decision-making. A number of these tests have been developed and are described in the literature, and have been used for a wide range of drugs and diseases, not just TAM and breast cancer. However, not all tests will be the same.

Table 2 presents examples of three possible *CYP2D6* tests that could be used. As can be seen, in test A, patients are simply tested for **4*. Those who are found not to possess **4* are considered to be *wt*. Even with this simple test, it is possible to classify a patient with the *wt/*4* genotype in three different ways: EM, IM or PM. As the number of alleles tested for increases (test B), the chances of detecting IMs and/or PMs are increased and the classification is complicated somewhat by the inclusion of the decreased activity allele (**10*) in test C.

These examples can also be used to show that the construction of phenotypes can change the way in which results are interpreted. Thus, if we had 30 patients and found from test A that 15 had the *wt/*4* genotype and that 10 of these patients had a side effect from taking TAM that was not detected in the other 20 patients then, depending on which classification we used, we would describe these patients as being IM, PM or EM. Consequently, we would assume from this sample of patients that there was an association between the phenotype and the side effects.

In addition, these examples also show that as a larger number of alleles are tested for, the chances of detecting IMs and PMs are increased. For example, a patient with the **3/*5* genotype identified by test B and labelled a PM would not have been detected as a PM by test A, which did not test for these two alleles, and so he or she would have been classified as *wt/wt*, i.e. EM. Test C may also be unable to identify this patient as a PM, not because of the number of alleles tested but

TABLE 2 Example of the different ways in which patients may be phenotyped for *CYP2D6* according to the alleles tested

		Possible genotypes and phenotypes			
			Classification		
Test	Alleles tested	Genotypes	1	2	3
A	**4*	*wt/wt*	EM	EM	EM
		*wt/*4*	IM	PM	EM
		**4/*4*	PM	PM	PM
B	**3, *4, *5*	*wt/wt*	EM	EM	EM
		*wt/*3*	IM	PM	EM
		*wt/*4*	IM	PM	EM
		*wt/*5*	IM	PM	EM
		**3/*3*	PM	PM	PM
		**3/*4*	PM	PM	PM
		**3/*5*	PM	PM	PM
		**4/*4*	PM	PM	PM
		**4/*5*	PM	PM	PM
		**5/*5*	PM	PM	PM
C	**3, *4, *10*	*wt/wt*	EM	EM	EM
		*wt/*3*	IM	PM	EM
		*wt/*4*	IM	PM	EM
		*wt/*10*	IM	IM	EM
		**3/*3*	PM	PM	PM
		**3/*4*	PM	PM	PM
		**3/*10*	IM	PM	IM
		**4/*4*	PM	PM	PM
		**4/*10*	IM	PM	IM
		**10/*10*	IM	IM	IM

because of the types of alleles tested, here this patient being identified as **3/wt*. Thus, the types of alleles tested for are just as crucial as the number tested.

To date, the majority of these tests are designed bespoke, 'in house', for specific research projects, often using commercially available technologies such as TaqMan® (Roche Molecular Systems). The only commercially available complete test that is available and used in clinical practice, albeit rarely, is the AmpliChip® (Roche Molecular Systems), which tests for 33 different alleles.

Chapter 2

Background

Description of health problem

Incidence/prevalence and health impact

Breast cancer is the most common cancer affecting women in the UK. In England and Wales, in 2007, around 45,000 new cases of breast cancer were diagnosed[1] and there were nearly 11,000 deaths due to breast cancer.[2] Breast cancer incidence rates increase with age; around 80% of breast cancers occur in women aged > 50 years, and women have a one in nine lifetime risk of developing breast cancer.[3] Breast cancer prevalence is around 172,000 women in the UK according to the most recently published data.[4] This relatively high prevalence rate has been attributed to high incidence rates combined with 5-year survival rates of > 75%.[5]

Aetiology

Breast cancer is the uncontrolled, abnormal growth of malignant breast tissue affecting predominantly women. The strongest risk factor for breast cancer (after gender) is age – the older the woman, the higher her risk – but other genetic and hormonal risk factors have also been identified in the aetiology of breast cancer.[5,6]

Carriers of the breast cancer 1 (*BRCA1*) or 2 (*BRCA2*) gene mutations[7,8] and women with a family history of breast cancer[9] both have an increased risk of developing breast cancer. Higher concentrations of some endogenous hormones appear to increase breast cancer risk.[10] Risk factors associated with endogenous oestrogen – including early age at menarche, late natural menopause, later age at first full-term pregnancy and never breastfeeding – are all associated with an increased risk of breast cancer,[11] while childbearing and a higher number of full-term pregnancies increase the protection.[11] Risk factors associated with the use of exogenous hormones, such as oral contraception, oestrogen replacement therapy and combined anti-oestrogen therapy, increase the risk of breast cancer, as do other factors such as breast density (a risk factor independent of endogenous hormones), a body mass index of > 25 kg/m^2 in postmenopausal women, moderate to heavy alcohol intake and a sedentary lifestyle.[11] Patients with a history of breast cancer[12] and radiation exposure[13] are also at increased risk.

Pathology, clinical staging and diagnosis

Breast cancer is classified into clinical stages according to tumour size, spread of cancer to lymph nodes and distant metastases. A number of different classification systems exist, including the tumour/nodes/metastasis (TNM) staging system developed and maintained by the American Joint Committee on Cancer (AJCC)[14] and the Union Internationale Contre le Cancer (UICC).[15] In this system, 'T' refers to the size of the tumour and its spread, 'N' to the number of lymph nodes involved and 'M' to the presence of metastases (*Table 3*). The TNM system can be categorised further into disease stages (*Table 4*).

The stage of disease is an indication of prognosis. Data reported by Cancer Research UK in 2004 and cited by Ward *et al.*[6] suggested that the 5-year survival rate was around 90% for those with stage I disease, dropping to 75% for stage II, 42% for stage III and 14% for stage IV.

TABLE 3 Tumour/nodes/metastasis staging classification system for breast cancer

Tumour stage (T)	
Tx	Cannot be assessed
Tis	Carcinoma in situ
T0	No evidence of primary tumour
T1	Tumour < 2 cm in greatest dimension
T2	Tumour 2–5 cm
T3	Tumour > 5 cm
T4	Tumour of any size with direct extension to skin or chest wall
Lymph node stage (N)	
Nx	Cannot be assessed
N0	No nodal metastases
N1	Metastases to ipsilateral nodes
N2	Metastases to ipsilateral nodes that are fixed to one another or other structures
N3	Metastasis to ipsilateral supraclavicular or infraclavicular nodes
Metastasis stage (M)	
Mx	Cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Sources: AJCC[14] and UICC.[15]

Alternatively, many clinicians in the UK use prognostic tools, such as the Nottingham Prognostic Index (NPI)[16] or the web-based tool 'Adjuvant! Online'.[17] The NPI takes into account three of the major prognostic factors, namely tumour size, lymph nodal status and grade according to the following formula:

> NPI = (0.2 × tumour diameter in cm) + lymph node stage ('1' if no nodes are affected, '2' if up to three glands are affected, '3' if more than three nodes are affected) + tumour grade (scored as '1', '2' or '3')

The formula gives scores, which fall into the following categories:

- excellent-prognosis group ≤ 2.4
- good-prognosis group > 2.4 and ≤ 3.4
- moderate-prognosis group > 3.4 and ≤ 5.4
- poor-prognosis group > 5.4.

The 10-year predictive survival rates are as follows:[18]

- excellent-prognosis group = 96%
- good-prognosis group = 93%
- moderate-prognosis group = 53%
- poor-prognosis group = 39%.

'Adjuvant! Online' also incorporates tumour oestrogen receptor (ER) status and patient comorbidity, and provides an estimate of the potential benefit of treatment, derived from clinical trial data. This programme also has the feature of a modifiable prognostic calculator to factor in

TABLE 4 Tumour/nodes/metastasis disease staging and AJCC description of disease

Stage	Description of disease	T	N	M
0	Ductal carcinoma in situ – cancer cells are located within a duct and have not invaded the surrounding fatty breast tissue	Tis	N0	M0
I	The tumour is ≤ 2 cm in diameter and has not spread to lymph nodes or distant sites	T1	N0	M0
IIA	No tumour is found in the breast but it is in one to three axillary lymph nodes, or the tumour is < 2 cm and has spread to one to three axillary lymph nodes or has been found by sentinel node biopsy as microscopic disease in internal mammary nodes but not on imaging studies or by clinical examination, or the tumour is > 2 cm in diameter and < 5 cm but has not spread to axillary nodes	T0 T1 T2	N1 N1 N0	M0 M0 M0
IIB	The tumour is > 2 cm in diameter and < 5 cm and has spread to one to three axillary lymph nodes or has been found by sentinel node biopsy as microscopic disease in internal mammary nodes, or the tumour is > 5 cm and does not grow into the chest wall and has not spread to lymph nodes	T2 T3	N1 N0	M0 M0
IIIA	The tumour is < 5 cm in diameter and has spread to four to nine axillary lymph nodes or has been found by imaging studies or clinical examination to have spread to internal mammary nodes, or the tumour is > 5 cm and has spread to one to nine axillary nodes or to internal mammary nodes	T0 T1 T2 T3 T3	N2 N2 N2 N1 N2	M0 M0 M0 M0 M0
IIIB	The tumour has grown into the chest wall or skin and may have spread to no lymph nodes or as many as nine axillary nodes	T4 T(any)	N(any) N3	M0 M0
IV	The cancer has spread from the breast to another part of the body (metastasis)	T(any)	N(any)	M(any)

Sources: AJCC[14] and UICC.[15]

other known poor prognostic features, such as lymphovascular invasion and human epidermal growth factor receptor 2 (HER2) expression.

Current service provision

Treatment for breast cancer can be divided into surgical treatment to control the disease locally (within the breast and axillary lymph nodes) and adjuvant treatment after surgical removal of the primary cancer. The aim of adjuvant treatment is to prevent recurrence and may involve radiotherapy, chemotherapy, biological therapy or anti-oestrogen therapy.

Radiotherapy is routinely given to women after breast-conserving surgery. After mastectomy, it is given to those who are considered to be at high risk of breast cancer recurrence. Owing to its side effects, adjuvant chemotherapy is usually given only to women at significant risk of recurrence, or if their cancers are ER negative (ER–). Biological therapy is given to women whose cancers overexpress the HER2 receptor. The majority of women who have been diagnosed with ER positive (ER+) breast cancers receive anti-oestrogen therapy, which typically comprises TAM and/or aromatase inhibitors. Anti-oestrogen therapy is not used for women with ER– breast cancers.

Because aromatase inhibitors are ineffective in women whose ovaries are functional and produce oestrogen,[19] TAM is considered the standard of care for premenopausal women with ER+ breast

cancer. TAM is a selective ER modulator, i.e. it is a compound that competes with oestrogen for binding to the ER.

For postmenopausal women with ER+ early breast cancer, the most recent National Institute for Health and Clinical Excellence (NICE) guidelines[18] state that in the UK 'Current practice is to give low-risk patients TAM for five years'. Risk is based on the NPI, and low-risk patients are those in the excellent- or good-prognosis groups. NICE recommends that women who are considered to be at higher risk of disease recurrence should be offered an aromatase inhibitor [anastrozole (ANA) or letrozole] as their adjuvant treatment.[18] Aromatase inhibitors (exemestane or ANA) are recommended for patients who have already received 2–3 years of adjuvant therapy with TAM but are not considered low risk for disease recurrence, who are intolerant of TAM or for whom TAM is contraindicated. After 5 years of treatment with TAM, aromatase inhibitor treatment (letrozole) is also recommended by NICE for 2–3 years for women with lymph node positive (LN+) ER+ early invasive breast cancer.

The National Institute for Health and Clinical Excellence also recommends the use of TAM and aromatase inhibitors for some women with ER+ advanced breast cancer.[20] TAM is the recommended first-line treatment for premenopausal and perimenopausal women not previously treated with TAM. In postmenopausal women, aromatase inhibitors are recommended for women with no prior history of anti-oestrogen therapy or for those who have been previously treated with TAM.

The NICE guidelines regarding the use of TAM and aromatase inhibitors in early breast cancer are based on randomised controlled trial (RCT) evidence. Two RCTs [ATAC[21] (Arimidex, Tamoxifen, Alone or in Combination) and BIG (Breast International Group) 1-98[22]] report 5 years of aromatase inhibitors to have modestly improved outcomes over 5 years of TAM use in terms of disease-free survival (DFS). Other RCTs also report a switch to an aromatase inhibitor after 2–3 years of TAM to be more efficacious than TAM alone for 5 years [ABCSG-6a,[23] ABSCG-8 (Austrian Breast and Colorectal Cancer Study Group)/ARNO-95 (Arimidex/Nolvadex),[24] IES[25] (Intergroup Exemestane Study), ITA[26] (Italian tamoxifen anastrozole)]. In addition, the MA.17 trial[27] has reported improved outcomes in patients who were given letrozole after 5 years of TAM. All of these findings have also been summarised in three systematic reviews,[28–30] and in an additional earlier review[31] that included three of the switching strategy trials.

As can be seen from *Figure 1*, significant differences between TAM and aromatase inhibitors are not evident in overall survival (OS). However, significantly modest improvements in DFS after 5 years of aromatase inhibitor (ANA or letrozole) or switching to an aromatase inhibitor (exemestane) 2–3 years after TAM treatment have been reported. Disease recurrence has also been reported to be significantly improved by 5 years' treatment with an aromatase inhibitor (ANA or letrozole) and switching to ANA after 2–3 years of TAM. The most recent systematic review[28] pooled findings for mortality and recurrence in meta-analyses. For 5 years of treatment with an aromatase inhibitor or TAM, the absolute difference in breast cancer mortality was 1.1% at 5 years (4.8% for aromatase inhibitor vs 5.9% for TAM; $p = 0.1$) and there was an absolute 2.9% decrease in recurrence (9.6% for aromatase inhibitor vs 12.6% for TAM; $p < 0.001$). The switching strategy resulted in an absolute difference of 0.7% at the same time point, which was also approximately 3 years since divergence from TAM (1.7% for aromatase inhibitor vs 2.4% for TAM since divergence; $p = 0.02$) and an absolute 3.1% decrease in recurrence (5.0% for aromatase inhibitor vs 8.1% for TAM since divergence; $p < 0.001$).

Side effect profiles differ between TAM and aromatase inhibitors. The long-term use of TAM may be associated with vaginal bleeding, endometrial thickening and increased risk of endometrial cancer and thromboembolic events.[30] Aromatase inhibitors have been reported to result in fewer

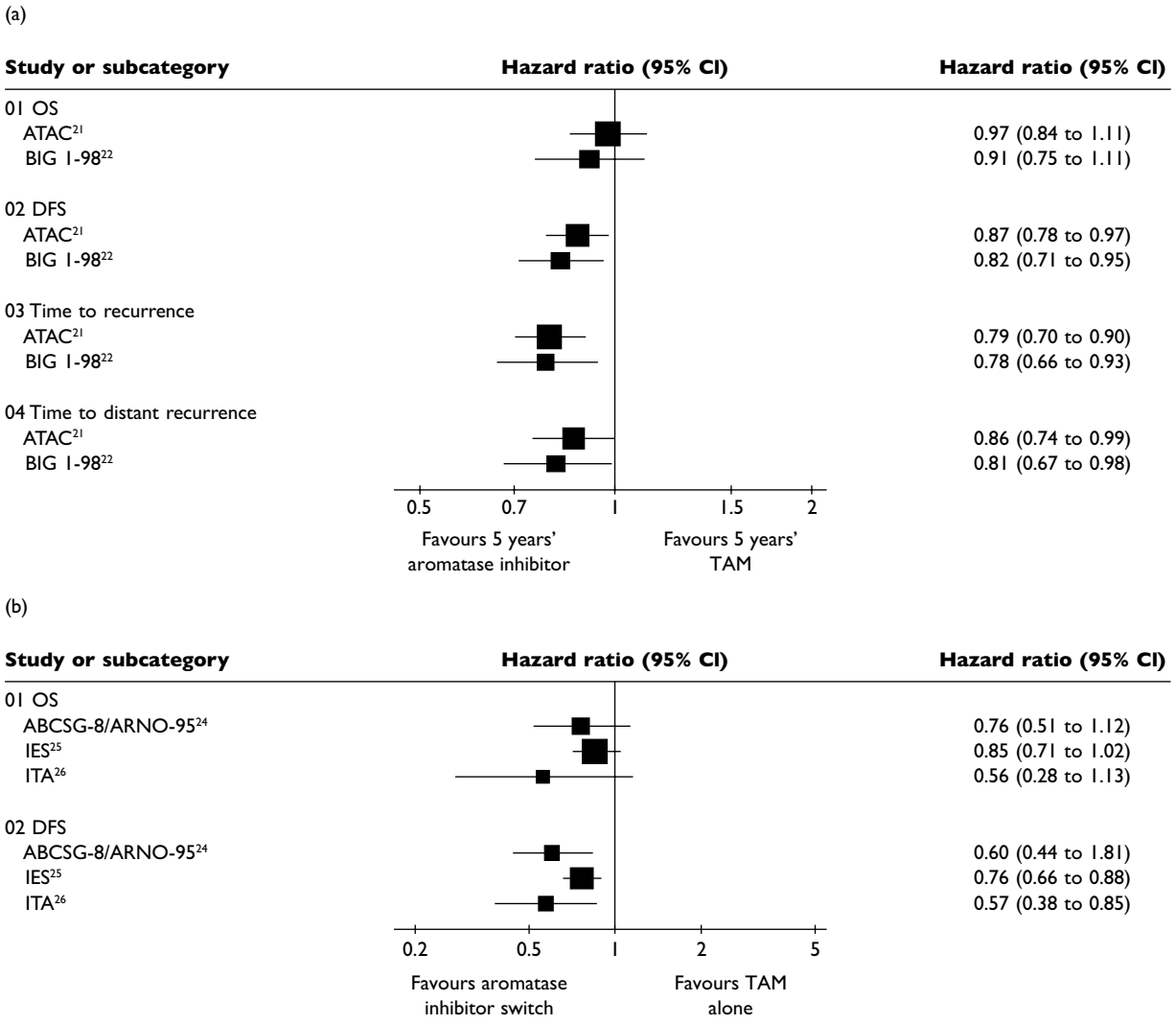

FIGURE 1 Differences in outcomes in patients receiving (a) either an aromatase inhibitor or TAM for 5 years and (b) an aromatase inhibitor after 2–3 years of TAM therapy compared with similar duration of TAM monotherapy. Data taken from the review by Eisen *et al*.[29] CI, confidence interval.

hot flushes but are also associated with increased joint pain and bone fractures, and may also be associated with increased cardiovascular risk.[30] This cardiovascular risk has also been reported in a subsequent meta-analysis,[32] although it was noted that the absolute difference was relatively low, and between 160 and 180 patients had to be treated to produce one event.

Assuming that these proportional benefits over TAM are maintained over 10 years, the cost per quality-adjusted life-year (QALY) gained for 5 years of ANA or letrozole compared with TAM has been reported to be between £10,000 and £12,000.[3,30] For the switch to exemestane or ANA after 2–3 years of TAM compared with TAM for 5 years, the estimated incremental cost per QALY gained was approximately £5000, and unplanned switching to letrozole compared with placebo after 5 years of TAM resulted in an incremental cost per QALY gained that was estimated to be £3000.[3,30]

There are limited data available on the use of adjuvant therapy in breast cancer.[18] However, it has been reported that aromatase inhibitor use has increased at the expense of TAM, with a US study finding an increase from 4.1% in 2000 to 40% in 2003 in postmenopausal women with ER+

breast cancer.[33] This increase has been attributed to the evidence base[28–31] suggesting aromatase inhibitors to be more efficacious.

Tamoxifen metabolism and pharmacogenetics

Wide variability in the response of individuals to drugs of the same dose may occur as a result of interindividual differences that may be inherited (pharmacogenetics). The CYP450 enzyme system has been identified as a major metabolic pathway for many drugs and a source of interindividual variability in patient response.[34] TAM is metabolised to its active metabolites *N*-desmethyl TAM and 4-hydroxytamoxifen by a number of CYP450 enzymes, including CYP2D6, CYP3A4, CYP2C9, CYP2C19 and CYP2B6.[35] *N*-desmethyl TAM is further metabolised to endoxifen by CYP2D6.[36] Endoxifen is 30- to 100-fold more potent than TAM in suppressing oestrogen-dependent cell proliferation, and is considered an entity that is responsible for significant pharmacological effects of TAM.[35]

Genes are made up of alleles that determine an individual's genotype and control the instructions that produce enzymes. The CYP2D6 enzyme is highly polymorphic (i.e. it can exist in many variant forms); there are >70 different alleles of the *CYP2D6* gene. These polymorphisms may be deficient or overactive in enzyme activity.

Based on studies which have examined the urinary metabolic ratios of debrisoquine and/or dextromethorphan to their metabolites, 4-hydroxydebrisoquine and dextrorphan, respectively, there is also believed to be an association between genotype and phenotype (i.e. expected drug effects). Sachse *et al.*[37] reported significant differences in metabolic ratio between carriers of one or two functional alleles. Thus, for patients with normal enzyme activity (commonly referred to as EMs) who are given TAM, usual doses should result in expected drug concentrations and normal therapeutic response. Patients with deficient alleles (commonly recognised as PMs) would be expected to have compromised clinical effects in terms of efficacy and possibly also adverse events (AEs).[35]

This study classified patients as only EMs or PMs, despite identifying the presence of slightly or moderately reduced activity alleles (e.g. **2* and **10*, respectively) and patients with multiple alleles (e.g. **2×2*), who were all classified as EMs. However, other studies have considered individuals with these alleles to be separate to, or subsets of, EMs. Thus, the literature also discusses both IMs (patients with decreased activity resulting from decreased activity alleles) and UMs (patients with increased enzymatic activity resulting from multiple alleles). Patients classified as IMs would be expected to experience effects from a drug somewhere between EMs and PMs, whereas UMs would be expected to have reduced efficacy and/or increased risk of AEs as a result of the faster metabolism of the drug.

CYP2D6 enzyme activity may also be affected by co-administration of drugs that inhibit the metabolic activity of enzyme. In particular, it has been reported that the selective serotonin reuptake inhibitors (SSRIs) fluoxetine and paroxetine effectively alter the EM phenotype to PM in some individuals.[38] Patients treated with TAM are commonly prescribed SSRIs for depression or to alleviate AEs such as hot flushes, and co-administration of such substances therefore needs to be taken into consideration. The most recent NICE guidelines state that paroxetine and fluoxetine should be offered only to breast cancer patients who are not taking TAM.[18]

Prevalence of *CYP450* gene polymorphisms vary across populations. *Table 5* presents a summary of frequencies of *CYP2D6* alleles in various populations, and also describes the predicted enzymatic function arising from genotypes derived from common alleles. Given that the four

most common loss-of-function alleles – **3*, **4*, **5* and **6* – are associated with up to 98% of the PM phenotypes, and given that the prevalence of these differs substantially by ethnicity, it is no surprise to find that there are ethnic differences in metaboliser status. For example, following a review of many studies examining *CYP2D6* allelic variation and frequency in various populations published in 2002,[39] it is commonly cited that around 7% of Caucasians are PMs compared with 1% of Asians. However, fewer Asians metabolise CYP2D6 substrates normally, and so there are fewer EMs in the Asian population. This is largely because of high frequencies of the **10* allele, which is thought to result in a higher prevalence of IMs in this population. It has been estimated that up to 51% of Asian populations may consist of IMs.[40] UMs are typically as uncommon as PMs, being around 4–5% in American Caucasians and African Americans, although it has been estimated that they may account for 29% of Ethiopians.[40]

Tests currently available for genotyping for *CYP2D6*

There is evidence suggesting that the AmpliChip is a highly accurate test (analytic validity),[42] and this test is the first pharmacogenetic test to be granted market approval in the USA and European Union, based on evidence demonstrating that the test had high analytical (but not clinical)

TABLE 5 Allele frequencies of selected *CYP2D6* variants in selected populations

CYP2D6 variant	Predicted enzymatic function	Associated phenotype(s)	Caucasian (%)	African American (%)	Asian (%)
**1*	Normal	EM	30–40	28–50	20–40
**2*	Normal	EM	20–35	10–80	9–20
**3*	Loss of function	PM, where the other variant is also loss of function, or IM[a]	1–4	<1	≤1
**4*	Loss of function	PM, where the other variant is also loss of function, or IM[a]	12–23	2–9	≤3
**5*	Loss of function	PM, where the other variant is also loss of function, or IM[a]	<2–7	≤7	4–6
**6*	Loss of function	PM, where the other variant is also loss of function, or IM[a]	≤1	<1	–
**9*	Decreased activity	IM	≤3	<1	–
**10*	Decreased activity	IM	≤8	3–8	40–70
**17*	Decreased activity	IM	<1	10–30	<1
**35*	Normal	EM	4–6	–	–
**41*	Decreased activity	IM	8–20	–	–
**1×N*	Increased activity, where *N*≥2	UM	≤1	<5	<1
**2×N*	Increased activity, where *N*=2, 3, 4, 5 or 13	UM	<2	<2	0–1
**4×N*	Loss of function, where *N*≥2	PM, where the other variant is also loss of function, or IM[a]	<1	2–3	–
**10×N*	Loss of function, where *N*≥2	PM, where the other variant is also loss of function, or IM[a]	–	–	–
**17×2*	Normal	EM	–	–	–
**35×2*	Increased activity	UM	–	–	–
**41×2*	Normal	EM	–	–	–

N, number of copies of the allele, e.g. two copies.

a It is important to note that there is not universal agreement about the phenotype derived from genotypes containing these alleles where the other allele is not a loss-of-function allele; thus, for example, studies have classified a patient with the **1/*4* phenotype to be a PM, IM or EM.

Source: adaptation of data reported by Bradford[39] and Ramon *et al.*[41]

validity,[43] increasing the possibilities that this may be one of the first licensed pharmacogenetic tests to be routinely used in clinical practice. Indeed, this is the only known commercially available *CYP2D6* test currently available, although it is known that other laboratories are producing their own tests 'in house', which focus on fewer alleles than in the AmpliChip. Such tests are often developed using commercially available technologies, such as TaqMan, mainly for research rather than clinical application purposes. The AmpliChip has been cited as costing between US$600 and US$1300 in the USA in June 2007[44] and £300 in the UK in April 2008.[45] These costs include administration fees and platform costs, and the actual cost of the AmpliChip is dependent on the laboratory purchasing the test. Eight laboratories were known to be using the AmpliChip in the USA as of June 2007, and a recent survey (March 2010) of breast oncologists in the UK found that 97% of the 69 clinicians who responded did not offer *CYP2D6* testing before commencing TAM treatment. Reasons cited were a lack of test availability (52%), insufficient evidence to recommend use (29%), cost (8%) or a combination of these reasons.

Rationale for the current review

There is growing anticipation among scientists, health-care providers and the general public that tests will soon be widely available to identify genetic differences and direct the prescribing of therapeutic agents and thus improve our ability to personalise therapies and subsequently improve clinical outcomes.[46]

Tests that are used for genotyping should have both analytical and clinical validity. Analytical validity relates to the accuracy and reliability of assays and commercial tests to appropriately identify the genotype, whereas clinical validity relates to whether or not the test is an accurate measure of a biomarker that reflects the effect of the specific gene on the development of the disease and/or metabolism of the drug in question, i.e. can relevant outcomes be predicted by genotype? However, pragmatically of greatest importance is whether or not a test has clinical utility, i.e. can the information from analytical and clinical validity be used in clinical practice, to change drugs and/or dose, and have an impact on health outcomes as a result? Finally, tests that are used for genotyping in clinical practice will also need to show they are cost-effective compared with a treatment strategy in which no genotyping is conducted.

Despite a US Food and Drug Administration (FDA) expert advisory panel announcing that the *CYP2D6* gene was considered to be a predictor of TAM efficacy, no consensus on whether testing should be recommended or considered an option has yet been reached.[47] In 2008, a review published by the Blue Cross and Blue Shield Association[47] reported that there was a lack of clinical evidence (clinical validity and clinical utility) to support the routine use of *CYP2D6* genotyping for patients being treated with TAM; this review did not consider cost-effectiveness.

It is important to note that in determining the cost-effectiveness of a pharmacogenetic test, it is not simply the additional cost and benefit of the test itself which need to be considered but also the impact of the test on subsequent choice of therapies and on patient care pathways and associated resource use. For example, it is likely that the number of women who are currently prescribed TAM and aromatase inhibitors would differ should a *CYP2D6* test be offered routinely, and there would thus be implications for future pathways of care.

Thus, the aim of this current review is to consider the evidence for the clinical effectiveness and cost-effectiveness of *CYP2D6* testing in relation to the use of TAM in women with ER+ breast cancer. The objectives of this review are listed in *Box 1*.

BOX 1 Review objectives

Clinical validity

In patients treated with TAM:

- Do women with breast cancer identified as EMs for *CYP2D6* have similar or different clinical outcomes to those identified as PMs, IMs or UMs?
- Is there a relationship between CYP2D6 status and endoxifen concentrations?
- Are endoxifen concentrations related to clinical outcomes?

Clinical utility

- Do women with breast cancer who are identified as EMs for *CYP2D6* have similar or different clinical outcomes with TAM compared with aromatase inhibitors?

Cost-effectiveness

- What is the relative cost-effectiveness of *CYP2D6* testing as a management option for women with breast cancer?

Chapter 3

Assessment of clinical effectiveness

Methods for reviewing effectiveness

Evidence for the clinical effectiveness of genotyping for *CYP2D6* for the management of women with breast cancer was assessed by conducting a systematic review of published research evidence. The review was undertaken following the general principles published in the Centre for Reviews and Dissemination's guidance for undertaking reviews in health care.[48]

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

Identification of studies

The search aimed to identify all studies relating to the genotyping of *CYP2D6* in the management of breast cancer, specifically related to TAM treatment. The following databases were searched on 19 June 2009: MEDLINE, EMBASE, The Cochrane Library (Cochrane Database of Systematic Reviews and Cochrane Controlled Trials Register), Web of Science (for the Science Citation Index and Conference Proceedings Citation Index) and the Centre for Reviews and Dissemination databases (Database of Abstracts of Reviews of Effects, NHS Economic Evaluation Database and Health Technology Assessment). Searches were not restricted by publication type. Because *CYP2D6* genotyping is a relatively new area, and because the earliest study[49] identified in the previous review of pharmacogenetics of TAM treatment was from 2003,[47] searches were limited to the year 2000 and onwards. To assess the link between endoxifen plasma concentrations and clinical outcomes, a further search of MEDLINE was conducted on 21 July 2009, in which the inclusion criteria were extended to include studies considering the link between endoxifen concentrations and clinical outcomes, regardless of whether or not subjects had been genotyped for *CYP2D6*. The search strategies are listed in *Appendix 1*.

There was additional searching of the Human Genome Epidemiology Network Published Literature database, Proceedings of the American Society of Clinical Oncology, the San Antonio Breast Cancer Symposium and the European Society for Medical Oncology. Current research was identified from database citations through searching the National Research Register), the Current Controlled Trials register, the Medical Research Council Clinical Trials Register and the US National Institutes of Health website (ClinicalTrials.gov). Relevant reviews were hand searched in order to identify any further studies. Further studies that became known to the authors via relevant conferences or e-mail alerts from an automatically updated search of the Scopus database were also included as they became available, up to and including 17 March 2010.

Two reviewers (NF and RD) independently screened all titles and abstracts. Full-paper manuscripts of any titles/abstracts that were considered relevant by either reviewer were obtained. The relevance of each study was assessed (NF and RD) according to the inclusion and exclusion criteria listed in *Box 2*. Studies that did not meet the criteria were excluded and their bibliographic details were listed alongside reasons for their exclusion. Any discrepancies were resolved by consensus and, where necessary, a third reviewer was consulted.

BOX 2 Eligibility criteria for the current review

Inclusion criteria

Women with ER+ breast cancer treated with TAM and genotyped for *CYP2D6*

Any study design other than single case reports

One or more of the following relevant clinical outcomes:

- OS, defined as hazard of death from any cause after any follow-up or the time to death from any cause expressed in months
- DFS, however defined
- local and distant recurrence, however defined
- AEs, however defined
- health-related quality of life, however defined
- plasma concentrations of endoxifen

Exclusion criteria

Studies of men with breast cancer

Editorials, opinions and reviews

Data extraction strategy

Data were extracted by one reviewer (NF) using a standardised data extraction form in Microsoft Word 2007 (Microsoft Corporation, Redmond, WA, USA) and checked independently by a second (JH). Disagreements were resolved by discussion.

Quality assessment strategy

As no universally accepted quality assessment criteria exist for assessing studies of pharmacogenetic testing, a tool based on elements of checklists developed to assess the methodological quality of prognostic factor studies[50] and pharmacogenetic studies[51] was used to assess specific issues considered important in terms of the reliability of such studies. Quality was independently assessed by two reviewers (NF and YD) and disagreements were resolved by discussion.

Methods of data synthesis

The results of the data extraction and quality assessment are summarised in structured tables and as a narrative description. Prespecified outcomes were tabulated and discussed within a descriptive synthesis. Additional relevant outcomes [breast cancer mortality and recurrence-free survival (RFS)] were also included.

Meta-analyses were planned in which binary outcomes were to be compared in terms of odds ratios, using either a fixed-effects or random-effects approach, depending on the degree of heterogeneity (to be assessed by visually inspecting the forest plots and by calculating the I^2-statistic,[52] which measures the proportion of variation across studies that is due to genuine differences rather than due to random error). In view of the controversy surrounding possible confounding from population stratification, and in keeping with the approach suggested in *The HuGENet HuGE review handbook*,[53] in which studies differed in terms of the ethnicity of included patients, separate effect estimates were planned for each ethnic group. When studies differed in terms of their study design, sensitivity analyses were planned including only studies of the same study design. However, heterogeneity of the alleles genotyped, phenotypes derived, patients included and outcomes measured (see *Results*, below) precluded any planned meta-analyses.

Given the absence of either clinical utility studies or meta-analyses of the clinical validity data, attempts were made in an exploratory analysis to measure the clinical sensitivity and specificity of testing for particular alleles, as recommended by Flockhart *et al.*[54] in an American College of Medical Genetics statement. Data to calculate sensitivity and specificity were derived from the number of events reported in studies in the text/tables.

Results

Number of studies identified and included

The literature search yielded 1186 citations after duplicates had been removed. Of the titles and abstracts screened at screening stage one, 57 were assessed in detail at screening stage two. At this stage, 27 citations[55–81] (reporting on 23 studies) were excluded (see *Appendix 2*), leaving 30 citations to be included (22 studies[41,73,82–101] reporting on clinical outcomes by CYP2D6 status and eight studies[49,73,89,102–106] reporting on endoxifen plasma concentrations by CYP2D6 status). No studies were found that met the criteria for clinical utility.

Following completion of the search in June 2009, a further nine citations were identified that met the inclusion criteria for the review (*Figure 2*): five studies[82,107–110] reported clinical outcomes by CYP2D6 status, another[111] presented additional data for one of these studies,[109] two[112,113] reported endoxifen plasma concentrations by CYP2D6 status, and one[114] included data on clinical

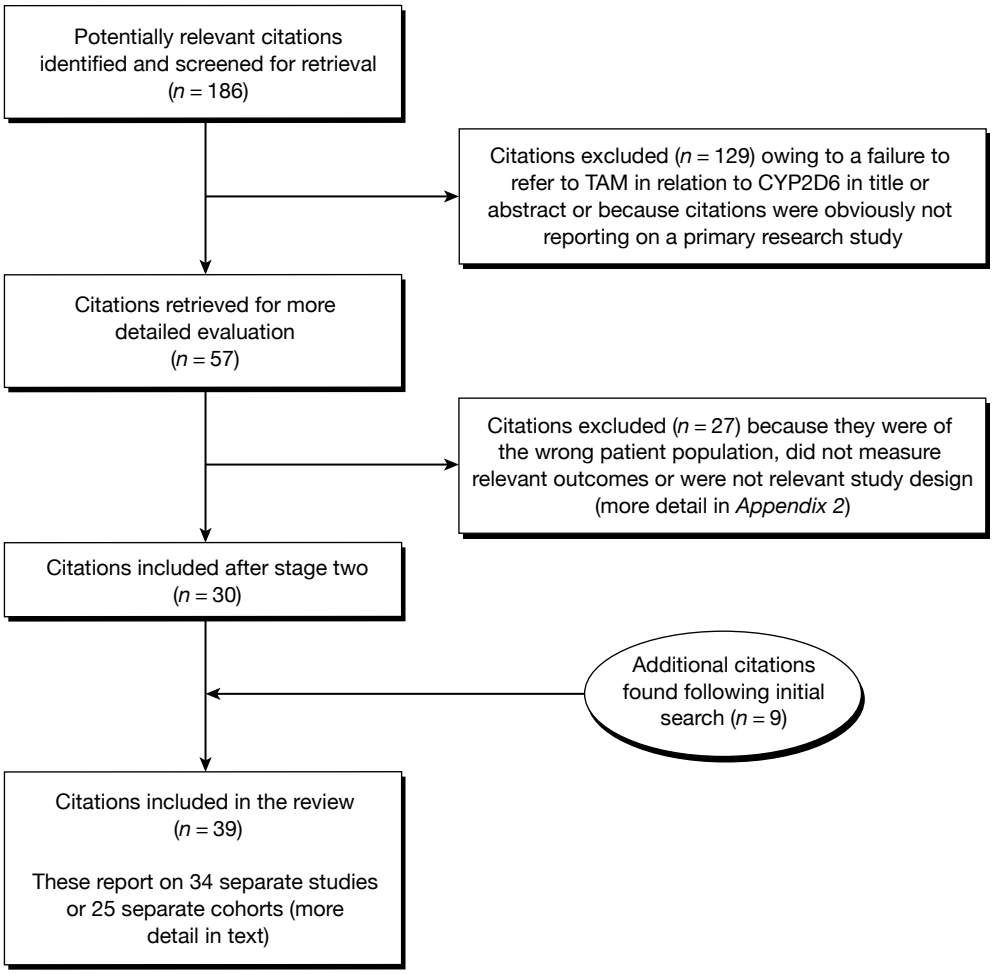

FIGURE 2 Identification of eligible studies.

outcomes (which also included patients from a study[88] previously identified by the literature search) and endoxifen plasma concentrations by CYP2D6 status, in two separate studies.[114]

The separate search for the link between endoxifen concentrations and clinical outcomes yielded 4998 citations after duplicates had been removed. Of these, none met the criteria for inclusion into the review.

Two ongoing studies[69,115] which are of some relevance to clinical utility but which do not meet the inclusion criteria have also since been identified. Both of these studies have been presented as conference posters. Details of these ongoing studies are provided in *Appendix 2*.

It is further apparent that many of the different studies included in the review are in fact reporting on the same cohort of patients but with a few subtle differences, such as using only a specific subgroup of patients, considering different genotypes, taking into account concomitant medication that inhibits CYP2D6 or analysing different alleles and genotype classifications. As these cohorts share the same patients and study characteristics, it is preferable to consider the quantity and quality of research available by cohort rather than individual study or paper. Thus, in total there are 25 cohorts (and where reference is made to the cohorts as a whole, rather than specific studies, the latest fully published study in the table is used to derive the name of the cohort, e.g. the cohort including the studies by Jin *et al.*,[105] Borges *et al.*,[102] Henry *et al.*[87,107] and Rae *et al.*[95] is referred to as the 'Henry *et al.* cohort[87]').

Quality assessment of included studies

Given that there are 25 distinct cohorts, the quality of each cohort as opposed to individual study is summarised here (see also *Appendix 3*). While the majority of the studies of these cohorts were published as full papers in peer-reviewed journals, it is important to note that six[82,86,90,98,109,113] cohorts have reported findings only at conferences.

All but seven[41,49,86,90,93,98,113] of the cohorts were explicit about both the source population from which the study population was derived, and the definition of the study population itself. Six[82,86,90,98,109,113] cohorts had reported their studies only as abstracts, not full papers, and so space was limited to present this information. 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,[51] the majority of the samples in this review are small.

The majority ($n = 12$) of cohorts[41,73,83,87,93,96,97,99–101,113,114] presented the rationale for the alleles tested for, with all but two[49,112] providing rationale for *CYP2D6* per se. All described the test used for genotyping and/or the specific procedure, with TaqMan or AmpliChip being the most commonly used in 12[83,86,87,91–94,96,97,104,108,114] and six[41,82,87,90,109,113] cohorts, respectively. Three cohorts[91,97,104] reported quality control methods and seven cohorts[87,91,96,97,104,114] reported on the Hardy–Weinberg equilibrium (two of these cohorts were reported in the same paper[114]).

In around half ($n = 12$) of the cohorts it was clear there were missing genotype data,[41,82,83,87,96–101,108,112] reasons being provided in seven of these.[82,83,87,97,99,108,112] Only three of the cohorts, all abstracts,[86,90,113] failed to present the number of patients contributing to each analysis.

Characteristics of included cohorts

The cohort characteristics are summarised in *Table 6*, where it is clearly evident that the size of the cohorts varied, with the smallest containing 12 subjects[49] compared with the largest of 2880[82] [the International Tamoxifen Pharmacogenomics Consortium (ITPC) cohort that included

TABLE 6 Cohort characteristics of the included studies

Cohort (and studies); number of patients genotyped for *CYP2D6*	Study design; country of origin; length of patient follow-up	TAM dose; duration	Types of patients and key characteristics	Concomitant CYP2D6 inhibitors/ chemotherapy accounted for?	Outcomes measured
Stearns *et al.* 2003;[49] *n* = 12	Prospective cohort; USA; 4 weeks	20 mg/day; 4 weeks	*Women with breast cancer receiving TAM adjuvant therapy and taking paroxetine for hot flushes* Postmenopausal: not reported ER+: not reported LN+: not reported Tumour size: not reported Metastatic disease: not reported	Women were not permitted any concomitant medications known to inhibit CYP2D6 activity except for paroxetine 10 mg/day	Endoxifen concentrations
Goetz *et al.* cohort:[83] Goetz *et al.* 2004[116] (conference abstract), Goetz *et al.* 2005,[84] *n* = 223 Goetz *et al.* 2007[83] (re-analysis); *n* = 180 Goetz *et al.* 2009[110] (longer-term follow-up); *n* = 210	Retrospective analysis of samples from RCT, TAM-only arm); USA; mean 11.4 (range 5.7–14.1) years and median 14.5 years (longer-term follow-up)	20 mg/day; 5 years	*Women with breast cancer receiving TAM adjuvant therapy (95% Caucasian)* Postmenopausal: 100% ER+: 100% LN+: 36% Tumour ≥ 3 cm: 22% Metastatic disease: 0%	Co-administration of CYP2D6 inhibitors was not accounted for in the initial analysis, hence the re-analysis No concomitant chemotherapy	Efficacy AEs (Goetz *et al.* 2005[84] only)
Henry *et al.* cohort:[87] Jin *et al.* 2005;[105] *n* = 50 Borges *et al.* 2006;[102] *n* = 158 Henry *et al.* 2009;[87] *n* = 276 Henry *et al.* 2009;[107] *n* = 276 Rae *et al.* 2009;[95] *n* = 280	Prospective, observational, open-label, registry study (analysed retrospectively by Henry *et al.* 2009,[87,107] Rae *et al.* 2009[95]); USA; 12 months (4 months in Henry *et al.* 2009[107])	20 mg/day; 5 years (planned)	*Women with breast cancer starting TAM adjuvant therapy, extended in the 2009 analysis to include chemoprevention (91% 'white' in Jin* et al. *2005[105] and Borges* et al. *2006[102])* Postmenopausal: 52% ER+ and/or PgR+: 100% LN+: not reported Tumour size: not reported Metastatic disease: 0%	Co-administration of SSRIs was permitted and accounted for in the analysis No concomitant chemotherapy	AEs (Henry *et al.* 2009,[87] Henry *et al.* 2009[107] and Rae *et al.* 2009[95] only) Endoxifen concentrations (Borges *et al.* 2006[102] and Jin *et al.* 2005[105])
Nowell *et al.* 2005;[92] *n* = 337 (165 TAM and 172 no TAM)	Retrospective study of archived paraffin blocks; USA; median 5.4 years	Not reported	*Women with breast cancer receiving TAM adjuvant therapy and women with breast cancer receiving no TAM as controls (81% Caucasian, 19% African American)* Postmenopausal: 59%[a] ER+: 67% LN+: 48% Tumour size: not reported Metastatic disease: 5%	No information was available concerning concomitant medications Concomitant chemotherapy is allowed	Efficacy

continued

TABLE 6 Cohort characteristics of the included studies *(continued)*

Cohort (and studies); number of patients genotyped for *CYP2D6*	Study design; country of origin; length of patient follow-up	TAM dose; duration	Types of patients and key characteristics	Concomitant CYP2D6 inhibitors/ chemotherapy accounted for?	Outcomes measured
Wegman *et al.* 2005;[100] *n* = 226 (112 TAM and 114 no TAM)	Retrospective analysis of frozen tumour tissues; Sweden; mean 10.7 (range 0.24–18.6) years	40 mg/day; 2 years	*Women with breast cancer receiving TAM adjuvant therapy and women with breast cancer receiving no TAM as controls* Postmenopausal: 100% ER+: 69% LN+: 89% Tumour > 2 cm: 61% Metastatic disease: not reported	Adjuvant chemotherapy was allowed	Efficacy
Gonzalez-Santiago *et al.* cohort:[86] Gonzalez-Santiago *et al.* 2006;[85] *n* = 85 Gonzalez-Santiago *et al.* 2007;[86] *n* = 84	Not reported; Spain; median 4.03 years in Gonzalez-Santiago *et al.* 2006[85] and mean 5.5 years in Gonzalez-Santiago *et al.* 2007[86]	Not reported	*Women with breast cancer receiving TAM adjuvant therapy* Postmenopausal: not reported ER+ and/or PgR+: 99% LN+: 62%[b] Tumour size: not reported Metastatic disease: 0%	Co-administration of CYP2D6 inhibitors was not accounted for in the initial analysis but was in the 2007 analysis	Efficacy
Gjerde *et al.* 2005[103] (conference abstract), 2007;[104] *n* = 151	Prospective cohort; Norway; not reported	20 mg/day; ≥ 80 days	*Women with breast cancer receiving TAM adjuvant therapy (100% Caucasian)* Postmenopausal: not reported ER+ and/or PgR+: 100% LN+: not reported Tumour size: not reported Metastatic disease: not reported	No information was available concerning concomitant medications (it is noted that SSRIs are not approved for hot flushes in Norway)	Endoxifen concentrations
Lim *et al.* 2006,[89] 2006[106] (conference abstracts); Lim *et al.* 2007;[73] *n* = 211	Prospective cohort (PK) Korea; not reported	20 mg/day; ≥ 8 weeks	*Women with early or metastatic breast cancer taking TAM in PK study (only patients with metastatic cancer were permitted in the efficacy study (100% South Korean)* Postmenopausal: not reported[b] ER+: not reported LN+: not reported Tumour size: not reported Metastatic disease: not reported	Patients taking SSRIs were excluded	Endoxifen concentrations
Schroth *et al.* 2007;[96] *n* = 486 (206 TAM and 280 no TAM)	Retrospective analysis of paraffin-embedded tumour samples from a single centre; Germany; median (range) 71 (4–227) months	Not reported	*Women with breast cancer receiving TAM adjuvant therapy and women with breast cancer receiving no TAM as controls* Postmenopausal: 100% (TAM) ER+: 100% (TAM) LN+: 31% (TAM) Tumour ≥ 2 cm: 55% (TAM) Metastatic disease: 0%	Information on SSRI use was incomplete No concomitant chemotherapy for patients taking TAM	Efficacy

TABLE 6 Cohort characteristics of the included studies *(continued)*

Cohort (and studies); number of patients genotyped for *CYP2D6*	Study design; country of origin; length of patient follow-up	TAM dose; duration	Types of patients and key characteristics	Concomitant CYP2D6 inhibitors/ chemotherapy accounted for?	Outcomes measured
Wang *et al.* 2007;[98] *n* = 58	Not reported; USA; not reported	Not reported	*Women with breast cancer receiving TAM adjuvant therapy who were described as 'ethnically diverse'* Postmenopausal: not reported ER+: not reported LN+: not reported Tumour size: not reported Metastatic disease: not reported	Not reported	AEs
Wegman *et al.* 2007;[99] *n* = 677 (of which 238 were randomised to either 2 or 5 years of adjuvant TAM)	Retrospective analysis of frozen tumour tissues; Sweden; mean (range) 7.3 (0.04–17.9) years (median 7.08)	20 or 40 mg/day; 2–5 years	*Women with breast cancer receiving TAM adjuvant therapy* Postmenopausal: 100% ER+: 100% LN+: 69% Tumour ≥ 2 cm: 72% Metastatic disease: 0%	SSRIs were rarely used	Efficacy
Kiyotani *et al.* cohort:[114] Kiyotani *et al.* 2008;[88] *n* = 67 Kiyotani *et al.* 2010;[114] *n* = 282	Retrospective analysis of samples of patients who were pathologically diagnosed and received surgical treatment; Japan; median (range) follow-up 8 years (1.6 to 21.6) years in Kiyotani *et al.* 2008[88] and median (range) follow-up 7.1 years (0.8 to 23.5 years) in Kiyotani *et al.* 2010[114]	20 mg/day; 5 years	*Women with breast cancer starting TAM adjuvant therapy (100% Japanese)* Postmenopausal: 53%[c] ER+: 74%[c] LN+: 17%[c] Tumour > 2 cm: 38%[c] Metastatic disease: 0%	Co-administration of SSRIs was not permitted No concomitant chemotherapy	Efficacy
Madlensky *et al.* 2008;[90] *n* = 1411	Retrospective analysis of samples from RCT; USA; mean (range) 7.3 (6 to 11) years	Not reported	*Women with breast cancer receiving TAM adjuvant therapy* Postmenopausal: not reported[b] ER+: not reported LN+: not reported Tumour size: not reported Metastatic disease: 0%	Not reported	AEs
Newman *et al.* 2008;[91] *n* = 115	Retrospective analysis of germline DNA samples from a single centre; UK; median 10 years	20 mg/day; median > 4 years	*Women with familial breast cancer and BRCA1 or BRCA2 mutations receiving TAM adjuvant therapy (100% Caucasian)* Postmenopausal: not reported[b] ER+: 77% LN+: 39% Tumour > 3 cm: 23% Metastatic disease: 0%	Four patients were co-prescribed drugs reported to inhibit CYP2D6, concomitant with TAM treatment	Efficacy

continued

TABLE 6 Cohort characteristics of the included studies *(continued)*

Cohort (and studies); number of patients genotyped for *CYP2D6*	Study design; country of origin; length of patient follow-up	TAM dose; duration	Types of patients and key characteristics	Concomitant CYP2D6 inhibitors/ chemotherapy accounted for?	Outcomes measured
Xu *et al.* 2008;[101] *n* = 293 (152 TAM and 141 no TAM)	Retrospective cohort; China; median (range) follow-up TAM = 63 (4 to 122) months and no TAM = 120 (4 to 193) months	20 mg/day; 5 years	*Women with breast cancer receiving TAM adjuvant therapy and women with breast cancer receiving no TAM adjuvant therapy as controls* Postmenopausal: 76%[a] (TAM) ER+: 82% (TAM) LN+: 7% (TAM) Tumour ≥ 2 cm: 27% (TAM) Metastatic disease: 0%	Medication known to inhibit CYP2D6 was not permitted No concomitant chemotherapy for patients taking TAM	Efficacy
Bonnanni *et al.* 2009;[112] *n* = 75 (25 TAM, 25 ANA + TAM, 25 ANA)	Prospective randomised, open-label phase IIb trial; Italy; 12 months	TAM: 10 mg/week; 1 year ANA + TAM: 10 mg/week; 1 year + ANA: 1 mg/day; 1 year ANA, no TAM, ANA: 10mg/week; 1 year	*Women with breast cancer receiving TAM* Postmenopausal: not reported ER+ and/or PgR+: 100% LN+: not reported Tumour size: not reported Metastatic disease: not reported	Not reported	Endoxifen concentrations
de Duenas *et al.* 2009;[113] *n* = 115	Prospective clinical study; Spain; not reported	Not reported	*Women with breast cancer receiving TAM adjuvant therapy* Postmenopausal: not reported ER+: not reported LN+: not reported Tumour size: not reported Metastatic disease: 0%	Concomitant use of CYP2D6 inhibitors not permitted	Endoxifen concentrations
[d]Goetz *et al.* 2009[82] on behalf of the ITPC; *n* = 2880	Requested patient data from 12 ITPC project sites; not reported	Any dose permitted but the majority (2151/2880) given 20 mg/day	*Women with breast cancer receiving TAM adjuvant therapy* Postmenopausal: 100% ER+: 100% LN+: 48% Tumour > 2 cm: 48% Metastatic disease: 0%	Data on co-administration of CYP2D6 inhibitors was missing for 61% of patients	Efficacy
Okishiro *et al.* 2009;[93] *n* = 173	Retrospective cohort; Japan; median (range) 56 (8–109) months	20 mg; median (range) 52 (9 to 60) months	*Women with breast cancer receiving TAM adjuvant therapy (100% Asian)* Postmenopausal: 22% ER+: 91% LN+: not reported Tumour > 2 cm: 43% Metastatic disease: 0%	Patients who received paroxetine concomitantly with TAM were excluded	Efficacy AEs

TABLE 6 Cohort characteristics of the included studies *(continued)*

Cohort (and studies); number of patients genotyped for *CYP2D6*	Study design; country of origin; length of patient follow-up	TAM dose; duration	Types of patients and key characteristics	Concomitant CYP2D6 inhibitors/ chemotherapy accounted for?	Outcomes measured
Onitilo *et al.* 2009;[94] *n* = 220	Restrospective analysis of samples held in a population based repository, USA; up to 12.68 years	Not reported	All patients were Caucasian (and one patient was a man)	Not reported	AEs
Ramon *et al.* 2010;[41] *n* = 91	Retrospective analysis of samples from a single centre; Spain; mean (range) 108 (91 to 133) months	Not reported	*Women with breast cancer receiving TAM adjuvant therapy* Postmenopausal: 40% ER+: 100% LN+: 50% Tumour: not reported Metastatic disease: 0%	Information on SSRI use was incomplete Concomitant chemotherapy is allowed	Efficacy AEs
Schroth *et al.* 2009;[108] *n* = 1361[e]	Retrospective analysis of German (see Schroth *et al.* 2007[96]) and US (see Goetz *et al.* cohort[83]) cohorts of patients treated with adjuvant TAM for early-stage breast cancer (retrospectively and prospectively collected); Germany and USA; median (range) 76.1 (2.1 to 243.6) months	Not reported	*Women with breast cancer receiving TAM adjuvant therapy* Postmenopausal: 96% ER+: 97% LN+: 34% Tumour > 2 cm: 47% Metastatic disease: 0%	Information on SSRI use was incomplete No concomitant chemotherapy	Efficacy
Thompson *et al.* 2009;[109] *n* = 618	Retrospective analysis of samples from two separate sites; UK; median follow-up 9.4 and 4.9 years in each respective cohort	20 mg/day; 5 years	*Women with breast cancer receiving TAM adjuvant therapy (100% Caucasian)* Postmenopausal: 85% ER+: 100% LN+: 45% Tumour > 2 cm: 64% Metastatic disease: 0%	The CYP2D6 metabolism status of patients was adjusted for co-medication Some patients received concomitant chemotherapy	Efficacy

continued

patients from three published studies: Matthew Goetz, Mayo Clinic, Minnesota, USA, 2010, personal communication]. Generally, however, cohorts included between 60 and 300 patients, two other exceptions being two larger cohorts of 677[99] and 1361[108] patients, this last cohort itself including patients from two previously published cohorts.[83,96]

Unsurprisingly, all seven cohorts that measured endoxifen plasma concentrations were followed up prospectively.[49,73,87,104,112–114] All other studies were analysed retrospectively, using archived samples. In five cohorts,[92,96,100,101,112] alongside data on patients receiving TAM, additional comparative data were provided for patients not receiving TAM.

TABLE 6 Cohort characteristics of the included studies *(continued)*

Cohort (and studies); number of patients genotyped for *CYP2D6*	Study design; country of origin; length of patient follow-up	TAM dose; duration	Types of patients and key characteristics	Concomitant CYP2D6 inhibitors/ chemotherapy accounted for?	Outcomes measured
Toyama *et al.* 2009;[97] *n*=154	Retrospective analysis of frozen tumours from single centre; Japan; median (range) 7.9 years (25 to 249 months)	20 mg/day; 2–5 years (average 3.2 years)	*Women with ER+ breast cancer receiving TAM adjuvant therapy (no metastatic breast cancer) (100% Asian)* Postmenopausal: not reported ER+: 96% LN+: 0% Tumour > 2 cm: 48% Metastatic disease: not reported	Concomitant use of SSRIs was permitted (Tatsuya Toyama, Nagoya City University Hospital, Nagoya, Japan, 2010, personal communication) It is assumed that no patient received chemotherapy, as patients are ER+ and LN–, who, as stated, are usually recommended for hormone therapy alone	Efficacy
Kiyotani *et al.* 2010;[114] *n*=98	Not reported; Japan; not reported	20 mg/day; not reported	*Women with breast cancer receiving TAM adjuvant therapy* Postmenopausal: not reported ER+: not reported LN+: not reported Tumour size: not reported Metastatic disease: not reported	Not reported	Efficacy Endoxifen concentrations

DNA, deoxyribonucleic acid; LN–, lymph node negative; PgR+, progesterone receptor positive; PK, pharmacokinetics; SD, standard deviation.
a Menopausal status estimated from age at diagnosis.
b Both premenopausal and postmenopausal women appear to be included but the proportion of patients by hormonal status is unknown.
c Figures taken from most recently published/presented study.
d Data taken from the Microsoft PowerPoint presentation given at the 32nd Annual San Antonio Breast Cancer Symposium, San Antonio, TX, 11 December 2009.
e Includes 350 patients included in either the Goetz *et al.*[83] or Schroth *et al.*[96] cohorts, 32nd Annual San Antonio Breast Cancer Symposium, San Antonio, TX, 11 December 2009.

Seven cohorts[49,83,87,90,92,94,98] were solely from the USA, 10[41,86,91,96,99,100,104,109,112,113] solely from Europe (including two from the UK[91,109]), six[73,88,93,97,101,114] from Asia, one[108] a combination of US and German patients and one[82] from 12 unspecified ITPC project sites in the USA, Europe and Asia. The average duration of the studies varied considerably, from 4 weeks[49] to 11.4 years,[83] although, where average duration data were provided, all retrospective analyses were of at least 5 years' duration.

Where cohorts provided data on TAM dose, this was 20 mg/day, the exceptions being two Swedish cohorts,[99,100] in which average doses were higher, and the pharmacokinetic study of plasma concentrations by Bonanni *et al.*[112] in which they were lower. The majority of patients in these cohorts also received their dose for 5 years, the Swedish cohorts[99,100] again being notable exceptions where 1–2 years' dose duration was not uncommon and three other cohorts where it varied from a matter of weeks[49,73,104] in pharmacokinetic studies to an average of 3 years.[97]

Five cohorts[83,87,96,108,114] were explicit in prohibiting adjuvant chemotherapy, while four[41,92,100,109] were explicit in stating that this was permitted, concomitant chemotherapy in the other studies being uncertain. Data on CYP2D6 inhibitor use were also often either lacking or incomplete, with four[93,101,113,114] cohorts explicitly prohibiting their use and five[83,86,87,91,109] accounting for these in their analysis (noticeably, where there was more than one study for any given cohort this account was made in the more recent studies[83,86,95,107]).

It is also known that the study of endoxifen plasma concentrations by Lim *et al.*[73] also included patients with metastatic disease. No other study appears to include patients with metastatic breast cancer except Nowell *et al.*,[92] in which 5% of patients have metastatic disease and possibly also Wegman *et al.*[100] in which the inclusion criteria state that patients were required to have either histological verified lymph node metastases or a tumour diameter > 3 cm. It is also impossible to be sure in five of the pharmacokinetic studies[49,102,104,112,114] and three of the efficacy studies whether or not the studies included patients with metastatic breast cancer.[94,98,100]

Very few cohorts provided information on ethnicity, this being mentioned in just under half ($n = 12$) of the cohorts.[73,83,87,91–94,97,98,104,109,114] When this information was provided, Caucasians or Asians were represented in the study by at least 90% of all participants in all studies except Nowell *et al.*[92] in which there were 81% Caucasians and 19% African Americans, and Wang *et al.*[98] who simply stated that their population was 'ethnically diverse'.

Not all cohorts provided data on the hormonal status of their patients. In six cohorts, all[83,96,99,100,116] or nearly all (96%)[108] of the women were known to be postmenopausal. In 10 others, there was a mix, although in only two instances[41,93] was there a minority of postmenopausal women (40% and 22%, respectively). Similarly, not all cohorts provided data on hormone receptor status. Where these data were provided, all, or nearly all (> 90%), of the women were ER+ (or ER+ and/or progesterone receptor positive) in nine[41,83,87,96,99,104,109,112,116] and five[73,86,93,97,108] cohorts, respectively. In the remaining five cohorts[91,92,100,101,114] in which this information was known, the proportion of ER+ women varied between 67% and 82%.

Less than half of the cohorts provided data on nodal status ($n = 13$)[83,86,91,92,96,97,99–101,108,109,114,116] or tumour size ($n = 12$).[83,91,93,96,97,99–101,108,109,114,116] It was noticeable that the proportion of LN+ patients varied considerably across the cohorts, from no such patients[97] to 89%,[100] with a minority of patients being node positive in the majority of the studies. The proportion of patients with a tumour size ≥ 2 cm also appeared to vary significantly across the studies, from 27%[101] to 72%,[99] with a further two cohorts reporting only tumour sizes ≥ 3 cm in just under one-quarter of patients.[83,91]

Fifteen cohorts measured efficacy.[41,82,83,86,91–93,96,97,99–101,108,109,114] Standard breast cancer study outcome measures, such as OS and DFS, were utilised; however, the definitions of these same outcomes often differed from study to study. In addition, depending on the cohort, the analysis was adjusted for in 14 cohorts.[82,83,86,91–93,96,99–101,104,108,109,114] Six cohorts[41,83,87,90,94,98] reported on AEs and seven cohorts[49,73,87,104,112–114] reported on endoxifen plasma concentrations. No cohort reported on health-related quality of life.

Derivation and classification of phenotypes

An important finding from our review was that currently there is no consensus about how *CYP2D6* phenotypes should be derived from their genotypes and how they should thus be compared. In the current review, a large number of classifications and comparisons were utilised by different cohorts, and in some instances within cohorts. The different classifications used are summarised in *Table 7*, where it is evident that 10 cohorts[82,83,87,90,91,96,104,108,112,113] used

TABLE 7 Phenotype classifications

Cohort (and studies); no. of patients genotyped for *CYP2D6*	*CYP2D6* alleles tested	Derivation of phenotype from *CYP2D6*	Comparisons (in paper)	'Standardised comparisons'
Stearns *et al.* 2003;[49] *n*=12	**4, *6, *8*	No specific phenotypes defined in initial study	*wt* genotype vs *vt* genotype	Other
Goetz *et al.* cohort:[83] Goetz *et al.* 2004[116] (conference abstract), Goetz *et al.* 2005;[84] *n*=223 Goetz *et al.* 2007[83] (re-analysis); *n*=180 Goetz *et al.* 2009[110] (longer-term follow-up); *n*=210	**4; *6 (*4* only in Goetz *et al.* 2007[83]) Also genotyped for *CYP3A5* in Goetz *et al.* 2005[84]	No specific phenotypes defined in initial study In re-analysis: ■ EM = *wt/wt* + no inhibitor ■ IM = *wt/wt* + moderate inhibitor; *wt/*4* + no inhibitor ■ PM = **4/*4* + no inhibitor; **4/*4* + CYP2D6 moderate inhibitor; **4/*4* + potent inhibitor; *wt/*4* + moderate inhibitor; *wt/*4* + potent inhibitor; *wt/wt* + potent inhibitor; genotype not known + potent inhibitor. Unclassified: Genotype not known + moderate inhibitor; *wt/*4* + inhibitor use not known	**4/*4* vs *wt/wt* + *wt/*4* (no **6* variants were detected) PM vs EM IM vs EM PM + IM vs EM	 PM vs EM + IM PM vs EM IM vs EM PM + IM vs EM
Henry *et al.* cohort[87] Jin *et al.* 2005;[105] *n*=50 Borges *et al.* 2006;[102] *n*=158 Henry *et al.* 2009;[87] *n*=276 Henry *et al.* 2009;[107] *n*=276 Rae *et al.* 2009;[95] *n*=280	**1–*10AB, *11, *14A, *14B, *15, *17, *19, *20, *25, *26, *29 to *31, *35, *36, *40, *41, *1× N, *2× N, *4× N, *10× N, *17× N, *35× N, *41× N* Fewer alleles were tested in the earliest study by Jin *et al.* 2005:[105] **3, *4, *5, *6* Also genotyped for *ESR1* and *ESR2 in* Henry *et al.* 2009[87]	No specific phenotypes defined in original study *In Borges* et al. *2006*[102] PM = **3, *4, *5, *6/*3, *4, *5, *6* IM = **9, *10, *17, *29, *41, *41× N/*3, *4, *5, *6* or **9, *10, *17, *29, *41, *41× N/*9, *10, *17, *29, *41, *41× N* or **1, *2, *35/*3, *4, *5, *6* or **1, *2, *35/*9, *10, *17, *29, *41, *41× N* EM = **1, *1× N, *2, *2× N, *35/*1, *1× N, *2, *2× N, *35* No specific phenotypes defined in Henry *et al.* 2009[87] *In Henry* et al. *2009*[107] *and Rae* et al. *2009*[95] Each *CYP2D6* allele was assigned a value from 0 (for non-functional alleles) to 1 (for fully functional alleles) based on its relative activity for dextromethorphan O-demethylation. For each subject, the two allele scores were summed. Patients were classified as PM if score < 1, IM if 1 to < 2, and EM if ≥ 2, i.e. per allele: ■ 1 = **1, *1× N, *2, *2× N, *35* ■ 0.5 = **9, *10, *17, *41* ■ 0 = **3, *4, *5, *6, *11* *In Rae et al. 2009*[95] For concomitant medication that inhibits CYP2D6, two points were deducted from each patient's CYP2D6 metabolism score for strong inhibitors, one point for moderate inhibitors and zero points for the weak inhibitor/no inhibitors	*vt/vt* vs *wt/vt* vs *wt/wt* PM vs IM vs EM PM vs EM + IM	Other PM vs EM PM vs IM IM vs EM Other PM vs EM + IM

TABLE 7 Phenotype classifications *(continued)*

Cohort (and studies); no. of patients genotyped for *CYP2D6*	*CYP2D6* alleles tested	Derivation of phenotype from *CYP2D6*	Comparisons (in paper)	'Standardised comparisons'
Nowell *et al.* 2005;[92] *n* = 337 (165 TAM and 172 no TAM)	**3, *4, *6* Also genotyped for *SULT1A1* and *UGT2B15*	No specific phenotypes defined	**4/*4 + wt/*4* vs *wt/wt*	PM + IM vs EM
Wegman *et al.* 2005;[100] *n* = 226 (112 TAM and 114 no TAM)	**4* Also genotyped for *SULT1A1*	No specific phenotypes defined	**4/*4 + wt/*4* vs *wt/wt*	PM + IM vs EM
Gonzalez-Santiago *et al.* cohort:[86] Gonzalez-Santiago *et al.* 2006;[85] *n* = 85 Gonzalez-Santiago *et al.* 2007;[86] *n* = 84	**4*	No specific phenotypes defined	**4/*4 + wt/*4* vs *wt/wt*	PM + IM vs EM
Gjerde *et al.* 2005[103] (conference abstract), Gjerde *et al.* 2007;[104] *n* = 151	**3, *4, *5, *6, *2 × 2* Also genotyped for *SULT1A1*	PM: *vt/vt* IM = *wt/vt* EM = *wt/wt* UM = **2 × 2*	PM vs IM vs EM vs UM	Other
Lim *et al.* 2006,[89] 2006[106] (conference abstracts), Lim *et al.* 2007;[73] *n* = 212	**5, *10, *2 × N*	No specific phenotypes defined	**10/*10* vs *wt/wt* vs **10/*10* and *vt/vt* vs *wt/wt* vs *vt/vt*	Other
Schroth *et al.* 2007;[96] *n* = 486 (206 TAM and 280 no TAM)	**4, *5, *10, *41* **3, *6, *7* and **8* were also genotyped for but excluded because PCR amplification rates were poor Also genotyped for *CYP2C19*, *CYP3A5*, *CYP2B6* and *CYP2C9*	EM = *wt/wt* hetEM = *4,*5, *10* or **41/wt* IM = **4,*5, *10* or **41/*10* or **41* PM = **4* or **5/*4* or **5* Decreased = hetEM + IM + PM	Decreased vs EM PM vs EM IM + PM vs EM IM vs EM hetEM vs EM	PM + IM vs EM PM vs EM IM vs EM
Wang *et al.* 2007;[98] *n* = 58	**4*	No specific phenotypes defined	*4/*4 + wt/*4 vs wt/wt*	PM + IM vs EM
Wegman *et al.* 2007;[99] *n* = 677 (of which 238 were randomised to either 2 or 5 years of adjuvant TAM)	**4* Also genotyped for *CYP3A5, SULT1A1* and *UGT2B15*	No specific phenotypes defined	*4/*4 + wt/*4 vs wt/wt*	PM + IM vs EM
Kiyotani *et al.* cohort:[114] Kiyotani *et al.* 2008;[88] *n* = 67 Kiyotani *et al.* 2010;[114] *n* = 282	**4, *5, *6, *10, *14, *18, *21, *41* In Kiyotani *et al.* 2010[114] also genotyped for **36*	No specific phenotypes defined in original study *wt* = **1* *vt* = **4, *5, *10, *14, *21, *36, *41*	**10/*10* vs *wt/wt* *wt/*10* vs *wt/wt* **10/*10* vs *wt/wt + wt/*10* *vt/vt* vs *wt/vt* vs *wt/wt*	Other Other

continued

TABLE 7 Phenotype classifications *(continued)*

Cohort (and studies); no. of patients genotyped for *CYP2D6*	*CYP2D6* alleles tested	Derivation of phenotype from *CYP2D6*	Comparisons (in paper)	'Standardised comparisons'
Madlensky *et al.* 2008;[90] *n*=1411	**1–*10AB, *11, *14A, *14B, *15, *17, *19, *20, *25, *26, *29–*31, *35, *36, *40, *41, *1xN, *2× N, *4× N, *10× N, *17× N, *35× N, *41× N*	Not reported how phenotypes are derived	EM vs hetEM vs IM vs PM vs UM	Other
Newman *et al.* 2008;[91] *n*=115	**3, *4, *5, *41*	PM1 = **3, *4, *5/*3, *4, *5* PM2 = concomitant use of a potent CYP2D6 inhibitor in *wt/wt* individuals or moderate inhibitor use in patients heterozygous for **3*, **4*, **5* or **41* IM = **3*, **4*, **5* or **41/*41* and no use of CYP2D6 inhibitors EM = *wt*, **3*, **4*, **5* or **41*/wt and no use of CYP2D6 inhibitors	PM1 vs EM PM2 vs EM PM1 + PM2 vs EM + IM	PM vs EM PM vs IM
Xu *et al.* 2008;[101] *n*=293 (152 TAM and 141 no TAM)	**10*	No specific phenotypes defined	*10/*10* vs *wt/wt + wt/*10*	Other
Bonnanni *et al.* 2009;[112] *n*=75 (25 TAM, 25 ANA + TAM, 25 ANA)	**2, *3, *4, *5, *6, *9, *29, *41A*	PM = **3, *4, *5, *6/*3, *4, *5, *6* EM = **2, *9, *29, *41/*2, *3, *4, *5, *6, *9, *29, *41*	PM vs EM	PM vs EM
de Duenas *et al.* 2009;[113] *n*=115	**1– *10AB, *11, *14A, *14B, *15, *17, *19, *20, *25, *26, *29 to *31, *35, *36, *40, *41, *1× N, *2× N, *4× N, *10× N, *17× N, *35× N, *41× N*	Not reported	PM vs EM	PM vs EM
Goetz *et al.* 2009[82] on behalf of the ITPC; *n*=2880[a]	Varies by ITPC site but all genotyped for **4* and the majority genotyped for **3, *5, *6, *10, *17* and **41* 1168/2880 used AmpliChip, i.e. **1–*10AB, *11, *14A, *14B, *15, *17, *19, *20, *25, *26, *29 to *31, *35, *36, *40, *41, *1xN, *2xN, *4xN, *10xN, *17xN, *35xN, *41xN*	EM = *wt/wt* or *wt/*10, *17, *41* IM = **10, *17, *41/*10, *17, *41* or *wt/*3, *4, *5, *6* or **10, *17, *41/*3, *4, *5, *6* PM = **3, *4, *5, *6/*3, *4, *5, *6*	PM vs EM	PM vs EM + IM
Okishiro *et al.* 2009;[93] *n*=173	**10* Also genotyped for *CYP2C19*	No specific phenotypes defined	**10/*10* vs *wt/wt + wt/*10*	Other
Onitilo *et al.* 2009;[94] *n*=220	**4* Also genotyped for *ESR1*, *ESR2* and *CYP19*	No specific phenotypes defined	**4/ *4 + wt/*4* vs *wt/wt*	PM + IM vs EM

TABLE 7 Phenotype classifications *(continued)*

Cohort (and studies); no. of patients genotyped for *CYP2D6*	*CYP2D6* alleles tested	Derivation of phenotype from *CYP2D6*	Comparisons (in paper)	'Standardised comparisons'
Ramon *et al.* 2010;[41] *n* = 91	**1– *10AB, *11, *14A, *14B, *15, *17, *19, *20, *25, *26, *29–*31, *35, *36, *40, *41, *1 × N, *2 × N, *4 × N, *10 × N, *17 × N, *35 × N, *41 × N*	Three-group analysis: ■ 1 = **3, *4, *5/*3, *4, *5* ■ 2 = **9, *10, *41/*9, *10, *41* or **1, *2, *35/*3, *4, *5, 9, *10, *20, *41* ■ 3 = **1, *2, *35/*1, *2, *35, *41, *1 × N* or **9, *10, *41/*2 × N* Two-group analysis: ■ A: **4/*4, *4/*41, *1/*5, *2/*5* ■ B: all other genotypes	1 vs 2 vs 3 A vs B	Other
Schroth *et al.* 2009;[108] *n* = 1361	**3, *4, *5, *10, *41, wt × 2, *2 × 2*	PM = *3, *4, *5/*3, *4, *5* IM = **10, *41/*3, *4, *5, *10, *41* hetEM = **1, *2, *35/*3, *4, *5, *10, *41* EM = **1, *2, *35/*1, *2, *35* UM = **1, *2, *35/*1 × 2, *2 × 2* Decreased = PM + IM + hetEM	PM vs EM + UM hetEM + IM vs EM + UM decreased v EM + UM	PM vs EM IM vs EM PM + IM vs EM
Thompson *et al.* 2009;[109] *n* = 618	**1–*10AB, *11, *14A, *14B, *15, *17, *19, *20, *25, *26, *29–*31, *35, *36, *40, *41, *1 × N, *2 × N, *4 × N, *10 × N, *17 × N, *35 × N, *41 × N*	Normal = **1, *2, *35/*1, *2, *35* Decreased = any other genotype Re-assignment of phenotypes using only 4 alleles: ■ decreased = **4, *5, *10*, *41/wt, **4, *5, *10, *41* ■ normal = any other phenotype (i.e. *wt/wt*)	Decreased vs normal (as determined by AmpliChip using many SNPs and then repeated just using four common alleles)	PM + IM vs EM
Toyama *et al.* 2009;[97] *n* = 154	**10*	No specific phenotypes defined	**10/*10* vs *wt/*10* vs *wt/wt*	Other
Kiyotani *et al.* 2010;[114] *n* = 98	**4, *5, *6, *10, *14, *18, *21, *36, *41*	*wt* = **1* *vt* = **4, *5, *10, *14, *21, *36, *41*	*vt/vt* vs *wt/vt* vs *wt/wt*	Other

CYP19, cytochrome P450 19; *CYP2B6*, cytochrome P450 2B6; *CYP2C19*, cytochrome P450 2C19; *CYP2C9*, cytochrome P450 2C9; *CYP3A5*, cytochrome P450 3A5; *ESR1*, estrogen receptor-*1* (alpha); *ESR2*, estrogen receptor-*2* (beta); hetEM, heterozygous EM; PCR, polymerase chain reaction; SNP, single nucleotide polymorphism; *SULT1A1*, sulfotransferase 1A1; *UGT2B15*, UDP-glucuronosyltransferase 2B15.

a Data taken from Microsoft PowerPoint presentation given at the 32nd Annual San Antonio Breast Cancer Symposium, San Antonio, TX, 11 December 2009.

standard phenotypes (PM, IM, EM and UM), even though these were not always classified in the same manner from study to study, while others considered enzymatic function or simply compared genotypes. This heterogeneity makes comparisons across studies problematic, which is compounded further when one considers each cohort genotyped for different alleles, which may also be summarised as follows:

- Number of cohorts that:
  - genotyped for **4* only = 5
  - genotyped for **4* plus at least one other allele = 16
  - genotyped for **10* only = 3
  - genotyped for **10* plus at least one other allele = 12

- genotyped for both **4* and **10* = 9
- used the AmpliChip = 6.

For the purposes of this review, when considering study outcomes, 'standardised comparisons' are made in the tables and text in which alleles are simply considered to be *wt* (i.e. normal function), *null* (i.e. loss of function) or *vt* (any allele that is not *wt*, which includes *null*), and phenotypes are considered to be EM (*wt/wt*), IM (*wt/vt*) or PM (*null/null*) [this classification is the same as classification 1 for Test C in *Table 2* (where *null* = *3, *4, *5 and *vt* = *10)]. It should be noted that for the purposes of these comparisons, UMs are likely to be classified as EMs. This is because not all genotyping methods are able to detect UMs and where studies have used methods that can, UMs appear to be classified with EMs, for example in Schroth *et al.*[108] Thus, the following comparisons can be considered:

- PM versus EM
- IM versus EM
- PM + IM versus EM
- PM versus EM + IM
- Asian patients genotyped for the **10* allele
- other comparisons that do not fit these categorisations.

Differences in cohort characteristics by genotype or phenotype

The cohort characteristics in *Table 6* are for all patients in the cohort, regardless of CYP2D6 status. Only eight cohorts[83,91,93,97,99–101,108] provided any of these data by genotype or phenotype, which is perhaps unsurprising given the retrospective nature of these studies (these data possibly not being originally collected).

It was noticeable in the Goetz *et al.* cohort[83] that, compared with the cohort as a whole genotyped by paraffin tissue, more patients in the **4/*4* group had a tumour size ≥ 3 cm (38% compared with 22%) and were LN+ (69% compared with 38%).[84] Patients with this genotype were also more likely to be older (median age 73 years compared with 68 years) and have had a mastectomy (92% compared with 83%). It should be noted, however, that the number of patients with the **4/*4* genotype was small ($n = 13$) compared with those with other genotypes ($n = 177$).

Similarly, in Newman *et al.*,[91] compared with patients with other phenotypes, patients with the PM phenotype had a larger tumour size (42% compared with 21% had tumour size > 3 cm) and were more likely to have one or more positive lymph nodes at diagnosis (55% compared with 39%). These patients were also more likely to have had a mastectomy (67% compared with 49%) and be ER+ (92% vs 76%), but the median age in both groups of patients was similar (43 years compared with 45 years). Again, the number of patients with the PM phenotype was very small ($n = 12$) compared with those with other genotypes ($n = 103$).

Wegman *et al.*[100] also presented demographic data but these were for the group of patients as a whole, i.e. including both the patients who received TAM and the control group who did not. For each of the groups compared, **4/*4*, *wt/*4* and *wt/wt*, the proportion of patients who were node negative but with a tumour > 3 cm was similar in each group (11%, 9% and 12%, respectively). However, some differences were evident in terms of patients who were node positive with a tumour > 2 cm (33%, 58% and 44%, respectively) and ER+ (44%, 22% and 31%, respectively). Once again, the number of patients with the **4/*4* genotype was extremely small ($n = 9$) compared with those with other genotypes ($n = 217$).

In their later (separate) study, in which all patients received TAM, Wegman *et al.*[99] reported no real differences in tumour size or nodal status (tumour ≥ 2 cm being 71% for **4/*4*, 75% for *wt/*4*

and 71% for *wt/wt*; patients with node > 0 cm being 71%, 69% and 69%, respectively). As with the previously mentioned studies, the number of patients with the **4/*4* genotype was small ($n = 34$) compared with those with other genotypes ($n = 643$).

The only study to compare patients with decreased activity as a whole ($n = 716$, of whom 79 were PM) with EMs ($n = 609$) was by Schroth *et al.*,[108] who reported no real differences in tumour size > 2 cm (48% compared with 47%), lymph nodal status (36% compared with 31%) or age at diagnosis (median age was 66 years in both groups) between groups. No real differences were evident for any other cohort characteristics presented by the authors.

Xu *et al.*[101] reported differences in cohort characteristics in Asian women across genotype groups, namely **10/*10, wt/*10* and *wt/wt.* While lymph nodal status appeared similar across the groups (6%, 8% and 7%, respectively, were node positive), more patients with the **10/*10* genotype appeared to have larger tumours (32% > 2 cm compared with 23% and 21%, respectively) and fewer were ER+ (86% compared with 92% and 96%, respectively). In this cohort, there were almost as many women with the **10/*10* genotype ($n = 72$) as with other genotypes ($n = 80$).

Toyama *et al.*[97] reported few differences between the three groups of Asian female patients, with the notable exception that more women with the *wt/wt* genotype had a tumour > 2 cm (59% compared with 44% in each of the other genotype groups). Data were not presented on nodal status. Age differed only slightly (median 56 years in the**10/*10* group compared with 60 years in the other two groups). The vast majority (> 96%) of patients were ER+ in all groups. The proportion of patients with the **10/*10* genotype was relatively small ($n = 28$) compared with other genotypes ($n = 126$).

In Okishiro *et al.*,[93] fewer differences were apparent when patients with the **10/*10* genotype were compared with patients with all other genotypes, the number of patients with tumour size > 2 cm and LN+ in each group being comparable (29% vs 28% and 43% vs 45%, respectively) and median age being similar (47 years compared with 46 years). However, it was noticeable that there were more patients with the **10/*10* genotype with ER+ breast cancer (92% compared with 60%). The number of patients with the **10/*10* genotype was again relatively small ($n = 40$) compared with other genotypes ($n = 133$).

While other studies neither presented cohort characteristics by genotype/phenotype nor reported any differences between groups, seven other cohorts did adjust for prognostic factors.[82,86,92,96,104,109,114]

Efficacy

The efficacy of TAM treatment was considered by genotype/phenotype, using the following comparisons as described above (see *Derivation and classification of phenotypes*):

- PM vs EM
- IM vs EM
- PM + IM vs EM
- PM vs EM + IM
- Asian patients genotyped for the **10* allele
- other comparisons that do not fit these categorisations.

Unfortunately, not all clinical end points measured by the cohorts were defined. Where end points were defined, it was apparent that different cohorts used different definitions for the same end points. Given these inconsistencies and/or a lack of information to correctly classify a clinical end point [e.g. information on censoring would enable recurrence outcomes to be classified

as DFS, RFS or time to recurrence (TTR)], the efficacy outcomes are presented below in terms of OS, breast cancer mortality (i.e. mortality attributed only to breast cancer and not from any cause as with OS) and outcomes such as DFS, RFS and TTR, which can be considered relating to relapse/recurrence.

Overall survival is considered the least ambiguous and most clinically relevant clinical end point.[117] Seven cohorts[82,83,91,92,96,97,108] examined OS by CYP2D6 status. One[108] of these studies also includes 350 patients from two of the other included cohorts,[83,96] and the large ITPC cohort[82] also contains data from three published data sets (Matthew Goetz, personal communication). Two cohorts considered breast cancer mortality[97,101] and 13 cohorts[41,82,83,86,91,93,96,97,99,100,108,109,114] reported outcomes relevant to relapse/recurrence.

Poor metaboliser versus extensive metaboliser

Five studies[83,91,96,108,110] from four cohorts[83,91,96,108] compared PMs with EMs. One cohort[83] genotyped for the **4* PM allele only, while the other three all genotyped for three or more alleles, all including **4* and **5*.[91,96,108] CYP2D6 inhibitors were accounted for in two cohorts[83,91] by altering an EM patient's phenotype to PM when a potent CYP2D6-inhibiting drug was taken concomitantly and an IM patient's phenotype to PM when a moderate CYP2D6 inhibitor was used.

Neither of the two cohorts reporting on OS[83,91] reported a significant difference between PMs and EMs. However, three cohorts[83,91,108] reported improved outcomes in terms of relapse/recurrence for EMs compared with PMs.

Overall survival

Two cohorts[83,91] considered differences in OS between PMs and EMs. One of these cohorts[83] genotyped for the **4* allele, whereas the other genotyped for **3*, **4* and **5*.[91] Both of these cohorts[83,91] appeared similar in terms of the tumour size and nodal status of patients; in terms of other cohort characteristics, there were differences in the proportions of postmenopausal women and women with ER+ breast cancer. While in some regards these cohorts appeared similar, in one cohort[83] it was known that, compared with all patients, a greater proportion of patients with the PM phenotype had a tumour size ≥ 3 cm and were LN+.

In these two cohorts,[83,91] OS appeared to be improved in EMs compared with PMs, with unadjusted hazard ratios (HRs) of between 1.9 and 3.5,[83,91] although confidence intervals (CIs) were wide and no significant differences in OS were reported (*Table 8*). It is unclear whether or not the unadjusted findings were influenced by differences in terms of cohort characteristics in the phenotype groups [for comparisons of other phenotype groups (PM + IM vs EM and PM vs

TABLE 8 Overall survival in patients taking TAM in relation to CYP2D6 status: PM versus EM

Cohort/study	Alleles tested	Outcome definition	Summary of findings
Goetz *et al.* cohort:[83] Goetz *et al.* 2007[83]	**4*	Time from registration to death from any cause	Cox HR (unadjusted) HR 2.00; 95% CI 0.92 to 4.17; $p=0.077$
Newman *et al.* 2008[91]	**3, *4, *5, *41*	Not reported	Cox HR (unadjusted) PM1 vs EM: HR 3.5; 95% CI 0.8 to 15.4; $p=0.079$ PM2 vs EM: HR 3.4; 95% CI 0.77 to 14.9; $p=0.084$

CI, confidence interval; HR, hazard ratio; PM1, poor metaboliser defined solely by genotype; PM2, poor metaboliser defined by genotype and/or concomitant use of CYP2D6 inhibitors.

EM + IM) in these cohorts, these HRs were adjusted for tumour size[83] and/or nodal status[83,91]]. Furthermore, while concomitant use of CYP2D6 inhibitors was taken into consideration in both cohorts, adjuvant chemotherapy use was unknown (in the Goetz *et al.* cohort,[83] it was prohibited).

Relapse/recurrence

Two studies[83,110] from the Goetz *et al.* cohort[83] compared DFS, and one study[83] compared RFS for PMs compared with EMs. This cohort genotyped for **4* and accounted for CYP2D6 inhibitors in one study[83] by altering an EM patient's phenotype to PM when a potent inhibitor was used and an IM patient's phenotype to PM when a moderate inhibitor was used. The Goetz *et al.* cohort[83] and two others[91,96] also measured TTR. These other two cohorts genotyped for a wider range of alleles (**3, *4, *5*[91] and **4, *5, *10, *41*[96]). There were also variations in the proportion of postmenopausal women and those with ER+ breast cancer across the three cohorts, although the majority (> 75%) of patients in all cohorts were ER+. The proportion of LN+ patients across the cohorts was also similar and, in two cohorts[83,91] the proportion of patients with a tumour ≥ 3 cm was also similar (it was not possible to compare with the other cohort[108] as this reported tumour size > 2 cm). In two of these cohorts,[83,91] there were differences between PMs and EMs in terms of tumour size and nodal size.

In the Goetz *et al.* cohort,[83] both DFS and RFS were reported to be significantly worse for PMs (*Table 9*). All three cohorts[83,91,108] that measured TTR also reported significant differences between PMs and EMs, although this applied only when patients whose phenotype was modified to PM were included in the group of PMs in one cohort.[91]

Intermediate metaboliser versus extensive metaboliser

Two studies[83,110] from one cohort[83] genotyped for **4* only when IMs were considered to be *wt/*4*. This cohort also accounted for CYP2D6 inhibitors by classifying patients who were *wt/wt* (but taking a moderate CYP2D6 inhibitor) to be IMs.

There was no evidence of a difference in OS or relapse/recurrence between IMs and EMs in this cohort.[83]

Overall survival

One cohort[83] considered differences in OS between IMs and EMs (*Table 10*). This cohort accounted for CYP2D6 inhibitors, but it was unclear whether or not adjuvant chemotherapy was permitted. No difference in OS or relapse/recurrence between IMs and EMs was reported.[83]

Relapse/recurrence

Only one cohort[83] reported on DFS, RFS and TTR between IMs and EMs (*Table 11*). This cohort adjusted for CYP2D6 inhibitors by altering phenotypes accordingly and also prohibited the use of adjuvant chemotherapy. No difference in DFS, RFS or TTR between IMs and EMs was reported.

Poor metaboliser plus intermediate metaboliser versus extensive metaboliser

Nine studies[83,85,86,92,96,99,100,108,109] from eight cohorts[83,86,92,96,99,100,108,109] compared PMs combined with IMs with EMs. Four of these cohorts[83,86,92,100] genotyped only for (or at least utilised in the analysis) **4*, whereas the other four[96,99,108,109] genotyped for a wider range of alleles. Three[83,86,109] of these cohorts considered the impact of CYP2D6 inhibitors on phenotype.

Four cohorts[83,92,96,108] reported on OS but not one reported significant differences between the PM + IM or EM groups. Seven cohorts[83,86,92,96,99,100,108] assessed relapse/recurrence, four[83,86,96,108] of these reporting significantly worse outcomes for the PM + IM group. An important finding

TABLE 9 Relapse/recurrence in patients taking TAM in relation to CYP2D6 status: PM versus EM

Cohort/study	Alleles tested	Outcome definition	Summary of findings
Goetz *et al.* cohort:[83] Goetz *et al.* 2007,[83] 2009[110]	**4*	DFS: time from randomisation to documentation of the first of the following events: any recurrence (local, regional or distant) of breast cancer, a contralateral breast cancer, a second primary cancer or death from any cause	*Cox HR (unadjusted), DFS:* HR 2.44; 95% CI 1.27 to 4.69; $p=0.008$ *Cox HR (adjusted for tumour size and nodal status), DFS:* HR 2.00; $p=0.02$ (longer-term follow-up)
		RFS: time from randomisation to documentation of the first of the following events: any recurrence (local, regional or distant) of breast cancer, a contralateral breast cancer or death	*Cox HR (unadjusted), RFS:* HR 2.69; 95% CI 1.34 to 5.37; $p=0.005$
		TTR: the time from randomisation to documentation of a breast event, where a breast event is any recurrence (local, regional or distant) of breast cancer or the documentation of contralateral breast cancer (including ductal carcinoma in situ)	*Cox HR (unadjusted), TTR:* HR 3.20; 95% CI 1.37 to 7.55; $p=0.007$ *Cox HR (adjusted for tumour size and nodal status), TTR:* HR 4.00; $p=0.01$ (longer-term follow-up)
Newman *et al.* 2008[91]	**3, *4, *5, *41*	TTR: time to tumour recurrence with contralateral, ipsilateral or metastatic disease	Cox HR (unadjusted), TTR: PM1 vs EM: HR 2.9; 95% CI 0.9 to 9.4; $p=0.076$ PM2 vs EM : HR 3.2; 95% CI 0.98 to 10.4; $p=0.044$
Schroth *et al.* 2009[108]	**3, *4, *5, *10, *41, wt× 2, *2× 2*	TTR: time from diagnosis or randomisation to documentation of a breast event, any local, regional or distant recurrence of breast cancer or a contralateral breast cancer	*Cox HR (unadjusted):* HR 2.12; 95% CI 1.28 to 3.50; $p=0.003$ *Cox HR (adjusted for tumour size, nodal status and histological grade, and stratified by menopause status and mode of patient recruitment):* HR 1.90; 95% CI 1.10 to 3.28; $p=0.02$

PM1, poor metaboliser defined solely by genotype; PM2, poor metaboliser defined by genotype and/or concomitant use of CYP2D6 inhibitors.

TABLE 10 Summary of OS in patients taking TAM in relation to CYP2D6 status: IM versus EM

Cohort/study	Alleles tested	Outcome definition	Summary of findings
Goetz *et al.* cohort,[83] Goetz *et al.* 2007[83]	**4*	Time from registration to death from any cause	*Cox HR (unadjusted):* HR 1.40; 95% CI 0.80 to 2.43; $p=0.240$

was that, in one of these cohorts,[104] the significant differences were found only when using the AmpliChip to genotype for an extensive number of alleles and not when only four common alleles were genotyped. In the three cohorts in which there were no significant differences, the data suggested, if anything, that the PM + IM group had better outcomes than EMs. Reasons for these contradictory findings are unknown but may be attributable to cohort characteristics.

Overall survival

Four cohorts[83,92,96,108] compared OS between PM + IMs and EMs. Three[83,96,108] of these cohorts appeared relatively similar in terms of the proportions of postmenopausal women with ER+ breast cancer and nodal status. It was not possible to compare tumour size across all three cohorts, as one cohort[83] reported > 3 cm and the other two[96,108] > 2 cm (where the cohorts did

TABLE 11 Summary of relapse/recurrence in patients taking TAM in relation to CYP2D6 status: IM versus EM

Cohort/study	Alleles tested	Outcome definition	Summary of findings
Goetz *et al.* cohort:[83] Goetz *et al.* 2007,[83] 2009[110]	**4*	DFS: time from randomisation to documentation of the first of the following events: any recurrence (local, regional or distant) of breast cancer, a contralateral breast cancer, a second primary cancer or death from any cause	*Cox HR (unadjusted), DFS:* HR 1.52; 95% CI 0.93 to 2.49; $p=0.097$ *Cox HR (adjusted for tumour size and nodal status), DFS:* HR 1.40; $p=0.10$ (longer-term follow-up)
		RFS: time from randomisation to documentation of the first of the following events: any recurrence (local, regional or distant) of breast cancer, a contralateral breast cancer or death	*Cox HR (unadjusted), RFS:* HR 1.63; 95% CI 0.95 to 2.78; $p=0.075$
		TTR: the time from randomisation to documentation of a breast event, where a breast event is any recurrence (local, regional or distant) of breast cancer or the documentation of contralateral breast cancer (including ductal carcinoma in situ)	*Cox HR (unadjusted), TTR:* HR 1.40; 95% CI 0.68 to 3.05; $p=0.337$ *Cox HR (adjusted for tumour size and nodal status), TTR:* HR 1.80; $p=0.08$ (longer-term follow-up)

appear similar). It should be noted that patients from two[83,96] of these cohorts were actually included in the other.[108] The fourth cohort[92] appeared to differ from these other cohorts in a number of ways: nearly one-fifth (19%) of all patients were African American; only three-fifths (59%) of women were postmenopausal and two-thirds (67%) had ER+ breast cancer. Over twice as many women were LN+ [four-fifths (79%) compared with no more than one-third in the other cohorts (31–36%)] and 5% had stage IV breast cancer (metastatic disease) compared with no patients in the other cohorts. Finally, this cohort permitted adjuvant chemotherapy, unlike the other three cohorts. However, these cohort characteristics do include data on patients in a control group who did not receive anti-oestrogen therapy.

While three[83,96,108] of the cohorts (all with similar cohort characteristics) presented a HR suggesting a slight increase in OS and the other[92] suggested an improved outcome for PMs; none of the differences was statistically significant (*Table 12*). This cohort[92] also compared HRs between patients taking TAM and those who were not; the HRs were similar in both groups, suggesting that genotype is not associated with disease and **4* is not associated with response in this TAM-treated cohort.

Relapse/recurrence

Eight cohorts[83,86,92,96,99,100,108,109] comparing PM + IM with EM reported on a number of relapse/recurrence outcomes. Ostensibly, two cohorts[83,108] reported on DFS, two[96,108] on event-free survival (EFS), two[92,109] on RFS, one[100] on distant RFS, one on recurrence-free time (RFT)[108] and one on TTR.[108] However, it is apparent from *Table 13* that definitions of the same end point varied from study to study and, moreover, in some instances, definitions of one end point in one cohort seemed to match those of another end point in another. For example, the definitions of EFS and RFT used in Schroth *et al.*[96] appear similar to those of DFS and RFS (respectively) used in the Goetz *et al.* cohort.[83]

The majority of these studies include a majority (> 85%) of postmenopausal women and the majority include a majority (> 97%) of women with ER+ breast cancer, the exceptions being Nowell *et al.*,[92] in which a significant minority of patients in this cohort were neither postmenopausal (41%) nor had ER+ breast cancer (33%) and the Wegman *et al.*[100] study, in which

TABLE 12 Summary of OS in patients taking TAM in relation to CYP2D6 status: PM+IM versus EM

Cohort/study	Alleles tested	Outcome definition	Summary of findings
Goetz *et al.* cohort,[83] Goetz *et al.* 2007[83]	**4*	Time from registration to death from any cause	*Cox HR (adjusted for tumour size and nodal status):* HR 1.34; 95% CI 0.83 to 2.16; $p=0.223$
Nowell *et al.* 2005[92]	**3, *4, *6* Only **4* used for the analysis	Time from diagnosis to death or last contact	*Cox HR (adjusted for the age, stage with nodal status at diagnosis, race, ER status and PgR status):* TAM: HR 0.77; 95% CI 0.32 to 1.81; $p=0.51$ No TAM: HR 0.79; 95% CI 0.42 to 1.26; $p=0.26$
Schroth *et al.* 2007[96]	**4, *5, *10, *41* **3, *6, *7* and **8* were also genotyped for but excluded because PCR amplification rates were poor	Time from surgery to death from any cause	*Cox HR (adjusted for tumour size and nodal status):* HR 1.73 95% CI 0.88 to 3.41; $p=0.11$
Schroth *et al.* 2009[108]	**3, *4, *5, *10, *41, wt×2, *2×2*	Time from registration to death from any cause	*Cox HR (unadjusted):* HR 1.13; 95% CI 0.88 to 1.47; $p=0.34$ *Cox HR (adjusted for tumour size, nodal status and histological grade and stratified by menopause status and mode of patient recruitment):* HR 1.15; 95% CI 0.88 to 1.51; $p=0.32$

No TAM, no tamoxifen treatment; PCR, polymerase chain reaction; PgR, progesterone receptor.

69% were ER+ (although analysis in this study was confined to those who were ER+). Alongside two other cohorts,[83,86] Wegman *et al.*[100] also had a majority (> 62%) of patients who were LN+, unlike the other cohorts, in which these were a minority (31–45%). Another noticeable difference about the Wegman *et al.* cohort[100] was that patients received 40 mg/day TAM for 2 years instead of the standard 20 mg/day for 5 years, and patients were permitted adjuvant chemotherapy. One other cohort[99] also reported a dose that was different to the standard (20 or 40 mg/day for 2 or 5 years) and two other cohorts[92,109] also permitted adjuvant chemotherapy. It should be noted that three cohorts[86,96,108] did not provide data on drug dose/duration and two[86,99] did not present information about adjuvant chemotherapy. Three cohorts[83,86,109] explicitly stated that they adjusted for CYP2D6 inhibitors in derivation of phenotype. Comparison of tumour size was possible only for those cohorts presenting data on tumour size ≥ 2 cm, where the proportion of women varied from 47%[108] to 72%.[99]

Five of the cohorts[83,86,96,108,109] reported statistically significantly more favourable outcomes for EMs than for PM + IMs in terms of relapse/recurrence (see *Table 13*), although the magnitude of the difference in terms of the HR was modest (between 1.6 and 3.5). Interestingly, a significant difference for RFS was found only in Thompson *et al.*[109] when comprehensive testing (i.e. genotyping using the AmpliChip) was conducted instead of just testing for a limited number of common alleles. This study was also able to consider the impact of adherence by reclassifying those with poor adherence as PMs. The difference between the two groups remained statistically significant, with the HR increasing to 3. Three cohorts[92,99,100] suggested PMs to have equal or improved outcomes in terms of RFS and distant RFS, although the findings were not statistically significant in any of the cohorts. As noted above, in two of these cohorts[99,100] the dose of TAM was known to be greater and duration of treatment shorter in some if not all of these patients than is standard, and a greater proportion of patients were also LN+ than in the other cohorts (although the authors did adjust for these as well as presenting unadjusted results).

TABLE 13 Summary of relapse/recurrence in patients taking TAM in relation to CYP2D6 status: PM + IM versus EM

Cohort/study	Alleles tested	Outcome definition	Summary of findings
Nowell *et al.* 2005[92]	**3, *4, *6* Only **4* used for the analysis	RFS: not reported	*Cox HR (adjusted for the age, stage with nodal status at diagnosis, race, ER status and PgR status), RFS:* TAM: HR 0.67; 95% CI 0.33 to 1.35; $p = 0.19$ No TAM: HR 0.69; 95% CI 0.40 to 1.18; $p = 0.19$
Goetz *et al.* cohort:[83] Goetz *et al.* 2007[83]	**4*	DFS: time from randomisation to documentation of the first of the following events: any recurrence (local, regional or distant) of breast cancer, a contralateral breast cancer, a second primary cancer or death from any cause	*Cox HR (adjusted for tumour size and nodal status), DFS:* HR 1.60; 95% CI 1.06 to 2.43; $p = 0.027$
		RFS: time from randomisation to documentation of the first of the following events: any recurrence (local, regional or distant) of breast cancer, a contralateral breast cancer or death	*Cox HR (adjusted for tumour size and nodal status), RFS:* HR 1.74; 95% CI 1.10 to 2.74; $p = 0.017$
		TTR: the time from randomisation to documentation of a breast event, where a breast event is any recurrence (local, regional or distant) of breast cancer or the documentation of contralateral breast cancer (including ductal carcinoma in situ)	*Cox HR (adjusted for tumour size and nodal status), TTR:* TTR: HR 1.91; 95% CI 1.05 to 3.45; $p = 0.034$
Wegman *et al.* 2005[100]	**4*	Distant RFS: not reported	*Distant recurrence rate ratio adjusted for age, tumour size, LN status), ER+ patients, TAM vs no TAM:* *wt/wt*: RR 0.91; 95% CI 0.53 to 1.57; $p = 0.75$ **4/*4 + wt/*4*: RR 0.28; 95% CI 0.11 to 0.74; $p = 0.008$
Gonzalez-Santiago *et al.* cohort:[86]	**4*		
Gonzalez-Santiago *et al.* 2006[85]		Relapse: not reported	*Cox HR (adjusted for unspecified variables), relapse:* HR 3.48; 95% CI 1.1 to 10.7; $p = 0.029$
Gonzalez-Santiago *et al.* 2007[86]		Recurrence: not reported	*Cox HR (adjusted for disease stage), RFS:* HR 2.82, 95% CI 1.0 to 7.9; $p = 0.049$
Schroth *et al.* 2007[96]	**4, *5, *10, *41* **3, *6, *7* and **8* were also genotyped for but excluded because PCR amplification rates were poor	EFS: time from surgery to the occurrence of either local or distant recurrence, contralateral breast cancer or death from any cause	*Cox HR (adjusted for tumour size and nodal status), EFS:* HR 1.89; 95% CI 1.10 to 3.25; $p = 0.02$
		RFT: time from surgery to the occurrence of a breast event (i.e., local or distant recurrence or contralateral breast cancer)	*Cox HR (adjusted for tumour size and nodal status), RFT:* HR 2.24; 95% CI 1.16 to 4.33; $p = 0.02$ Differences in RFT were not observed in the control group

continued

TABLE 13 Summary of relapse/recurrence in patients taking TAM in relation to CYP2D6 status: PM + IM versus EM *(continued)*

Cohort/study	Alleles tested	Outcome definition	Summary of findings
Wegman *et al.* 2007[99]	**4*	RFS: not reported	*Cox HR (unadjusted), RFS:* 2 years of TAM ($n=103$): HR 0.87; 95% CI 0.38 to 1.97; $p=0.74$ 5 years of TAM ($n=108$): HR 0.33; 95% CI 0.08 to 1.43; $p=0.14$ *Cox HR (adjusted for TAM duration, tumour stage, tumour size and LN status):* 'No differences could be seen'
Schroth *et al.* 2009[108]	**3, *4, *5, *10, *41, wt×2, *2×2*	DFS: time to first occurrence of a breast event, a second non-breast primary cancer or death from any cause EFS: time to the first occurrence of a breast event or death from any cause TTR: time from diagnosis or randomisation to documentation of a breast event, any local, regional or distant recurrence of breast cancer or a contralateral breast cancer	*Cox HR (unadjusted), DFS:* HR 1.31; 95% CI 1.06 to 1.61; $p=0.02$ *Cox HR (adjusted for tumour size, nodal status and histological grade and stratified by menopause status and mode of patient recruitment), DFS:* HR 1.29; 95% CI 1.03 to 1.61; $p=0.02$ *Cox HR (unadjusted), EFS:* HR 1.35; 95% CI 1.08 to 1.68; $p=0.07$ *Cox HR (adjusted for tumour size, nodal status and histological grade and stratified by menopause status and mode of patient recruitment), EFS:* HR 1.33; 95% CI 1.06 to 1.68; $p=0.01$ *Cox HR (unadjusted), TTR:* HR 1.57; 95% CI 1.18 to 2.08; $p=0.02$
Thompson *et al.* 2009;[109] $n=618$	Comprehensive testing: **1–*10AB, *11, *14A, *14B, *15, *17, *19, *20, *25, *26, *29–*31, *35, *36, *40, *41, *1×N, *2×N, *4×N, *10×N, *17×N, *35×N, *41×N* Limited testing: **4,*5,*10,*41*	RFS: locoregional recurrence, DCIS, distant metastases, contralateral DCIS or death due to breast cancer	*Cox HR (adjusted for tumour size and nodal status), RFS:* *All women* Comprehensive testing:[a] HR 1.52; 95% CI 0.98 to 2.36; $p=0.06$ Limited testing:[a] HR 1.03; 95% CI 0.67 to 1.58; $p=0.88$ *Postmenopausal* Comprehensive testing:[a] HR 1.96; 95% CI 1.05 to 3.66; $p=0.04$ Limited testing:[a] HR 1.26; 95% CI 0.74 to 2.16; $p=0.88$ Taking into account adherence:[b] HR 3.02; 95% CI 1.07 to 8.47; $p=0.04$

DCIS, ductal carcinoma in situ; *N*, number of copies of the allele; PCR, polymerase chain reaction; PgR, progesterone receptor; RR, relative risk.
a Comprehensive testing was genotyping with the AmpliChip; limited testing was testing for four common alleles: **4, *5, *10 and *41.*
b Patients with an adherence index < 80% were assigned to PM + IM group.

Three cohorts[92,96,100] also included a control group of patients not taking TAM (but receiving adjuvant chemotherapy and/or radiotherapy or no drug treatment). Wegman *et al.*[100] reported that patients with the **4* allele taking TAM still had a better distant RFS than those in the control group (relative risk 0.28, 95% CI 0.11 to 0.74; $p=0.0089$). In Nowell *et al.*,[92] the HRs in the control group were similar to those in the TAM group, whereas, in Schroth *et al.*,[96] it was stated that significant differences between PM + IMs and EMs found in the TAM group were not found in the control group.

Poor metaboliser versus extensive metaboliser plus intermediate metaboliser

Three cohorts[82,83,91] examined differences between PMs and EM + IMs, including the large ITPC study.[82] Different alleles were genotyped for in each cohort (**4*,[83] **3*, **4* and **5*[91]) and different alleles at different study sites in the ITPC study.[82] Only one of the studies[91] adjusted for CYP2D6 inhibitors in deriving the phenotype.

There was no evidence of a difference in OS or relapse/recurrence between PMs and EMs + IMs in any of the three cohorts.[82,83,91]

Overall survival

Three cohorts[82,83,91] reported on OS (*Table 14*). Two of these cohorts included only postmenopausal women with ER+ breast cancer,[82,83] the other cohort[91] included women of any menopausal status and in which 77% had ER+ breast cancer. Differences in cohort characteristics between PMs and the other phenotypes were noted in two[83,91] of these cohorts, where a greater proportion of PMs had tumour size ≥ 3 cm and were LN+.

No significant differences were found in any cohort when the HR between groups was adjusted for nodal status. The only study[84] reporting an unadjusted analysis also reported no significant differences between the two groups. However, a subgroup analysis of *BRCA* status by Newman *et al.*[91] reported a significantly worse median OS in patients with *BRCA2* mutations and low CYP2D6 activity (adjusted HR 9.7; 95% CI 2.3 to 41.0; $p = 0.008$). A formal test of the interaction showed that this difference between *BRCA1* and *BRCA2* patients was significant between the two groups for survival ($p = 0.022$ after adjustment for nodal status) and remained significant when also adjusted for ER status. Importantly, when the entire ER+ group was considered, CYP2D6

TABLE 14 Summary of OS in patients taking TAM in relation to CYP2D6 status: PM versus EM + IM

Cohort/study	Alleles tested	Outcome definition	Summary of findings
Goetz *et al.* cohort:[83] Goetz *et al.* 2005[84]	**4, *6* Only **4* used for the analysis	Time from registration to death from any cause	*Cox HR (unadjusted):* HR 1.73; 95% CI 0.79 to 3.76; $p = 0.169$ *Cox HR (adjusted for tumour size and nodal status):* HR 1.12; 95% CI 0.50 to 2.50; $p = 0.78$
Newman *et al.* 2008[91]	**3, *4, *5, *41*	Not reported	*Cox HR (adjusted for nodal status):* HR 2.5; 95% CI 0.8 to 8.2; $p = 0.17$ *BRCA1* HR 0; 95% CI NA; $p = 0.18$ *BRCA2* HR 9.7; 95% CI 2.3 to 41.0; $p = 0.008$
Goetz *et al.* 2009[82] on behalf of the ITPC; $n = 2880$[a]	Varies by ITPC site but all genotyped for **4* and the majority genotyped for **3, *5, *6, *10, *17, *41* 1168/2880 tested for **1–*10AB, *11, *14A, *14B, *15, *17, *19, *20, *25, *26, *29–*31, *35, *36, *40, *41, *1 × N, *2 × N, *4 × N, *10 × N, *17 × N, *35 × N, *41 × N*	Not reported	Not known *Cox HR adjusted for positive nodes and project sites:* HR 0.92 ($p = 0.50$)

N, number of copies of the allele; NA, not applicable.

a Data taken from Microsoft PowerPoint presentation given at the 32nd Annual San Antonio Breast Cancer Symposium, San Antonio, TX, 11 December 2009.

status was not associated with outcome, but the positive association persisted in ER+ patients in the *BRCA2* tumour group.

Relapse/recurrence

One cohort[82] reported on DFS, two cohorts[83,91] reported on RFS and one[91] of these also reported on TTR (*Table 15*). Two[82,83] of these cohorts included only postmenopausal women with ER+ breast cancer, the other cohort[91] included 77% with ER+ breast cancer and women of any menopausal status. In the Goetz *et al.* cohort[83] there was a greater proportion of PMs than EMs + IMs with tumour size ≥ 3 cm and who were LN+.

When an unadjusted HR was presented, the Goetz *et al.* cohort[83] reported significantly worse RFS for PMs than for EMs + IMs. However, when the HR was adjusted for tumour size and nodal status, no significant differences were reported. The large ITPC cohort[82] reported no significant differences in DFS, whereas in the other cohort[91] significant differences in RFS and TTR were apparent only in the subgroup of patients with *BRCA2* mutations.

Asian patients genotyped for the **10* allele

Four cohorts[93,97,101,114] studied associations between efficacy and CYP2D6 status in which only the **10* allele was genotyped for in three cohorts[93,97,101] and additional common alleles in the other.[114] These four cohorts[93,97,101,114] prohibited the concomitant use of CYP2D6 inhibitors.

TABLE 15 Summary of relapse/recurrence in patients taking TAM in relation to CYP2D6 status: PM versus EM + IM

Cohort/study	Alleles tested	Outcome definition	Summary of findings
Goetz *et al.* cohort:[83] Goetz *et al.* 2005[84]	**4, *6* Only **4* used for the analysis	RFS: time from randomisation to documentation of the first of the following events: any recurrence (local, regional or distant) of breast cancer, a contralateral breast cancer or death	*Cox HR (unadjusted), RFS:* HR 2.71; 95% CI 1.15 to 6.41; $p = 0.023$ *Cox HR (adjusted for tumour size and nodal status):* HR 1.85; 95% CI 0.76 to 4.52; $p = 0.176$
Newman *et al.* 2008[91]	**3, *4, *5, *41*	RFS: time from surgery to first of the following events: any recurrence (local, regional or distant) of breast cancer, a contralateral breast cancer or death TTR: time to tumour recurrence with contralateral, ipsilateral or metastatic disease	*Cox HR (adjusted for nodal status), RFS:* All patients: HR 1.9; 95% CI 0.8 to 4.8; $p = 0.19$ *BRCA1*: HR 1.1; 95% CI 0.2 to 5.5; $p = 0.90$ *BRCA2*: HR 3.6; 95% CI 0.9 to 13.4; $p = 0.094$ *Cox HR (adjusted for nodal status), TTR:* All patients: HR 2.1; 95% CI 0.84 to 5.4; $p = 0.14$ *BRCA1*: HR 1.3; 95% CI 0.3 to 6.2; $p = 0.73$ *BRCA2*: HR 3.8; 95% CI 1.0 to 14.5; $p = 0.083$
Goetz *et al.* 2009 on behalf of the ITPC;[82] $n = 2880$[a]	Varies by ITPC site but all genotyped for **4* and the majority genotyped for **3, *5, *6, *10, *17, *41* 1168/2880 tested for **1–*10AB, *11, *14A, *14B, *15, *17, *19, *20, *25, *26, *29–*31, *35, *36, *40, *41, *1 × N, *2 × N, *4 × N, *10 × N, *17 × N, *35 × N, *41 × N*	Not reported	*Cox HR adjusted for positive nodes and project sites, DFS* HR 1.07 ($p = 0.51$)

N, number of copies of the allele.

a Data taken from Microsoft PowerPoint presentation given at the 32nd Annual San Antonio Breast Cancer Symposium, San Antonio, TX, 11 December 2009.

There was no convincing evidence of differences by genotypes for OS, breast cancer mortality or relapse/recurrence in any of the four cohorts of Asian patients genotyped for the **10* allele.[93,97,101,114]

Overall survival

One cohort[97] examining only OS genotyped for **10* (*Table 16*). The Kaplan–Meier curve suggests that **10/*10* may have had a slightly improved OS compared with *wt/*10* or *wt/wt*, but differences were not statistically significant. In this cohort, the majority (96%) of patients had ER+ breast cancer and 48% had a tumour size > 2 cm, but it was reported that a greater proportion (59%) of patients with the *wt/wt* genotype had a tumour > 2 cm. No patients in this cohort were LN+. It was not known how many, if any, women were postmenopausal or received adjuvant chemotherapy or CYP2D6 inhibitors.

Breast cancer mortality

Two[97,101] cohorts of Asian patients were examined for breast cancer mortality by **10* genotypes (*Table 17*). The majority of women had ER+ breast cancer in both cohorts, although this varied from 82% to 96%. Three-quarters of women in Xu *et al.*[101] were postmenopausal; these data were not reported in the other cohort.[97] While the proportion of patients with tumour size ≥ 2 cm varied in the cohorts (from 27% to 48%), few if any patients were LN+ (0–7%). Adjuvant chemotherapy was not permitted in Xu *et al.*;[101] it was unclear if patients received this in the other cohort.[97] Interestingly, in one cohort a greater proportion (32%) of patients with the **10/*10* genotype than other genotypes had tumours ≥ 2 cm, whereas in the other cohort[97] a greater proportion (59%) of patients with the *wt/wt* genotype had a tumour size > 2 cm.

The findings are summarised in *Table 17*. While Xu *et al.*[101] suggested that, compared with *wt/wt + wt/*10*, breast cancer mortality was higher for women with the **10/*10* genotype, the CIs were wide and the finding was not statistically significant. From the Kaplan–Meier curve, the other cohort suggested that **10/*10* patients may actually have improved mortality from breast

TABLE 16 Summary of OS in patients taking TAM in relation to CYP2D6 status: Asian patients genotyped for only the **10* allele

Cohort/study	Alleles tested	Outcome definition	Summary of findings
Toyama *et al.* 2009[97]	**10*	Interval from the date of primary surgery to death from any cause	It is stated that no associations were found between the **10* genotype and OS. No HRs have yet been calculated (Tatsuya Toyama, personal communication)

TABLE 17 Summary of breast cancer mortality in patients taking TAM in relation to CYP2D6 status: Asian patients genotyped for the **10* allele

Cohort/study	Alleles tested	Outcome definition	Summary of findings
Xu *et al.* 2008[101]	**10*	Time from date of diagnosis to death where breast cancer was the primary or underlying cause of death	Cox HR (adjusted for age, clinical stage, LN status, tumour size, adjuvant therapy, surgery, C-erbB2 status, and ER or progesterone receptor) **10/*10* vs *wt/wt + wt/*10:* HR 2.7; 95% CI 0.4 to 17.3; $p = 0.28$ No TAM ($n = 141$) *CYP2D6 *10* genotype was not significantly associated with breast cancer mortality ($p = 0.78$)
Toyama *et al.* 2009[97]	**10*	Time from the date of primary surgery to death from breast cancer recurrence	It is stated that no associations were found between the **10* genotype and breast cancer mortality. No HRs have yet been calculated (Tatsuya Toyama, personal communication)

cancer when compared with patients with either the *wt/wt* or *wt/*10* genotypes, but again the findings were not statistically significant.

One cohort also compared breast cancer mortality in patients taking TAM with a control group of patients receiving chemotherapy, the majority of whom had ER– breast cancer. As with patients taking TAM, there was no significant association between patients with **10* alleles and DFS in this group, suggesting that **10* is not a prognostic factor for breast cancer independent of TAM.

Relapse/recurrence

Five studies[88,93,97,101,114] from four cohorts[93,97,101,114] reported on relapse/recurrence outcomes. Ostensibly two cohorts[97,101] reported on DFS and two[93,114] reported on RFS, although, as can be seen in *Table 18*, the outcome definitions were very similar for both DFS and RFS.

TABLE 18 Summary of relapse/recurrence in patients taking TAM in relation to CYP2D6 status: Asian patients genotyped for the **10* allele

Cohort/study	Alleles tested	Outcome definition	Summary of findings
Kiyotani *et al.* cohort:[114] Kiyotani *et al.* 2008[88]	**4, *5, *6, *10, *14, *18, *21, *41*	RFS: the period between surgical treatment to the recurrence of a breast cancer (i.e. local or distant recurrence or contralateral breast cancer)	*Cox HR (unadjusted), RFS:* **10/*10* vs *wt/*10*: HR 2.19; 95% CI 0.24 to 19.79; $p=0.49$ **10/*10* vs *wt/wt*: HR 8.67; 95% CI 1.06 to 71.09; $p=0.036$ *Cox HR (adjusted for tumour size), RFS:* **10/*10* vs *wt/wt*: HR 10.04; 95% CI 1.17 to 86.27; $p=0.044$
Kiyotani *et al.* 2010[114]	In Kiyotani *et al.* 2010[114] also genotyped for **36*		*Cox HR (adjusted for tumour size and nodal status), RFS:* *wt/*10* vs *wt/wt*: HR 4.44; 95% CI 1.31 to 15.00 **10/*10* vs *wt/wt*: HR 9.52; 95% CI 2.79 to 32.45; $p<0.001$
Xu *et al.* 2008[101]	**10*	DFS: time from date of diagnosis to first distant metastasis or death from breast cancer without a recorded relapse	*Cox HR (adjusted for age, clinical stage, LN status, tumour size, adjuvant therapy, surgery, C-erbB2 status, and ER or PgR):* TAM: **10/*10* vs *wt/wt+ wt/*10*: HR 4.7; 95% CI 1.1 to 20.0; $p=0.04$ No TAM: *CYP2D6 *10* genotype was not significantly associated with DFS ($p=0.99$)
Okishiro *et al.* 2009[93]	**10*	RFS: distant recurrences, locoregional recurrences, ipsilateral in-breast recurrences, and contralateral breast cancers were included	*Cox HR (unadjusted):* **10/*10* vs. *wt/wt+ wt/*10*: HR 0.94; 95% CI 0.34 to 2.60; $p=0.95$ *Cox HR (adjusted for tumour size, LN status, histological grade, PgR status, HER2 status and adjuvant therapy)* **10/*10* vs. *wt/wt+ wt/*10*: HR 0.6; 95% CI 0.18 to 1.92; $p=0.39$
Toyama *et al.* 2009[97]	**10*	DFS: time from the date of primary surgery to the first locoregional recurrence, distant metastasis, ipsilateral breast recurrence or contralateral breast cancers	It is stated that no associations were found between the **10* genotype and DFS. No HRs have yet been calculated (Tatsuya Toyama, personal communication)

PgR, progesterone receptor.

The proportion of postmenopausal women in each cohort differed, varying from 22% to 76% in the three[93,101,114] cohorts that reported these data. In all cohorts, the majority of women had ER+ breast cancer, although this varied from 74% to 82% in two[101,114] cohorts to 91–96% in the other two.[93,97] Differences also existed for tumour size and nodal status, the proportion of women with tumours ≥ 2 cm varying from 27% to 48% and LN+ patients varying from 0% to 17%, although nodal status was not reported in one cohort.[93] Three[93,101,114] of the studies explicitly excluded patients with CYP2D6 inhibitors, and two[101,114] did not allow adjuvant chemotherapy, these data not being reported in the other cohort(s). There were, however, some differences within cohorts by genotype in the three[93,97,101] cohorts that reported these data. In one cohort, a greater proportion (32%) of patients with the **10/*10* genotype had tumours ≥ 2 cm, whereas, in the other,[97] a greater proportion (59%) of patients with the *wt/wt* genotype had a tumour > 2 cm. No such differences were apparent in the third cohort,[93] although 90% of patients with the **10/*10* genotype had ER+ cancer compared with 60% with the other genotypes.

Compared with other genotypes, all four cohorts[93,97,101,114] suggest that there may be modestly poorer outcomes in terms of DFS and RFS for patients with the **10/*10* genotype, but CIs are extremely wide and a significant difference was reported in only one[114] of these cohorts. This cohort still reports wide CIs, suggesting that the finding should be treated with caution.

One cohort also compared DFS in patients taking TAM with a control group of patients receiving chemotherapy, the majority of whom had ER– breast cancer. As with patients taking TAM, there was no significant association between patients with **10* alleles and DFS in this group, suggesting that **10* is not a prognostic factor for breast cancer independent of TAM.

Other genotype/phenotype/functional classification comparisons

Three cohorts[41,96,108] reported outcomes by phenotypes that do not fit the 'standard comparisons' explored above. Unlike all of the other studies that genotyped for multiple alleles, two[96,108] of these cohorts were unique in differentiating between patients who could be classified as IMs and those who could be classified as heterozygous EMs (hetEMs). Thus, in these cohorts, both the IMs and hetEMs would be considered subsets of patients who fit the IM phenotype in other studies. The other cohort[41] conducted two comparisons, the first, which could equate to PMs, IMs and EMs, but then a secondary analysis in which the rationale for combining particular genotypes into two groups (A and B) was less clear.

Summarising the data from the three cohorts is problematic owing to the different genotype/phenotype/functional classifications used, although there was some suggestive evidence that EMs have better relapse/recurrence outcomes than patients with other phenotypes in one of these cohorts.[108]

Relapse/recurrence

One cohort[41] considered DFS by CYP2D6 status by comparing patients in two separate analyses. First, patients were split into three groups. These groups could broadly be considered to be PM, IM and EM in which no significant differences were reported when all were compared with each other, although the authors highlighted the gradual improvement in DFS in function of CYP2D6. The second analysis did report a significant difference between two groups (*Table 19*), although, as discussed above, there appears to be no obvious rationale behind the groupings of genotypes into these two groups. In the other two cohorts,[96,108] RFT was significantly worse for IM + PMs (in effect, a subset of PM + IMs using the 'standardised comparisons' above) and also worse (but not statistically significant) for hetEMs[96] and TTR was significantly worse for hetEMs + IMs than for EMs.[108] As reported above, using the 'standardised comparisons' of PM + IM versus EM, the HRs were actually greater for both RFT (adjusted HR 2.24; 95% CI 1.16 to 4.33; $p = 0.02$)[96] and TTR (unadjusted HR 1.57; 95% CI 1.18 to 2.08; $p = 0.02$).[108]

TABLE 19 Summary of relapse/recurrence in patients taking TAM in relation to CYP2D6 status: comparisons grouping genotypes in unique ways

Cohort/study	Alleles tested	Outcome definition	Summary of findings
Schroth *et al.* 2007[96]	**4, *5, *10, *41* **3, *6, *7* and **8* were also genotyped for but excluded because PCR amplification rates were poor	RFT was defined as the time from surgery to the occurrence of a breast event (i.e. local or distant recurrence or contralateral breast cancer)	*Cox HR (adjusted for tumour size and nodal status), RFT:* hetEM vs EM:[a] HR 1.88; 95% CI 0.89 to 4.02; $p = 0.09$ IM + PM vs EM:[a] HR 1.63; 95% CI 1.07 to 2.46; $p = 0.02$
Ramon *et al.* 2010[41]	**1–*10AB, *11, *14A, *14B, *15, *17, *19, *20, *25, *26, *29–*31, *35, *36, *40, *41, *1× N, *2× N, *4× N, *10× N, *17× N, *35× N, *41× N*	DFS: calculated from the beginning of therapy to (a) the time of relapse, (b) the appearance of a contralateral breast cancer or (c) death	*Mean DFS (months): three-group analysis*[b] 1: 98 2: 114 3: 118 $p = 0.413$ *Mean DFS (months): two-group analysis*[b] A: 95 B: 119 $p = 0.016$
Schroth *et al.* 2009[108]	**3, *4, *5, *10, *41, wt× 2, *2× 2*	TTR: time from diagnosis or randomisation to documentation of a breast event, any local, regional or distant recurrence of breast cancer or a contralateral breast cancer	*Cox HR (unadjusted), TTR:* hetEM + IM vs EM: HR 1.49; 95% CI 1.12 to 2.00; $p = 0.06$ *Cox HR (adjusted for tumour size, nodal status and histological grade and stratified by menopause status and mode of patient recruitment), TTR:* HR = 1.40; 95% CI 1.04 to 1.90; $p = 0.03$

PCR, polymerase chain reaction.

a The IM + PM group in Schroth *et al.*[96] differs from the decreased group in this same study and it is this decreased group that meets the criteria for the 'standardised comparison' of PM + IM above, hence IM + PM being included here.

b Three-group analysis: 1 = **3, *4, *5/*3, *4, *5*; 2 = **9, *10, *41/*9, *10, *41* or **1, *2, *35/*3, *4, *5, 9, *10, *20, *41*; 3 = **1, *2, *35/*1, *2, *35, *41, *1× N* or **9, *10, *41/*2× N*. Two-group analysis: A, **4/*4, *4/*41, *1/*5, *2/*5*; B, all other genotypes.

Adverse events

Nine studies[41,84,87,90,93–95,98,107] from seven cohorts[41,83,87,90,93,94,98] have considered any AEs in relation to CYP2D6 status (*Table 20*).

The only AEs that appeared to differ by CYP2D6 status in any of the cohorts were hot flushes.[83,87,90] Here EMs and/or IMs appeared to be more prone to suffer hot flushes than PMs,[83,87,90] more prone to experience severe hot flushes[83,87] and more likely to discontinue treatment because of hot flushes.[87]

Adverse event frequency

One cohort[98] did not find a significant difference in the risk of AEs based on presence or absence of the **4* allele.[98] However, the number of patients with the **4/*4* genotype was very small, making comparisons difficult.

Toxicity

Severe, mild and no toxicity were considered in one cohort[90] with regard to CYP2D6 status using an aggregation of genotypes that had produced significant results in relation to DFS, the rationale behind this grouping of genotypes in terms of enzyme function being unclear. No significant relationship between genotype and toxicity was found.

TABLE 20 Summary of AEs in patients taking TAM in relation to CYP2D6 status

Cohort/study	Alleles tested	Summary of findings
Goetz *et al.* cohort:[83] Goetz *et al.* 2005[84]	**4, *6* Only **4* used for the analysis	Incidence of moderate (grade 2) or severe (grade 3) hot flushes, *n* (%): ■ **4/*4*: 0/13 (0) ■ *wt/*4*: 9/40 (23) ■ *wt/wt*: 27/137 (20) For *CYP2D6 *4/*4* patients, 0 (0%) of 13 patients experienced grade 2 or 3 hot flushes compared with 36 (20%) of 177 patients with the *wt/wt* or *wt/*4* genotypes ($p = 0.064$)
Henry *et al.* cohort:[87] Henry *et al.* 2009,[87] 2009[107]	**1*10AB, *11, *14A, *14B, *15, *17, *19, *20, *25, *26, *29–*31, *35, *36, *40, *41, *1 × N, *2 × N, *4 × N, *10 × N, *17 × N, *35 × N, *41 × N*	The authors did not observe a statistically significant association between the *CYP2D6* genotype and either baseline BMD or percentage change in BMD (data not presented in the paper) *Change in hot flush score*: ■ EM: 26.9 ± 8.8 ■ IM: 44.3 ± 10.2 ■ PM: 20.6 ± 16.9 IM significantly higher than EM ($p = 0.011$) and PM ($p = 0.038$) *Change in hot flush score,*[a] *ITT analysis*: ■ EM: 25.3 ± 4.7 ■ IM: 41.8 ± 6.2 ■ $p = 0.040$ Trend suggesting that EMs and PMs were more likely to remain free of hot flushes during TAM therapy than IMs ($p = 0.100$ and $p = 0.089$, respectively) *Severity,* n *(%)*: EM ■ no hot flushes: 50/208 (24.0) ■ mild/moderate: 96/208 (46.2) ■ severe/very severe: 62/208 (29.8) PM + IM ■ no hot flushes: 9/21 (42.9) ■ mild/moderate: 10/21 (47.6) ■ severe/very severe: 2/21 (9.5)
Rae *et al.* 2009[95]		Significant correlation between increasing CYP2D6 score and drug discontinuation due to side effects ($r^2 = 0.935$, $p = 0.018$) Adjustment of scores for concomitant medications that alter CYP2D6 activity eliminated the relationship between CYP2D6 score and treatment discontinuation rates
Wang *et al.* 2007[98]	**4*	Risk of AE by **4* status ■ OR = 1.9 to 8.0; $p = 0.1$ to 0.6
Madlensky *et al.* 2008[90]	**1–*10AB, *11, *14A, *14B, *15, *17, *19, *20, *25, *26, *29–*31, *35, *36, *40, *41, *1 × N, *2 × N, *4 × N, *10 × N, *17 × N, *35 × N, *41 × N*	*Hot flushes*: ■ EM: 79.8% ■ hetEM: 76.3 ■ IM: 80.1 ■ PM: 63.9 ■ UM: 75% ■ $\chi^2 = 11.3$; $p = 0.02$) After controlling for age, menopausal status and time since diagnosis, the PM group was half as likely to report hot flushes as the referent EM group (OR 0.46; 95% CI 0.28 to 0.78; $p = 0.003$)

continued

TABLE 20 Summary of AEs in patients taking TAM in relation to CYP2D6 status *(continued)*

Cohort/study	Alleles tested	Summary of findings
Okishiro *et al.* 2009[93]	**10*	There was no significant difference in the extent of changes in BMD and total cholesterol concentrations between patients with the **10/*10* genotype and those with the *wt/w+ wt/*10* genotype
Onitilo *et al.* 2009[94]	**4*	**4/+ *4+ wt/*4* was compared with *wt/wt*. No significant difference in time to deep-venous thrombosis was noted ($p=0.3$)
Ramon *et al.* 2010[41]	**1–*10AB, *11, *14A, *14B, *15, *17, *19, *20, *25, *26, *29–*31, *35, *36, *40, *41, *1×N, *2×N, *4×N, *10×N, *17×N, *35×N, *41×N*	*No toxicity* n *(%):* ■ A (**4/*4, *4/*41, *1/*5, *2/*5*): 6/16 (37.5) ■ B (all other genotypes): 40/75 (53.3) *Mild toxicity* n *(%):* ■ A (**4/*4, *4/*41, *1/*5, *2/*5*): 7/16 (43.8) ■ B (all other genotypes): 27/75 (36.0) *Severe toxicity* n *(%):* ■ A (**4/*4, *4/*41, *1/*5, *2/*5*): 3/16 (18.8) ■ B (all other genotypes): 8/75 (10.7) ■ $p=0.2$

BMD, bone mineral density; ITT, intention to treat; *N*, number of copies of the allele; OR, odds ratio.
a Summary of hot flush frequency and severity.

Deep-venous thrombosis

One cohort[94] considered deep-venous thrombosis by CYP2D6 status. Patients were genotyped for **4* and it was reported that there was no difference in time to deep-venous thrombosis between patients with the **4/*4 + wt/wt* genotypes and those with the *wt/wt* (EM).

Bone mineral density

Two cohorts[87,93] examined the association between bone mineral density (BMD) and genotype. Whether patients were simply genotyped for **10*[93] (and those with the **10/*10* genotype were compared with those with the *wt/wt + wt/*10* genotype) or whether a greater number of polymorphisms were tested,[87] both studies suggest that change in BMD is not related to CYP2D6 status.

Hot flushes

Three cohorts[83,87,90] examined hot flushes. It was found in one cohort that, after controlling for age, menopausal status and time since diagnosis, PMs were half as likely as EMs to report hot flushes.[90] Another cohort[107] suggested that IMs (as defined using an 'activity score'[118]) may be more prone to hot flushes than either EMs or PMs. This cohort also found that PMs were less likely than EMs + IMs to develop severe or very severe hot flushes. An earlier cohort[84] found that no patients with the PM phenotype (**4/*4*) developed moderate or severe hot flushes, compared with 20% of those with the EM + IM phenotypes (*wt/wt + wt/*4*), although the number of patients with the PM phenotype was small.

Discontinuation of treatment because of adverse events

In one cohort,[87] it was reported that after 4 months 41/280 (14.6%) patients had discontinued treatment, 28/41 (68.3%) of these because of TAM side effects, most commonly as a result of hot flushes [13/28 (46.4%)]. None of these patients was found to be a PM. In fact, this study suggests that the greater the CYP2D6 activity, the greater the chance of withdrawal because of AEs, i.e. EMs are the phenotype at greatest risk.

Endoxifen concentrations

There were eight studies[49,73,102,104,105,112–114] from seven cohorts[49,73,87,104,112–114] that examined endoxifen concentrations in relation to *CYP2D6*. Four studies reported mean plasma concentrations[102,105,112,113] and three reported median plasma concentrations.[104,112,114] Two studies reported decreases in endoxifen following the administration of an SSRI (paroxetine).[49,102] In five cohorts[49,73,87,104,114] the TAM dose was known to be 20 mg/day, whereas in Bonanni *et al.*[112] the drug dose was only 10 mg/day as half of the patients receiving TAM in this cohort also received ANA 1 mg/day. In the other cohort[113] the TAM dose was not stated.

The findings from each individual cohort appear to suggest differences in concentrations between PMs[87,104] or those with the **10/*10* genotype[73,114] and EMs (or those with the *wt/wt* genotype). However, in the Caucasian population, one cohort[104] reported the levels for the IMs to be closer to those of EMs than PMs. The other cohort[87] reported *wt/vt* genotypes (which may be equated as IM) to have levels closer to *vt/vt* genotypes. Reduced decreases in mean endoxifen plasma concentrations were also evident in patients taking potent CYP2D6 inhibitors in two cohorts.[49,102]

Genotype studies

Four[49,73,105,114] of the studies examined endoxifen levels in relation to genotype (*Table 21*). The earliest study[49] included in this review examined the decrease in endoxifen concentrations in patients who were also taking the CYP2D6 inhibitor paroxetine. Decreases in endoxifen levels were greatest in patients with the *wt/wt* genotype, which suggests that TAM metabolism is vulnerable to drug interactions with this particular SSRI.

From the other three studies,[73,105,114] it is evident that endoxifen concentrations in patients with the *vt/vt* genotype were lower than in those with the *wt/wt* genotype, regardless of which alleles were tested. In the two cohorts[73,114] of Asian patients, in which **10* was one of the alleles tested and was thus the most common *vt* allele, endoxifen levels in those with the *wt/vt* genotype were nearer to those reported in patients with the *wt/wt* genotype. In US patients, in whom only **3, *4, *5* and **6* were tested, the mean endoxifen concentration in those with the *wt/vt* genotype was nearer to that of patients with the *vt/vt* genotype.[87]

Phenotype studies

Four[102,104,112,113] of the studies examined endoxifen levels in relation to phenotype (*Table 22*). As with the early study by Stearns *et al.*,[49] decreases in endoxifen levels were greatest in patients with the *wt/wt* genotype (i.e. EMs), with potent CYP2D6 inhibitors (such as paroxetine) reducing the amount by which the levels decreased to levels similar to PMs. An interesting finding from this study was that the group of patients with alleles associated with UMs were the only ones who were not converted into PM status by CYP2D6 potent inhibitors.[102]

Two studies[103,113] reported mean or median endoxifen levels to be significantly different between EMs and PMs, with one[103] of these suggesting levels in IMs to be nearer those of EMs than of PMs. The other study[112] did not report significant differences between EMs and PMs; however, in this study, one-third of patients received TAM alone, one-third received ANA alone and one-third received both TAM and ANA. Thus, the TAM dose in this study was lower than is standard (10 mg/week instead of 20 mg/day), which may explain this lack of difference. In addition, this study also considered effects on ANA concentrations from patients taking TAM and this aromatase inhibitor (data not presented in table). While ANA concentrations were not affected by the combination with low-dose TAM, endoxifen levels were lower in patients taking TAM and ANA [median (range) 3.18 (2.22 to 4.32) ng/ml] than those taking TAM alone [4.83 (3.65 to 6.19) ng/ml]. In a further analysis based on the *CYP2D6* genotype, the differences for endoxifen were no longer significant after excluding PMs [median (range) 4.65 (2.07 to 6.49) ng/ml and 4.6 (3.98 to 6.85) ng/ml, respectively).

TABLE 21 Summary of endoxifen concentrations in relation to CYP2D6 status by genotype

Cohort/study	Alleles tested	Summary of findings
Stearns *et al.* 2003[49]	**4, *6, *8*	*Decrease in endoxifen concentrations after taking the CYP2D6 inhibitor paroxetine:* *wt/wt* genotype: 64% (95% CI 39% to 89%) *wt/vt* or *vt/vt* genotype: 24% (95% CI 23% to 71%) $p=0.03$ Where *vt= *4, *6, *8* Baseline plasma endoxifen concentrations were lower in women with **4, *6* or **8* alleles than in those with *wt* ($p=0.002$)
Henry *et al.* cohort:[87] Jin *et al.* 2005[105]	**3, *4, *5, *6*	Mean (range) endoxifen plasma concentrations, ng/ml: *wt/wt:* 78.0 (65.9 to 90.1) *wt/vt*: 43.1 (33.3 to 52.9) *vt/vt*: 20.0 (11.1 to 28.9) $p<0.01$ *vt=*3, *4, *5, *6*
Lim *et al.* 2007[73]	**5, *10, *2× N*	Mean (range) endoxifen plasma concentrations, ng/ml: *wt/wt* ($n=64$): 19.9 (18.0 to 21.9) *wt/*10* ($n=89$): 18.1 (16.8 to 19.5) **10/*10* ($n=49$): 7.9 (7.1 to 8.8) $p<0.0001$ Where *wt*= allele not containing **10* Mean (range) endoxifen plasma concentrations, ng/ml: *wt/wt*: ($n=55$): 20.7 (18.5 to 22.9) *wt/vt* ($n=96$): 18.0 (16.7 to 19.2) *vt/vt* ($n=51$): 8.1 (7.2 to 9.0) $p<0.0001$ Where *wt*= allele not containing **5* and **10*
Kiyotani *et al.* cohort:[114] Kiyotani *et al.* 2010[114]	**4, *5, *6, *10, *14, *18, *21, *36, *41*	Median endoxifen plasma concentrations, ng/ml: *wt/wt* ($n=24$): 35.4 *wt/vt* ($n=45$): 27.2 *vt/vt* ($n=29$): 15.5

N, number of copies of the allele.

Exploratory analysis: clinical sensitivity and specificity

Because of the lack of definitive clinical validity evidence, in particular evidence for differences between groups of patients apparently being complicated depending on which alleles were tested, attempts were made to measure the clinical sensitivity and specificity of testing for particular alleles. This was possible for only nine studies[85,86,88,92,96,99,100,108,114] from seven cohorts[86,92,96,99,100,108,114] that presented data on events in the text or tables.

Exploring the clinical sensitivity and specificity is an approach recommended by Flockhart *et al.*[54] in an American College of Medical Genetics statement that defined clinical sensitivity as 'the proportion of individuals with an event that have a genotype other than *wt/wt* (true positives) and clinical specificity is defined as the proportion of individuals that do not have the event who possess the *wt/wt* genotype (true negatives)'. The same definitions of true positives and

TABLE 22 Summary of endoxifen concentrations in relation to CYP2D6 status by phenotype

Cohort/study	Alleles tested	Summary of findings
Henry *et al.* cohort:[87] Borges *et al.* 2006[102]	**1–*10AB, *11, *14A, *14B, *15, *17, *19, *20, *25, *26, *29–*31, *35, *36, *40, *41, *1×N, *2×N, *4×N, *10×N, *17×N, *35×N, *41×N*	*Decrease in mean (SD) endoxifen plasma concentrations, nmol/l, 12 months:* EM: 84.1 (39.4) PM: 19.4 (6.1) Potent CYP2D6 inhibitors: 24.6 (16.6) Weak CYP2D6 inhibitors: 50.1 (30.4)
Gjerde *et al.* 2007[104]	**3, *4, *5, *6, *2×2*	*Median (range) endoxifen plasma concentrations, ng/ml:* UM: 46.3 (37.6 to 141.4) EM: 52.3 (24.3 to 184.8) IM: 49.6 (27.3 to 108.2) PM: 36.7 (30.7 to 68.6) $p=0.003$ (based on logistic regression analysis in which each variable was adjusted for age)
Bonnanni *et al.* 2009[112]	**2, *3, *4, *5, *6, *9, *29, *41A*	*Median (Q1, Q3) endoxifen concentrations, ng/ml, 6 months:* EM ($n=43$): 4.62 (3.52, 5.62) PM ($n=7$): 5.00 (4.18, 6.79) Median (Q1, Q3) endoxifen concentrations, ng/ml, 12 months: EM ($n=42$): 4.63 (2.98, 6.62) PM ($n=7$): 3.67 (3.03, 5.13)
de Duenas *et al.* 2009[113]	**1–*10AB, *11, *14A, *14B, *15, *17, *19, *20, *25, *26, *29–*31, *35, *36, *40, *41, *1×N, *2×N, *4×N, *10×N, *17×N, *35×N, *41×N*	Mean (SD) plasma concentrations of endoxifen, nmol/l: EM = 21.0 (13.6) PM = 7.7 (1.5) $p=0.029$

N, number of copies of the allele; Q, quartile; SD, standard deviation.

true negatives were thus utilised for this exploratory analysis, although it should be noted that this previous paper by Flockhart *et al.*[54] referred to a test for *CYP2C9* (cytochrome P450 2C9) and *VKORC1* (Vitamin K epoxide reductase complex subunit 1) in relation to treatment with warfarin, and so the assumptions about what constitutes a true positive or true negative may not be directly applicable. However, given that there appears to be the greatest amount of suggestive evidence from our review for differences in clinical outcomes (if not endoxifen concentrations) between EMs (i.e. *wt/wt*) and those with other genotypes, it could be argued that these same assumptions may be appropriate.

Aside from testing for different alleles, there are a number of other notable differences in terms of cohort characteristics across the eight cohorts included in our exploratory analysis. The Kiyotani *et al.* cohort[114] is perhaps the most notably different in that it is a study of Asian patients who appear to have notable differences in terms of nodal status (17% compared with >60% in the majority of the other cohorts). However, other cohorts also stand out as differing from the rest: Nowell *et al.*[92] includes fewer postmenopausal women (59%), allows adjuvant chemotherapy and also includes 5% of women with metastatic disease. Wegman *et al.*[100] also allows adjuvant chemotherapy and has a large proportion of patients who are LN+ (89%) and the TAM dose was 40 mg/day for 2 years. In Wegman *et al.*,[99] the TAM dose was either 20 or 40 mg/day and for some patients again only lasted for 2 years. Schroth *et al.*[96,108] reported the smallest proportion (34%) of women who were LN+ aside from the Kiyotani *et al.* cohort.[114]

Estimates of clinical sensitivity and specificity were made in relation to each of the different outcomes for which we had these data, namely OS, breast cancer mortality and recurrence/relapse. Overall, our exploratory analysis suggested that testing for a greater number of alleles increased specificity but that sensitivity was generally low, no matter how many alleles were genotyped.

Overall survival

Taking into account the differences between the cohorts, the data suggest that the sensitivity and specificity of testing simply for **4* in the adjuvant setting may be 15% and 73%, respectively, for OS[92] (*Table 23*). A more comprehensive genotype test (in terms of the number of alleles tested) appears to increase sensitivity and specificity to 18% and 83%, respectively.[108]

Relapse/recurrence

The data from four cohorts[86,92,99,100] suggest that the sensitivity of testing simply for **4* in the adjuvant setting may be between 21% and 37% for relapse/recurrence and specificity may be between 52% and 86% for relapse/recurrence (*Table 24*). If, in testing for **4*, phenotype status is altered based on concomitant CYP2D6 use, based on a small number of patients ($n = 84$), for relapse/recurrence, sensitivity may be 50% and specificity 73%.[86] Utilising data from the only cohort to test simply for **10* suggests a sensitivity of between 19% and 50% and specificity of between 95% and 96%. If a more comprehensive genotyping strategy is used, data from the largest cohort of Schroth *et al.*[108] and Schroth *et al.*[96] (whose patients are actually included in the Schroth *et al.*[108] cohort) suggest a sensitivity of between 18% and 30% and a specificity of between 86% and 88%.

Summary of clinical effectiveness evidence

No studies were found that explored the relationship between endoxifen levels and clinical outcomes or which considered the clinical utility of *CYP2D6* testing. The clinical validity evidence was thus limited to studies which examined differences in clinical outcome (OS, breast cancer survival, relapse/recurrence and AEs) and endoxifen levels by genotype. Unfortunately, the heterogeneity between studies in terms of patient characteristics, alleles studied, comparisons made and clinical end points defined and measured has made meta-analyses inappropriate and comparisons difficult.

Taking into account these caveats, there is suggestive evidence from six cohorts[83,86,91,96,108,109] that patients with the *wt/wt* genotype (EM phenotype) may have better outcomes in terms of relapse/recurrence than patients with other genotypes. However, three cohorts[83,87,90] suggest that, alongside IMs, these EMs may also be more prone to hot flushes. The findings are confused when endoxifen plasma concentrations in Caucasians are considered. While there are differences in concentrations between patients with *wt/wt* and *vt/vt* genotypes[87] or EM and PM phenotypes,[104]

TABLE 23 Summary of clinical sensitivity and specificity for studies where data available on number of events: OS

Cohort/study; number of patients	Alleles tested	Length of follow-up (years)	Events[a]		Sensitivity (%)	Specificity (%)
			wt/wt	Other		
Nowell *et al.* 2005;[92] 165	**4*	Median 5.4	27/101	7/48	15	73
Schroth *et al.* 2009;[108] 206	**3, *4, *5, *10, *41, wt×2, *2×2*	Median 6.3	132/716	102/609	18	83

a Number of deaths.

TABLE 24 Summary of clinical sensitivity and specificity for studies where data available on number of events: recurrence/relapse

Cohort/study; number of patients	Alleles tested	Length of follow-up (years)	Events[a]		Sensitivity (%)	Specificity (%)
			wt/wt	Other		
Nowell *et al.* 2005;[92] 165	**4*	Median 5.4	38/112	10/48	21	66
Wegman *et al.* 2005;[100] 112	**4*	Mean 10.7	25/52	6/24	25	52
***Gonzalez-Santiago* et al. *cohort*:[86]**						
Gonzalez-Santiago *et al.* 2006;[85] 85	**4*	Median 4	10/49	13/35	37	80
Gonzalez-Santiago *et al.* 2007;[86] 84	**4* accounting for CYP2D6 inhibitors	Mean 5.5	13/48	18/36	50	73
Wegman *et al.* 2007;[99] 677	**4*	Mean 7	103/480	45/137	33	79
***Kiyotani* et al. *cohort*[114]**						
Kiyotani *et al.* 2008;[88] 67	**10*	Median 8	1/20	27/54	50	95
Kiyotani *et al.* 2010;[114] 282	**10*	Median 7.1	3/84	38/198	19	96
Schroth *et al.* 2007;[96] 486	**4, *5, *10, *41*	Median 5.9	17/118	24/79	30	86
Schroth *et al.* 2009;[108] 1361	**3, *4, *5, *10, *41, wt× 2, *2× 2*	Median 6.3	135/609	202/716	18	88

a Number of women who experienced a recurrence/relapse.

one of these cohorts[104] reports that those with the *wt/vt* genotype have levels closer to those with the *wt/wt* genotype and not the *vt/vt* genotype, as would arguably be expected from the suggestive evidence for relapse/recurrence from the aforementioned six cohorts[83,86,91,96,108,109] in which relapse/recurrence outcomes were improved in EMs or, more specifically, compared with PMs + IMs.[83,86,96,108,109] There is no convincing evidence that Asian patients with the **10/*10* genotype have different outcomes to EMs in terms of efficacy or AEs, although there are clear differences in terms of mean and median endoxifen concentrations.

Given the absence of clinical utility studies and our inability to conduct meta-analyses of the clinical validity data, we carried out exploratory analyses of sensitivity and specificity. These were based on data from only a limited number of the cohorts and on the assumption that EMs should be considered separately to all other phenotypes in determining true negatives and true positives. Thus, these data should only be considered as exploratory, highlighting the type of data that may be useful for future studies. Based on the limited data presented here, the cohorts suggest that testing for a greater number of alleles increases specificity but that sensitivity is generally low no matter how many alleles are tested for.

Chapter 4

Assessment of cost-effectiveness

Systematic review of existing cost-effectiveness evidence

A systematic review of the economic literature was conducted to identify the existing evidence that assesses the cost-effectiveness of genotyping for *CYP2D6* for the management of women with breast cancer. It followed the same principles stated in Chapter 3 (see *Methods for reviewing effectiveness*). The search strategies are listed in *Appendix 1*.

Identification of studies

A total of 63 studies were identified from the literature search for evidence relating to the costs and benefits of *CYP2D6* for the management of women with breast cancer. None of these papers met the inclusion criteria of being an economic evaluation comparing TAM with any aromatase inhibitor and genotyped for *CYP2D6.* All excluded studies are listed in *Appendix 2*. However, two of these studies[79,119] conducted a modelling exercise of the pharmacogenetic variation of *CYP2D6* and considered the choice of optimal adjuvant endocrine therapy in women with early ER+ breast cancer (thus conducting a partial evaluation of the research question). Owing to the lack of any other published evidence, we have described both studies below as these studies offer a good starting point for the development of an economic evaluation; it is noted that one of these studies[79] has been presented only as an abstract.

Study characteristics and model overview

Punglia *et al.*[119] undertook a modelling analysis to determine whether TAM or aromatase inhibitor monotherapy maximises DFS after 5 years of treatment. In this model, patients could be genotyped for only the **4* allele and treated with TAM or not genotypically selected and treated with TAM or aromatase inhibitors.

Veenstra *et al.*[79] developed a decision-analytic lifetime Markov model to evaluate pharmacogenetic testing for *CYP2D6* variants to identify postmenopausal women who would be good candidates for alternative therapies. This paper classified women as PMs or EMs; in other words, the authors used the phenotype instead of the genotype to classify patients. The study by Punglia *et al.*[119] classified patients by genotype.

Model inputs and data sources

The Punglia *et al.*[119] model simulates the transition between two states: being well with no evidence of any cancer recurrence ('being well') and having a local or regional recurrence or a new primary breast cancer. Women starting in the 'being well' state face a monthly probability of experiencing a recurrence derived from the annual HRs from the BIG 1-98 trial.[120] The model estimates recurrence probabilities only for each *CYP2D6*4* genotype: *wt/wt*, *wt/*4* and **4/*4*.

The frequencies for any of the genotypes in the population were derived from a study by Goetz *et al.*[84] and so the model used recurrence probabilities weighted for the genotypic frequency. The authors also re-ran the model using new data from a re-analysis of the same cohort of patients,[83] where patients who had received SSRIs were reclassified to allow for a more accurate assessment of the effect of *CYP2D6* on outcomes. A two-way sensitivity analysis was performed to test the uncertainty around the model, varying the HR for patients with the **4/*4* genotype and the HR for patients with the *wt/*4* genotype.

The model briefly defined in the abstract by Veenstra *et al.*[79] consists of six health states and assesses a hypothetical cohort of 64-year-old women with ER+ breast cancer receiving TAM. The incidences of local regional relapse, metastasis and breast cancer death was obtained from the ATAC trial.[21] The HR for disease recurrence in PMs versus EMs was derived from a study by Goetz *et al.* (this study was not referenced in the abstract). Costs, utilities and background mortality rates were obtained from the published literature or publicly available sources.

Results and sensitivity analysis

In the Punglia *et al.* study,[119] the base-case results reported 5-year DFS rates to be 84.0% for patients receiving aromatase inhibitors and 81.3% for those receiving TAM. DFS rates for *wt/wt* patients treated with TAM were 83.9%, i.e. similar to those unselected and treated with aromatase inhibitors. A two-way sensitivity analysis was performed, varying the increased HR for recurrence for **4/*4* patients relative to *wt/wt* patients from 1.0 to 3.0 and the increased HR for recurrence for *wt/*4* patients relative to *wt/wt* patients from 0 to 1.0. The sensitivity analysis found that when a greater HR for **4/*4* patients was used, DFS rates for *wt/wt* patients treated with TAM exceeded those of patients treated with aromatase inhibitors. Thus, the authors concluded that this modelling exercise suggests that *CYP2D6* testing could be considered for women newly diagnosed with breast cancer.

The results presented in the abstract by Veenstra *et al.*[79] are related to the projected DFS at 5 years, which is 81.4% for TAM and 83.3% for ANA compared with 81.0% (TAM) and 83.8% (ANA) from the ATAC trial.[21] These results are confused because it is not stated whether or not the first pair of data is in the *CYP2D6*-guided therapy. In terms of utility, treatment with TAM resulted in 11.95 QALYs, ANA in 12.15 QALYs and *CYP2D6*-guided therapy in 12.19 QALYs. The abstract states that a one-way sensitivity analysis and scenario analyses were conducted to evaluate uncertainty, but the results of these analyses have not been reported.

Critique of published models

Although the two examples are not full economic evaluations, it was felt that it would be beneficial to critique the approaches.

The Punglia *et al.*[119] modelling exercise can be critiqued as follows:

- *Methods of deriving the effectiveness data* Data were collected from the BIG 1-98 trial[120] but take account of only the direct effects of either TAM or aromatase inhibitors on DFS and do not account for any AEs. Women taking SSRIs are also excluded from the model.
- *Measurement of resource data* No resources have been measured in the study.
- *Valuation of resource data* As stated above, no resources have been described in the study.
- *Measurement and valuation of health benefits (utilities)* There are no utility measures described in the study; in terms of clinical effectiveness, DFS was measured.

- *Method of synthesising the costs and effects* Only effects have been measured, using HR on DFS between strategies.
- *Analysis of uncertainty* Two-way sensitivity analysis is used to explore uncertainty, and the effect of varying the HR on the results are described. A probabilistic sensitivity analysis could be used to explore all of the parameters together, but, owing to the simple structure of the model and the lack of costs and utility data, it would not be very useful.
- *Generalisability of the results* Finally, and arguably most crucially, the model considers testing only for the *CYP2D6*4* allele. Although **4* is the most frequent allele with 'loss of function' (PM) enzymatic activity in the Caucasian population (see *Table 5*), other alleles should also be considered given the findings emerging from recent studies suggesting that differences in outcomes depend on which alleles are tested for[109] and that up to one-third of patients are misclassified based on testing for **4* only.[121]

The model described by Veenstra *et al.*[79] can be critiqued as follows:

- *Methods of deriving the effectiveness data* Effectiveness data have been taken from one trial[21] and from a 'recent study' (unreferenced). From the limited data available, the accuracy/reliability of the effectiveness data is unknown.
- *Measurement of resource data* Insufficient details of resource measurement are presented; the abstract states that data were obtained from the published literature or publicly available sources.
- *Valuation of resource data* Insufficient details of resource valuation are available from the abstract.
- *Measurement and valuation of health benefits (utilities)* The utilities have been obtained from published literature but the abstract does not give more information.
- *Method of synthesising the costs and effects* Results have been reported as QALYs gained for each strategy, but there are no cost data or cost-effectiveness ratios reported. Results on projected DFS have been inadequately reported.
- *Analysis of uncertainty* The results of the sensitivity analysis are not reported.
- *Generalisability of the results* Owing to the limited information included in the abstract, it is difficult to assess the generalisability of the results. The authors have not stated the methods used to phenotype women, in other words data describing the alleles that have been tested to categorise women as PMs and EMs are missing; this makes it difficult to determine to what extent the study is able to accomplish its primary objective.

Independent economic assessment

Given the lack of studies relevant to the research question and UK clinical practice, we aimed to structure and populate an economic model to evaluate the incremental costs and benefits of *CYP2D6* testing for the management of women with breast cancer potentially eligible for management with TAM.

Requirements for a de novo economic evaluation

In order to undertake an economic evaluation of pharmacogenetic testing within the framework of the wider model of breast cancer care, the following clinical data requirements are considered to be most important:

1. *Epidemiological data* Data related to allele frequencies for selected genetic variants and how these are distributed in populations; in particular, the data should indicate which groups of patients (as defined by genotype and/or phenotype) would need to be identified by the pharmacogenetic test.

2. *Clinical effectiveness* Evidence of a link between phenotypes and drug metabolism and data describing clinical outcomes and AEs, including long-term effects of the drugs. It will be necessary to pay special attention to the choice of the time horizon of the economic evaluation which will be related to the length of the treatment (e.g. as stated in guidelines) and 'carry-over' effects of the treatment (i.e. delayed effects of the treatment after discontinuation).
3. *Test accuracy* Data are required on both the sensitivity and specificity of the test and how accurate the test is in linking genotypes to phenotypes and then to clinical events and predictive value of the test.
4. *Uptake of the test* The degree of test uptake, by patients or clinicians, will have an impact on cost-effectiveness.
5. *The impact that pharmacogenetic test results will have on clinicians' behaviour* Data are required including the impact that test results have on prescribing decisions, and how this affects the overall delivery of care.

From a health economics perspective, the key elements that need to be considered when undertaking a de novo economic evaluation of *CYP2D6* testing as a management option for women with breast cancer after surgery are discussed below.

Study question

The economic question of interest: what is the relative cost-effectiveness of *CYP2D6* testing as a management option for women with breast cancer after surgery? Both the costs and benefits (utility) of the alternatives being compared require identification, measurement and valuation.

Selection of alternatives

The current standard of care for women with ER+ breast cancer after surgery is 5 years of TAM for women with ER+ breast cancer. This could be compared with the following potential comparators:

- *Five years of TAM or aromatase inhibitors based on the results of genotyping for CYP2D6* This strategy represents the three different pathways of care as a result of the genotyping for *CYP2D6* as explained in *Chapter 2* (see *Current service provision*):*
  - poor metaboliser pathway – five years of aromatase inhibitors
  - intermediate pathway – five years of aromatase inhibitors
  - *extensive metaboliser pathway* – five years of TAM.
- *Five years of aromatase inhibitors* This strategy represents people taking aromatase inhibitors for 5 years.
- *Two years of TAM then aromatase inhibitors* As stated in *Chapter 2* (see *Current service provision*), this strategy is recommended for postmenopausal women who have received 2 years of TAM and who are not considered to be at low risk of recurrence, who are intolerant to TAM or for whom TAM is contraindicated because of toxicities.

*Unfortunately, there is no consensus about how to define each of the phenotypes from genotypes.

Effectiveness data

Every economic evaluation is reliant on good-quality clinical effectiveness data. Currently, the quality and quantity of the data available from published clinical studies are limited and so the data are not easily incorporated into any form of economic evaluation. As mentioned previously, there are 34 relevant published clinical studies describing 25 cohorts. However, owing to the heterogeneity of the studies, data from these studies cannot be synthesised for use in an economic evaluation.

Outcome measurement and valuation

Our clinical review has identified a number of outcomes that have been used to measure the efficacy of genotyping for *CYP2D6*. Of these, it is likely that a relapse/recurrence outcome, such as DFS, would be most appropriate for a condition such as breast cancer. These data would then need to be extrapolated and the life-years gained estimated. It then needs to be considered whether we adjust these adjusted life-years on a quality basis with appropriate utility data for the health states relevant to breast cancer. Owing to the treatments under evaluation, it is also necessary to include AEs in the model. These should include the following AEs:

- *hot flushes*: presented in women treated with either TAM or with aromatase inhibitors[21,22]
- *endometrial cancer*: more likely to occur in women treated with TAM[21,22]
- *hip fractures*: more likely to occur in women treated with aromatase inhibitors than those treated with TAM[21,22]
- *spine fractures*: more likely to occur in women treated with aromatase inhibitors than those treated with TAM[21,22]
- *vaginal bleeding*: more likely in women treated with TAM[21]
- *ischaemic cerebral events*: more likely in women treated with TAM[21]
- *cardiovascular events*: increased risk in women treated with aromatase inhibitors[22,122]
- *deep-venous thrombosis*: more likely in women treated with TAM[21,22]
- *arthralgia*: more likely in women treated with aromatase inhibitors.[22]

Costing

No *CYP2D6* genotyping is currently provided by the NHS and so there is no national price list for these tests. This means that the cost of the test used in the economic evaluation should be varied in sensitivity analyses.

Modelling

A simple decision tree could be used to model the sensitivity and specificity of the genotyping test (*Figure 3*). Beyond this point, a de novo Markov model would be more appropriate. A Markov model structure is considered appropriate because it is assumed that breast cancer is a condition that causes patients to move between a limited number of relevant health states during their lives. This type of model allows a large number of cycles to be simulated without the need to create a new decision tree in each cycle. *Figure 4* depicts the schematic model that includes the possible health states and possible transitions between these states.

As can be seen from *Figure 4*, the Markov model reflects seven health states:

- *DFS without AEs*: women at risk of an AE owing to the medication received or at risk of any relapse/recurrence
- *DFS with AEs*: women at risk of any relapse/recurrence with AEs
- *contralateral disease*: those women with a new primary tumour in the contralateral breast
- *locoregional disease*: women suffering a locoregional recurrence or ipsilateral second primary tumour
- *metastatic disease*: women with metastases (detail relating to different sites of metastases could be incorporated if relevant data are available)
- *breast cancer death*: death from metastatic disease only, as death from either contralateral disease or locoregional disease is unlikely
- *non-breast cancer death*: death from any cause apart from breast cancer.

Trying to model the cost-effectiveness of this technology seems to be premature given the quantity and quality of the clinical effectiveness and cost-effectiveness evidence available. It

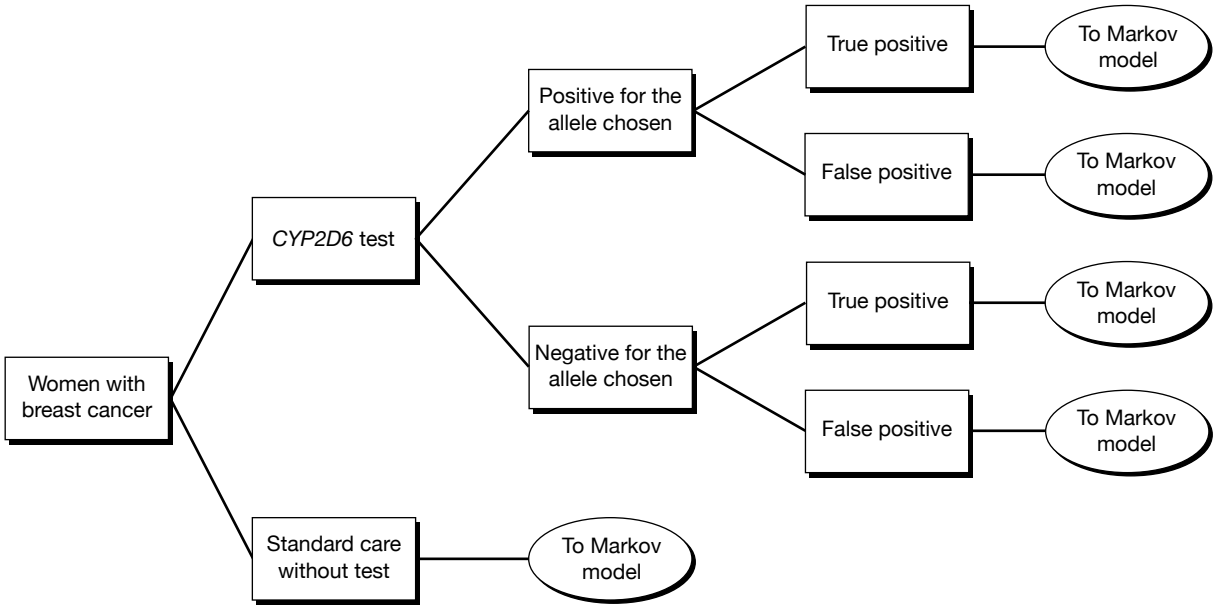

FIGURE 3 Decision tree for genotyping for *CYP2D6.* The Markov model referenced in this figure is depicted in *Figure 4.*

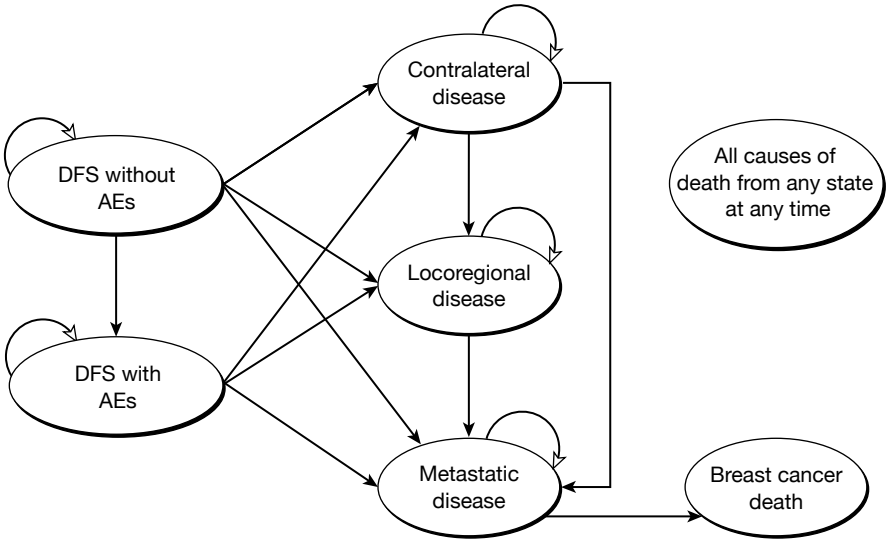

FIGURE 4 Markov model for genotyping for *CYP2D6.*

is particularly challenging because there are problems with identifying the alleles to test for, derivation of phenotypes and the lack of cost information available.

Adjustments for timing of costs and outcomes

The model should be developed with a cycle length of 1 year (a 1-year cycle has been used in previous economic evaluations of TAM versus aromatase inhibitors[123–126]) and be simulated for the remaining lifetime of all patients. The starting age should be derived from the nature of the evidence available. The mean age of the patients in the reviewed cohorts ranged from 43 to 73 years; such wide variation makes it difficult to establish a starting age.

Costs and QALYs should be discounted using a 3.5% annual rate.

Is it appropriate to develop a de novo model with the data available?

In trying to develop a de novo model, it is apparent there are too many uncertainties around the data from the clinical review, as well as other important parameters, to produce even a very simple early economic model. Thus, instead of being able to present findings from a de novo Markov model, our economic assessment has only been able to identify a number of important parameters, and relevant data, which we believe need to be included in a cost-effectiveness model. These important parameters and data requirements are discussed in detail below.

Patient population

As TAM is considered the standard of care for premenopausal women with ER+ breast cancer, and as anti-oestrogen therapy is not used for patients with ER– breast cancer, the only situation in which genotyping for *CYP2D6* might prove to be useful is if alternative treatment options to TAM, namely aromatase inhibitors, are considered to be at least as appropriate. Currently, aromatase inhibitors are recommended for women with ER+ early breast cancer deemed not to be at low risk of disease recurrence, and for women with ER+ advanced breast cancer with no prior history of anti-oestrogen therapy.[20] The decision to offer aromatase inhibitors to higher risk patients is largely based on the results of published RCTs[21–27] and systematic reviews[28–31] of women with ER+ early breast cancer suggesting a modest benefit for patients taking aromatase inhibitors over those taking TAM. Thus, the population of interest is likely to be postmenopausal women with ER+ breast cancer.

It has been proposed that patients be given TAM or an aromatase inhibitor depending on the test results. This decision may be based on their genotype or phenotype. Thus, it is important to know the distribution of postmenopausal patients with early breast cancer with each of these genotypes or phenotypes. This distribution could be inferred from the studies included in the review.

Concomitant CYP2D6 inhibitor medication

While NICE[18] states that neither paroxetine nor fluoxetine should be given to women taking TAM, a few studies included in our review state that women on TAM are taking these SSRIs.[49,86,87,91,97,99,109] To accurately reflect this situation in the model, it is necessary to know how SSRIs change the phenotype of these women, as well as the extent to which women with breast cancer are taking paroxetine or fluoxetine in clinical practice. Ferraldeschi *et al.*[127] conducted a survey to assess the current practice of breast oncologists in the UK with respect to *CYP2D6* testing and SSRI co-treatment. The authors reported that 22% of respondents stated that there was enough evidence to routinely use *CYP2D6* testing, 37% required more evidence and 41% were unsure. There was general agreement (80%) that concomitant medications might affect the clinical efficacy of TAM, and 86% indicated that they discuss drug interactions with their patients. Importantly, 93% would not prescribe a potent CYP2D6 inhibitor concomitant with TAM and would prescribe alternative treatments, where available.

Adherence to treatment

Two separate studies from the USA[128] and the UK[129] have reported that non-adherence to TAM ranges from 13% to 22% after the first year of treatment to 50% in years 4 and 5 of treatment. Data on aromatase inhibitor non-adherence suggests that this rises from 14–22% in year 1 to 21–38% in year 3.[130] However, crucially, there is a lack of data with regard to TAM adherence by genotype. Data on adherence are important because what few data we have suggest that the most common reason for discontinuing treatment is experience of hot flushes,[95] which are most common in EMs and IMs.[84,90,107]

Timing of test

In the absence of any clinical guidelines or prospective clinical studies, it is difficult to know where one would model the *CYP2D6* test along the treatment pathway. Currently, the decision to

prescribe TAM or an aromatase inhibitor (or indeed, a switching strategy) is made depending on the risk of disease recurrence. However, other factors are also taken into account, for example in relation to AEs from each drug. Thus, would *CYP2D6* testing be required only after risk and these other factors been taken into account or would the results from *CYP2D6* be another of these other factors to consider? From a practical point of view, as patients are already tested for ER and HER2 status before they are treated, it may be surmised that *CYP2D6* testing would occur at the same time, even if the *CYP2D6* test results are considered only at a later stage. Finally, in the absence of any clinical guidelines or prospective clinical studies, it is also unclear which pathways patients would follow after *CYP2D6* testing, although current treatment pathways for those treated with TAM and aromatase inhibitors would seem logical.

CYP2D6 *test availability, cost and accuracy*

A number of genotyping tests exist. Many are designed 'in house' (using techniques such as TaqMan) to test for specific alleles. Others are offered commercially, such as the AmpliChip. No *CYP2D6* genotyping is currently provided by the NHS and so there is no national price list for these tests. Many of these tests are designed specifically for research studies; therefore, the test performance in clinical practice is unknown, although generally genotyping has been shown to have high analytical validity.[45] The greatest uncertainty is in determining clinical sensitivity and specificity and predictive value, i.e. how accurate the test is in linking phenotypes to clinical events. Although we have conducted some exploratory post hoc analyses of sensitivity and specificity for some tests used in the studies included within our systematic review (see *Chapter 3, Exploratory analysis: clinical sensitivity and specificity*), it should be noted that these are from only a selected sample of studies reporting the necessary data to calculate these values. It is important to note that these are not tests that may be used in clinical practice. They are indicative, however, of the types of data that would be required for an economic model.

Penetrance, the degree of phenotypic expression of genetic variation, is a key parameter for an economic evaluation of pharmacogenetic genetic testing.[131] It is possible to design a test with almost perfect characteristics in terms of test sensitivity and specificity, but the test can still have poor positive predictive value because of the impact of low penetrance, which will affect the cost-effectiveness of the test. We were not able to estimate the degree of gene penetrance and associated positive predictive value for the *CYP2D6* test because the clinical data were not able to inform which alleles should be tested. This information is a prerequisite before gene penetrance and test positive predictive value can be established.

Anticipating the importance of the types of tests, alleles tested and their cost to the model, we undertook a survey of several laboratories with regard to their current practices in relation to *CYP2D6* testing for patients to be treated with TAM. We chose five laboratories that are currently testing patients for several genes, not only *CYP2D6*, and, to gain greater insight, chose three from the UK, one from the Netherlands and one from the USA. These laboratories were chosen because they were known to us as laboratories offering the services, often in relation to research studies, and we therefore knew that they were likely to be using the most up-to-date techniques. The survey was conducted between January 2010 and June 2010 and the questions were submitted via e-mail.

The findings from this brief consultation exercise are summarised in *Table 25*, where it can be seen that there is wide variation regarding the number of alleles tested. The costs also vary considerably by laboratory, from as little as £30 to as much as £500. This wide variation in alleles tested is concordant with the wide variation in the number of alleles tested across the studies included in our review. The wide variation in cost is likely to be due in part to the wide variation in the number of alleles tested, as most assays (e.g. TaqMan) require each allele to be tested individually, so increasing the materials required, time taken, etc. It is perhaps worth noting here

TABLE 25 Summary of laboratory survey responses

Question	Laboratory				
	LAB21 (Cambridge, UK)	Mayo Clinic (Rochester, MN, USA)	DxS (Manchester, UK)	LGC (Middlesex, UK)	Erasmus University Medical Centre (Rotterdam)
How many requests per year do you get for *CYP2D6* testing for TAM?	Overall number is small but increasing, last 12 months: 12 requests	1500 tests per year	Two per month	No tests	300 tests per year
When you do clinical testing for *CYP2D6* which alleles do you test?	**2, *2A, *3 *4, *6, *7 *8, *9, *10, *11, *12, *17* and *N*	**2* through **12, *14, *15, *17* and **41*	NS	No tests	**3, *4, *5, *6, *9, *10, *41*
Do you use TaqMan?	Yes, along with a kit from Luminex® and sequencing	No, use a kit from Luminex Molecular Diagnostics	No, use Amplification-Refractory Mutation System and Scorpions technology® (DxS Surrey, UK)	No, use a fluorescent probe called HyBeacon® (LGC Middlesex, UK)	Yes
Do you offer AmpliChip testing?	No	No, it is too costly	No	No	Yes, and TaqMan analysis as duplicate to confirm the eight most prevalent alleles and the gene duplication
How much do you charge for a *CYP2D6* test?	£500	US$439.30	£30	NS	€382

N, number of copies of the allele; NS, not stated.

that the AmpliChip, which tests for 33 alleles, has been quoted as costing US$500 per test in the USA[132] and £300 per test in the UK.[45] The AmpliChip is, to date, the only test that is licensed for use by the FDA and, unlike many tests, is able to test multiple alleles simultaneously.

The number of alleles tested is important to correctly classify patients into their correct phenotype. A recent paper by Schroth *et al.*,[121] re-analysed data from German patients in the large Schroth *et al.* cohort[108] and reported that one-third of patients identified as PMs by the AmpliChip were also identified as PMs by testing for only **4*. This proportion rose to 62% when testing for three alleles (**3–*5*) and 100% when testing for five (**3–*7*). If replicated, the findings from this analysis could suggest that only five alleles need to be tested, if the treatment decision is made on whether or not a patient is a PM. Unfortunately, we do not know this to be true. The clinical evidence from our review suggests that it may be more important to correctly identify EMs (although the evidence relating to endoxifen levels does not seem to support this). Thus, a wider range of alleles would need to be incorporated, in particular those associated with the IM phenotype, such as **10*.

Test uptake

The degree of test uptake is an important parameter to consider when evaluating the incremental costs and benefits of pharmacogenetic testing. Low test uptake could affect the cost-effectiveness of the testing, i.e. low uptake reduces the cost-effectiveness. The uptake of pharmacogenetic tests, and whether uptake is driven by the patient or the clinician, are not known and are topics for future research. There are some data that have reported test uptake for breast cancer chemoprevention.[133,134] Uptake rates range between 11.7% in populations with poor genetic counselling and 31% in populations informed by genetic counselling.[133]

Time horizon

The time horizon of the model must reflect, at the very least, the duration of the treatment and differences in resource use and/or changes in patient outcomes. Where the time frame of the model exceeds the duration of treatment, it is therefore also important to know how long patients are likely to live for, how long they are likely to be disease free, what other treatments they will receive subsequently, etc. Given that 75% of patients have a life expectancy > 5 years,[5] it would seem appropriate to model beyond treatment and until death. As noted above, this means taking into account 'carry-over' effects from treatment but (also noted above) may also be problematic given the current lack of established pathways of care. Nevertheless, it would seem feasible to populate a model that followed patients up to death.

Uncertainty

Understanding the impact of uncertainty is a key aspect of any economic model. A model of *CYP2D6* testing that is subsequently structured and populated is likely to be an early economic model that in part will aim to inform the need for further research to collect data on key parameters. As a minimum, two key types of uncertainty should be addressed: parameter and structural uncertainty. Parameter uncertainty would be addressed using probabilistic sensitivity analysis, which would allow the analyst to estimate the expected value of perfect information for future research and types of future research required. Structural uncertainty reflecting different possible care pathways should also be explored and included in the model in such a way that allows the analyst to explore the impact of structural uncertainty on whether or not additional evidence is needed.[135]

Summary

It is not known if testing for *CYP2D6* is cost-effective because no economic evaluations relevant to the UK addressing this question were identified by our review. Two studies[79,119] did conduct a modelling exercise but crucially they did not include any data on costs. Other notable weaknesses of these models include the limitation of genotyping to only **4,* and the omission of data on AEs.

We have also been unable to produce our own de novo economic model. To a large extent, this is because there is a lack of convincing evidence from the clinical review suggesting that genotyping for *CYP2D6* would have any clinical benefit. In addition, there are a number of other important parameters where data would be required for modelling, which are currently lacking. Thus, we have outlined the structure and information requirements appropriate to developing such a Markov model, highlighting the important parameters where more data are required.

Chapter 5

Discussion

From the 25 cohorts included in our clinical review, the evidence is arguably at best suggestive, but not convincing, that genotyping for *CYP2D6* may have a role to play in the management of breast cancer. Given that six cohorts[83,86,91,96,108,109] suggest that EMs appear to have better outcomes than either PMs or PMs + IMs in terms of relapse/recurrence, this could translate to EMs being suitable candidates for TAM and PMs (and possibly IMs) being offered aromatase inhibitors instead, assuming that the differences in relapse/recurrence outcomes between the two phenotypes are similar in magnitude to the differences found in studies comparing aromatase inhibitors with TAM. However, the suggestive evidence is taken from cohorts that, with two exceptions,[108,109] are relatively small in number (≤ 500 patients). In addition, three cohorts[92,99,100] have failed to report a similar association. Thus, the evidence must be treated with caution.

Uncertainty in the clinical evidence is compounded further from heterogeneity across the cohorts in terms of patient populations, alleles tested and the manner in which phenotypes are defined. Even within the cohorts there appear to be differences between patients with different genotypes/phenotypes in the few cohorts ($n = 8$)[83,91,93,97,99–101,108] that report these data. To illustrate, two cohorts[83,91] appear to show that PMs have poorer outcomes in terms of relapse/recurrence than EMs, and that PMs are more likely to have larger tumours and a greater number of positive lymph nodes, whereas a different cohort[100] (which suggests that PMs may have better outcomes than EMs) reported PMs to be less likely to have larger tumours and be LN+. Although the findings were adjusted for these factors, there is still a concern that CYP2D6 status may not be related to outcomes – or at least not directly.

Not only are there differences in terms of patient characteristics, but there are also, just as crucially, differences in outcome definitions. The most unambiguous end point to define is OS, but the only consistent finding across all studies is that there is no relationship between OS and genotype or phenotype. This lack of effect may be because there are indeed no differences or may indicate that longer-term studies are required. Interestingly, evidence published to date comparing OS in patients taking TAM versus aromatase inhibitors has failed to find any significant differences in OS.[28–31]

However, perhaps most important of all, there are also differences in terms of the alleles that are being tested. At the very least, all the US and European cohorts[41,49,83,86,87,90–92,94,96,98–100,104,108,109,112,113] have genotyped for **4* and all the Asian cohorts[73,88,93,97,101,114] have genotyped for **10*, the only two alleles for which there appears to be consensus about their importance in these respective populations. However, additional alleles tested for vary from study to study, and only nine cohorts[41,82,87,90,96,108,109,113,114] have tested for both **4* and **10*. Furthermore, the derivation of phenotypes from these tests also varies from cohort to cohort. An important finding from our review, therefore, is that there does not appear to be any consensus about what alleles to test for or how to derive phenotypes and make meaningful comparisons.

The AmpliChip is an approved *CYP2D6* test that could be used in clinical practice and which includes **4* and **10* alongside another 31 alleles. However, only six cohorts[41,82,87,90,109,113] in our review utilised the AmpliChip and only two[41,87] of these have published findings in full papers. The only other relevant evidence published on the AmpliChip to date has focused on its analytical sensitivity and specificity.[43,136–141]

Perhaps the most significant finding from the cohorts using the AmpliChip is that one cohort[109] has reported that differences in RFS between PMs and EMs are significant only when the AmpliChip is used and not when testing for just four common alleles (**4, *5, *10* and **41*). More recently, a paper by Schroth *et al.*[121] re-analysed data from German patients in the large Schroth *et al.* cohort[108] and reported that one-third of patients identified as PMs by the AmpliChip were also identified as PMs by testing for only **4* instead. This proportion rose to 62% when testing for three alleles (**3–*5*) and to 100% when testing for five (**3–*7*). Alongside this evidence, which suggests that a greater number of alleles are required to accurately classify patients, we have undertaken exploratory analysis that also seems to confirm that sensitivity and specificity are increased when the number of alleles tested is increased. However, despite the increase, sensitivity is generally low no matter how many alleles are tested for.

Each of the seven cohorts[49,73,87,104,112–114] examining endoxifen concentrations show evidence of an association between these and CYP2D6 status in Caucasians and Asians. Endoxifen levels were reported to be markedly different between both PMs and EMs[49,87,104,112,113] and those with the **10/*10* and the *wt/wt* (EM phenotype) genotypes.[73,114] However, there is conflicting evidence from the two cohorts[87,104] regarding IMs (or those with the *wt/vt* genotype), with one cohort suggesting that IMs have levels closer to EMs[104] and the other suggesting that they are closer to PMs.[87]

Our review intended to examine the evidence base for an association between endoxifen levels and clinical outcomes, but no study was found which examined this relationship. Assuming that endoxifen concentrations translate into improved outcomes, based on the evidence from the six cohorts[83,86,91,96,108,109] that suggest that EMs appear to have better outcomes than either PMs or PMs + IMs in terms of recurrence/relapse, we would probably expect endoxifen concentrations of IMs to be closer to those of PMs. As noted above, in Caucasians, one cohort[104] suggested that, on the contrary, endoxifen levels for IMs are closer to EMs than PMs, whereas the other cohort[87] did indeed suggest that the levels of IMs are closer to PMs. It is difficult to reconcile these apparently contradictory findings without conducting further studies but reasons for this may be because of the number of patients taking CYP2D6 inhibitors in these studies and/or adherence to TAM or because other enzymes are playing a more important role. It should also be noted that the number of patients included in these two cohorts was small (between 50[87] and 151 patients[104]).

We also intended to review the evidence for clinical utility but, again, our research failed to identify any such studies. Given the lack of convincing evidence for clinical validity, however, this is unsurprising as it would be inappropriate to conduct any clinical utility studies until such evidence becomes available.

Similarly, given the lack of convincing evidence for clinical validity, it is also unsurprising that we identified no full economic evaluations. However, we did identify two decision models that may be informative to later work.[79,119] The findings from these evaluations must be treated with caution, however, because models assume testing only for **4* and include no data on costs. It should also be emphasised that the actual cost of the pharmacogenetic test itself would form only a very small proportion of the overall costs of implementing pharmacogenetic testing into patient care pathways.

Given these deficiencies in the evidence base, we thus encountered a number of problems in attempting to develop a Markov model to address the cost-effectiveness of *CYP2D6* testing. Instead, we have been able to identify the important parameters for which additional data are needed to populate an economic model. As we have discussed above, we believe, crucially, that there is too much uncertainty as to which alleles to test for, how to derive phenotypes, which patients would subsequently be considered appropriate to receive TAM and which patients

would be considered suitable for aromatase inhibitors. Uncertainty about the type and quantity of alleles to test for makes it difficult to comment on the sensitivity/specificity requirements of any pharmacogenetic test that might be considered for routine use in UK clinical practice; estimating what the cost of such a test might be is also impossible. We also lack evidence of any impact on OS or convincing evidence for other outcomes such as DFS and we need more robust clinical utility data. Crucially, in the absence of any clinical utility studies about *CYP2D6* testing, it is impossible to predict how prescribing behaviour may change as a result of genotyping for *CYP2D6* and to model future pathways of care, including costs and benefits.

Chapter 6

Conclusions

Our review aimed to answer a number of questions, namely:

- In patients treated with TAM, do women with breast cancer identified as EMs for *CYP2D6* have similar or different clinical outcomes to those identified as PMs, IMs or UMs?
- Is there a relationship between CYP2D6 status and endoxifen concentrations?
- Are endoxifen concentrations related to clinical outcomes?
  - Do women with breast cancer who are identified as EMs for *CYP2D6* have similar or different clinical outcomes with TAM compared with aromatase inhibitors?
- What is the relative cost-effectiveness of *CYP2D6* testing as a management option for women with breast cancer?

This is a relatively new area of research that is evolving rapidly and, although international consortia are collaborating, the data are limited and conflicting, which limited the ability of the review to answer the questions above.

Six individual cohorts[83,86,91,96,108,109] suggest that EMs may have different outcomes in terms of relapse/recurrence (but not OS) to PMs and PMs + IMs. However, this evidence is far from conclusive, based on typically small numbers of patients and heterogeneous patient populations, clinical outcomes and alleles tested, not to mention differences in how both phenotypes and clinical outcomes are defined. In addition, three other cohorts have failed to find an association. There also appears to be evidence of a link between endoxifen concentrations and CYP2D6 status, from even smaller cohorts than have been used to assess efficacy, but this seems to suggest a contrary finding – that PMs are different to EMs + IMs – not supported from the evidence to date in terms of clinical outcomes. Unfortunately, we found no studies that measured the association between endoxifen levels and clinical outcomes, and we found no studies that directly assess whether patients who are identified as EMs for *CYP2D6* have similar or different clinical outcomes with TAM when compared with aromatase inhibitors. It might be inferred, however, that if patients who are EMs have better outcomes than PMs and if the magnitude of this difference was similar to that identified in studies comparing aromatase inhibitors with TAM, then EMs might be suitable candidates for TAM, whereas aromatase inhibitors might be more suitable for the PMs. However, as just stated, there is no convincing evidence to support this. Finally, given the lack of data available to address the previous clinical questions and given additional uncertainties surrounding costs and pathways of care, it has been impossible to assess the cost-effectiveness of testing for *CYP2D6*.

Thus, our review has raised more questions than answers, the most pertinent question being 'what alleles would one test for in clinical practice?'. The evidence base around *CYP2D6* testing to date is at too early a stage of development to be able to ascertain which alleles should be genotyped for and how phenotypes should then be derived. In the absence of any clinical utility studies, there are also too many uncertainties about expected future pathways of care, assuming that a *CYP2D6* test were to be conducted. Thus, it is impossible to recommend routine *CYP2D6* testing in clinical practice based on the evidence so far available.

Implications for service provision

Owing to a lack of relevant data, it has not been possible to ascertain whether testing for *CYP2D6* is clinically effective or cost-effective. In particular, it is unclear which alleles would need to be tested and therefore which test, if any, should be used. Consequently, it is not possible to recommend *CYP2D6* testing for routine clinical practice.

Suggested research priorities

There are many areas in which there is a need for further data and thus we have identified the following as research questions to be addressed:

- *How many and what type of alleles should be tested for?* It is important that studies are able to determine the alleles which appear to be related to clinical outcomes and which would need to be included in any *CYP2D6* test. To achieve this, studies need to include adequate numbers of patients, or at least samples that can be genotyped using techniques that can test for a number of different alleles. To date, there is also no evidence surrounding patients with multiple copies of an allele, i.e. UMs, and so testing to identify UMs may also be prudent.
- *What are acceptable levels of sensitivity and specificity for these tests when measuring different outcomes?* To date we have found no literature assessing the sensitivity and specificity of *CYP2D6* testing, and this is a matter that needs addressing. Although it is accepted that in the absence of a number of standard test alternatives it is difficult to assess sensitivity and specificity, given the high analytical validity of genotype tests these values may be calculated for testing for specific alleles. Acceptable values for sensitivity and specificity should also be agreed a priori.
- *How should phenotypes for the metabolism of TAM be defined?* This is another research question that can be adequately addressed only once the relevant alleles have been determined. It may well be that there is no need to define phenotypes and it is enough to use only genotypes, although such classifications would arguably be of greater utility for patients as well as medical professionals who need to interpret tests.
- *What are the important health outcomes for women with breast cancer, and how should these be defined?* The most unambiguous outcome to define is OS, but to date there has been no evidence of any difference in this outcome between genotypes or phenotypes, or indeed between TAM and aromatase inhibitors. This is no reason to dismiss it as an important outcome but, arguably, outcomes that measure relapse/recurrence, such as DFS, are more important for a condition such as breast cancer. While DFS is an outcome measure used in many studies, unfortunately, it is not a standardised outcome measure. For example, some definitions include death from any cause, whereas others include only breast cancer mortality. This is not a problem unique to pharmacogenetic studies, however, but occurs in all breast cancer studies.
- *Do different ethnic populations need to be tested using different tests?* This is a research question that can really be addressed only once the relevant alleles have been determined. Initially, it might be useful to use standardised tests across different populations, with the possibility of refining the alleles tested for in different ethnic populations once these alleles have been established. The need to carry out such tests would largely be driven by costs of resources (materials, time, etc.) and, ultimately, it may be safer, simpler and no less cost-effective to use the same test in all populations.
- *What pathways of care would a patient follow if pharmacogenetic testing were to be introduced? Would testing be required for women of any menopausal status?* To answer these questions, we need more evidence of differences (if they exist) in outcomes by CYP2D6 status in

premenopausal women and a better understanding on current pathways of care. While NICE currently does have recommendations for the use of TAM or aromatase inhibitors based largely on risk of disease recurrence, data on the numbers of women using these are currently lacking; an estimate of the current use of TAM and aromatase inhibitors in the UK is required as the basis for calculating resource use data for an economic model.

- *If pharmacogenetic testing were to be introduced, what would be the uptake of pharmacogenetic testing and would uptake be driven mainly by clinicians or patients?* A survey of clinicians' intentions may be informative. Evidence from other areas in which pharmacogenetic testing has been introduced may also be useful.

Ideally, clinical studies will constitute companion studies to previously conducted RCTs of TAM. We are aware of such studies being undertaken by the ITPC, as well as of previously conducted trials of aromatase inhibitors versus TAM, and the results from these analyses are eagerly awaited.

Finally, TAM metabolism is complex and CYP2D6 does not appear to account for all variability in endoxifen levels. Studies examining the link between endoxifen levels and clinical outcomes are also needed, as are studies that examine polymorphisms in other TAM metabolic pathway enzymes.

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Rumona Dickson Participated in protocol development and the initial clinical study selection and commented on draft versions of the final report.

Yenal Dundar Conducted literature searches, assisted with quality assessment and commented on draft versions of the final report.

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Appendix 1

Literature search strategies

Searches for studies linking outcomes to CYP2D6

Ovid MEDLINE, 2000 to June week 2 2009

		Hits
1	exp Genotype/	145,874
2	exp Phenotype/	98,789
3	(genotype$or phenotype$).tw.	198,382
4	exp Cytochrome P-450 Enzyme System/	31,587
5	(CYP2D6 or CYP 2D6).mp.	9297
6	AmpliChip®$.tw.	17
7	or/1-6	349,228
8	(tamoxifen or endoxifen or aromatase inhibitor$or anastrozole or arimidex or letrozole or femara or exemestane or aromasin or nolvadex or 4-hydroxy-N-desmethyl-tamoxifen).af.	12,954
9	exp Tamoxifen/	9297
10	exp Aromatase Inhibitors/	2726
11	or/8-10	14,339
12	exp Breast Neoplasms/	91,430
13	(breast$adj5 (neoplasm$or cancer$or tumo?r$or carcinoma$or adenocarcinoma$or sarcoma$or dcis or ductal or infiltrat$or intraductal$or lobular or medullary)).mp.	112,215
14	or/12-13	112,255
15	7 and 11 and 14	683
16	animals/not (animals/and humans/)	1,231,707
17	15 not 16	653
18	limit 17 to (yr = "2000 - 2009")	544

EMBASE, 2000–9 week 24

		Hits
1	exp Genotype/	102,077
2	exp Phenotype/	122,694
3	(genotype$or phenotype$).tw.	181,223
4	exp Cytochrome P450/	16,955
5	(CYP2D6 or CYP 2D6).mp.	2854
6	AmpliChip®$.tw.	22
7	or/1-6	275,475
8	(tamoxifen or endoxifen or aromatase inhibitor$or anastrozole or arimidex or letrozole or femara or exemestane or aromasin or nolvadex or 4-hydroxy-N-desmethyl-tamoxifen).af.	25,169
9	exp Tamoxifen/	21,139
10	exp Aromatase Inhibitor/	8089
11	or/8-10	26,043
12	exp Breast Tumour/	115,251

		Hits
13	(breast$adj5 (neoplasm$or cancer$or tumo?r$or carcinoma$or adenocarcinoma$or sarcoma$or dcis or ductal or infiltrat$or intraductal$or lobular or medullary)).mp.	127,487
14	or/12-13	128,366
15	7 and 11 and 14	656
16	limit 15 to (human and yr = "2000 - 2009")	543

Web of Science, Science Citations Index and Conference Proceedings Science Index

	Hits
Topic = ((genotype* or phenotype* or CYP2D6 or CYP 2D6 or Cytochrome P-450 or AmpliChip®*)) AND Topic = ((tamoxifen or endoxifen or aromatase inhibitor* or anastrozole or arimidex or letrozole or femara or exemestane or aromasin or nolvadex or 4-hydroxy-N-desmethyl-tamoxifen)) AND Topic = ((breast neoplasm* or breast cancer* or breast tumour* or breast tumour* or breast carcinoma* or breast adenocarcinoma* or breast sarcoma*))	365

The Cochrane Library, issue 2

	Hits
(genotype* or phenotype* or CYP2D6 or CYP 2D6 or Cytochrome P-450 or AmpliChip®*) and (tamoxifen or endoxifen or aromatase inhibitor* or anastrozole or arimidex or letrozole or femara or exemestane or aromasin or nolvadex or 4-hydroxy-N-desmethyl-tamoxifen) and (breast neoplasm* or breast cancer* or breast tumour* or breast tumour* or breast carcinoma* or breast adenocarcinoma* or breast sarcoma*)	7

Searches for studies linking outcomes to endoxifen

Ovid MEDLINE, 2000 to June Week 2 2009

		Hits
1	(tamoxifen or endoxifen or 4-hydroxy-N-desmethyl-tamoxifen).af. or exp Tamoxifen/	12,129
2	exp Breast Neoplasms/or (breast$adj5 (neoplasm$or cancer$or tumo?r$or carcinoma$or adenocarcinoma$or sarcoma$or dcis or ductal or infiltrat$or intraductal$or lobular or medullary)).mp.	113,203
3	1 and 2	7187
4	animals/not (animals/and humans/)	1,240,444
5	3 not 4	6968
6	limit 5 to yr = "2000 - 2009"	5403
7	limit 6 to english language	4974

The searches for the studies for the economics review were identified from the combined searches above.

Appendix 2

Table of excluded studies with rationale

Excluded studies from clinical review

The following citations were excluded at screening stage 2:

Study	Reason for exclusion
Bijl *et al.* 2009[55,56]	Includes mostly patients with metastatic disease (≥75%) (Bijl *et al.* 2009[55] is a conference abstract)
Boocock *et al.* 2002[57]	Wrong outcome (*N*-desmethyl-TAM, not endoxifen)
Burton 2006[58]	Not a research study (description of Goetz *et al.* 2005[84])
Chubak *et al.* 2008[59]	Does not consider outcomes by *CYP2D6* genotype
Coller 2003[60]	Not a primary research study (review)
Connolly *et al.* 2007[61]	Does not consider outcomes by *CYP2D6* genotype
Crewe *et al.* 2002[62]	PK study that does not consider endoxifen
Desta *et al.* 2004[63]	PK study that does not consider endoxifen
Dezentje *et al.* 2008[64]	Not a primary research study (review, subsequently published in 2009[142])
Dieudonne *et al.* 2009[65]	Wrong outcome (changes in follicle-stimulating hormone and sex hormone-binding globulin)
[a]Goetz *et al.* 2006,[66] 2008[67]	Does not consider outcomes by *CYP2D6* genotype (index including *HOXB13/IL17BR*) (Goetz *et al.* 2006[66] is interim analysis presented as abstract)
Grabinski *et al.* 2006[68]	Wrong outcome (plasma levels of TAM and 4-hydroxytamoxifen, not endoxifen)
Johnson *et al.* 2004[70]	Does not link endoxifen to clinical outcomes
	Does not consider endoxifen plasma levels by *CYP2D6* genotype
Lash *et al.* 2008[71]	Does not consider outcomes by *CYP2D6* genotype
[a]Lim *et al.* 2006[72]	Does not link endoxifen to clinical outcomes[a]
	Does not consider endoxifen plasma levels by *CYP2D6* genotype[a]
[a]Lim *et al.* 2007[73]	Includes only patients with metastatic disease in efficacy study[a]
[a]Mortimer *et al.* 2008[74]	Does not consider outcomes by *CYP2D6* genotype
[a]Ntukidem *et al.* 2008[75]	Wrong outcome (serum total cholesterol)
Ro *et al.* 2008[76]	Single case reports
Serrano *et al.* 2009[77]	Wrong outcome (plasma levels of *N*-desmethyl-TAM, not endoxifen)
	Wrong setting (chemoprevention)
Sridar *et al.* 2002[78]	PK study that does not consider endoxifen or *CYP2D6*
Veenstra *et al.* 2009[79]	Not a primary research study (economic analysis)
Wu *et al.* 2009[80] and Hawse *et al.* 2008[81]	Does not link endoxifen to clinical outcomes (considers metabolism of endoxifen in vitro) (Hawse *et al.* 2008[81] is interim analysis presented as conference abstract)

PK, pharmacokinetics.

a Data on relevant outcomes from the cohort of patients included this study is included, however, in separate publications that have been included in the review.

In addition, one of the included citations by Lim *et al.*[73] also included data on an efficacy study containing only patients with metastatic disease. These data were excluded from the review, but as the citation also included data on a separate pharmacokinetic study of patients with early and metastatic breast cancer, this citation is included in the review.

Excluded studies from economics review

Study	Reason for exclusion
Anderson *et al.* 2006[143]	Does not consider *CYP2D6* testing
Annemans 2008[144]	Does not consider *CYP2D6* testing
Armstrong *et al.* 2001[145]	Does not consider *CYP2D6* testing
Benedict and Brown 2005[146]	Does not consider *CYP2D6* testing
BlueCross BlueShield 2001[147]	Does not consider *CYP2D6* testing
Borgstrom *et al.* 2004[148]	Does not consider *CYP2D6* testing
Cuzick *et al.* 2006[149]	Does not consider *CYP2D6* testing
Delea *et al.* 2006[150]	Does not consider *CYP2D6* testing
Delea *et al.* 2007[124]	Does not consider *CYP2D6* testing
Delea *et al.* 2008[123]	Does not consider *CYP2D6* testing
Dranitsaris *et al.* 2003[151]	Does not consider *CYP2D6* testing
Duelge and Hillner 2000[152]	Does not consider *CYP2D6* testing
Dunn and Keam 2006[153]	Does not consider *CYP2D6* testing
Eckermann *et al.* 2003[154]	Does not consider *CYP2D6* testing
Eisinger 2008[155]	Not an economic evaluation
El Ouagari *et al.* 2007[125]	Does not consider *CYP2D6* testing
[a]Fleeman *et al.* 2010[45]	Not related to breast cancer
Gil *et al.* 2006[156]	Does not consider *CYP2D6* testing
Goeree *et al.* 2006[157]	Does not consider *CYP2D6* testing
Hershman *et al.* 2002[158]	Does not consider *CYP2D6* testing
Higa 2000[159]	Does not consider *CYP2D6* testing
Higa 2001[160]	Does not consider *CYP2D6* testing
Hillner and Radice 2001[161]	Does not consider *CYP2D6* testing
Hillner 2004[162]	Does not consider *CYP2D6* testing
Hind *et al.* 2007[30]	Does not consider *CYP2D6* testing
Imai *et al.* 2007[163]	Does not consider *CYP2D6* testing
Kanis *et al.* 2005[164]	Does not consider *CYP2D6* testing
Karnon and Jones 2003[165]	Does not consider *CYP2D6* testing
Karnon *et al.* 2003[166]	Does not consider *CYP2D6* testing
Karnon 2006[126]	Does not consider *CYP2D6* testing
Karnon *et al.* 2006[167]	Does not consider *CYP2D6* testing
Karnon *et al.* 2008[168]	Does not consider *CYP2D6* testing
Keyzer *et al.* 2005[169]	Does not consider *CYP2D6* testing
Kellokumpu-Lehtinen *et al.* 2007[170]	Does not consider *CYP2D6* testing
Kilian and Porzsolt 2005[171]	Does not consider *CYP2D6* testing
Lindgren *et al.* 2002[172]	Does not consider *CYP2D6* testing
Locker *et al.* 2007[173]	Does not consider *CYP2D6* testing
Lonning 2006[174]	Does not consider *CYP2D6* testing
Lundkvist *et al.* 2007[175]	Does not consider *CYP2D6* testing
Mansel *et al.* 2007[176]	Does not consider *CYP2D6* testing
Marchetti *et al.* 2004[177]	Does not consider *CYP2D6* testing
Meadows *et al.* 2007[178]	Does not consider *CYP2D6* testing
Melnikow *et al.* 2008[179]	Does not consider *CYP2D6* testing
Miller *et al.* 2007[180]	Does not consider *CYP2D6* testing
Moeremans and Annemans 2006[181]	Does not consider *CYP2D6* testing
Mullins and Ohsfeldt 2003[182]	Does not consider *CYP2D6* testing
Naeim and Keeler 2005[183]	Does not consider *CYP2D6* testing

Study	Reason for exclusion
NICE 2006[184]	Does not consider *CYP2D6* testing
Okubo *et al.* 2005[185]	Does not consider *CYP2D6* testing
Ozanne and Esserman 2004[186]	Does not consider *CYP2D6* testing
Punglia *et al.* 2008[119]	Includes *CYP2D6* testing but does not include costs
Risebrough *et al.* 2007[187]	Does not consider *CYP2D6* testing
Rocchi and Verma 2006[188]	Does not consider *CYP2D6* testing
Rodriguez-Antona *et al.* 2009[189]	Not related to breast cancer
Sher *et al.* 2009[190]	Does not consider *CYP2D6* testing
Simons *et al.* 2003[191]	Does not consider *CYP2D6* testing
Skedgel *et al.* 2007[192]	Does not consider *CYP2D6* testing
Skedgel *et al.* 2007[193]	Does not consider *CYP2D6* testing
Smith and Hillner 2000[194]	Does not consider *CYP2D6* testing
Thompson *et al.* 2007[195]	Does not consider *CYP2D6* testing
Veenstra *et al.* 2009[79]	Includes *CYP2D6* testing but does not include costs
Williams *et al.* 2006[196]	Does not consider *CYP2D6* testing
Younis *et al.* 2007[197]	Does not consider *CYP2D6* testing

a When the search was conducted, this review was 'in press'.

Ongoing studies

One study appears to meet inclusion criteria of this review, but has not yet reported:

Study	Outcomes to be measured
Irvin *et al.* 2009[69,198]	Change in endoxifen levels after an increase in the TAM dose from 20 to 40 mg in patients with *CYP2D6* IM genotypes Tolerability of increasing the dose of TAM from 20 to 40 mg per day in patients with *CYP2D6* IM genotypes Feasibility of obtaining pharmacogenomic information from patients in the clinical setting and using it to guide changes in therapy *CYP2D6* allele frequencies and endoxifen levels among African American women taking TAM Change in plasma endoxifen levels after an increase in TAM dose from 20 to 40 mg daily in patients with poor-metabolising genotypes

Another ongoing study may be of interest regarding clinical utility:

Study	Study details
Lorizio *et al.* 2009[115]	Patients taking TAM, or for whom TAM was recommended, participate in a teaching session that discusses both positive and negative results regarding *CYP2D6* genotype and breast cancer recurrence. *CYP2D6* testing offered to all participants at the end of the session; results then released to their clinician. Clinicians informed of test results but no specific treatment recommendation provided. To determine whether or not a change in medication occurred, a follow-up phone call is conducted 4–6 months later. To date, 180 women have been enrolled, 100 have received the follow-up call, of which five were classified PM. Of these, four (80%) have had their treatment changed based on physician recommendation compared with 10 (11%) in IM or EM ($p = 0.001$)

Appendix 3

Quality assessment

To assesses quality, the following questions were posed, based on elements of checklists developed to assess the methodological quality of prognostic factor studies[50] and pharmacogenetic studies,[51] with the corresponding responses presented in the table:

Patient sample (sample)

1. Is the source population clearly defined?
2. Is the study population clearly defined?
3. Does the study population clearly represent the source population or population of interest?
4. Are details given of how the sample size was calculated?

Choosing the genes/single nucleotide polymorphisms to genotype (see 'SNP', table below)

5. Are reasons given for choosing the genes and SNPs genotyped?

Reliability of genotypes (see 'Test', table below)

6. Is the genotyping procedure described?
7. Are the primers described?
8. Were quality control methods used and described?
9. Were findings from quality control methods, if used, described?
10. Are any genotype frequencies previously reported quoted?

Missing genotype data (see 'Data', table below)

11. Is it evident that there are any missing data?
12. Where missing data are evident, are reasons given?
13. Are checks for missingness at random reported?
14. Is missing genotype data imputed?
15. Does paper quote number of patients contributing to each analysis?

Confounding measurement and account (see 'Confound', table below)

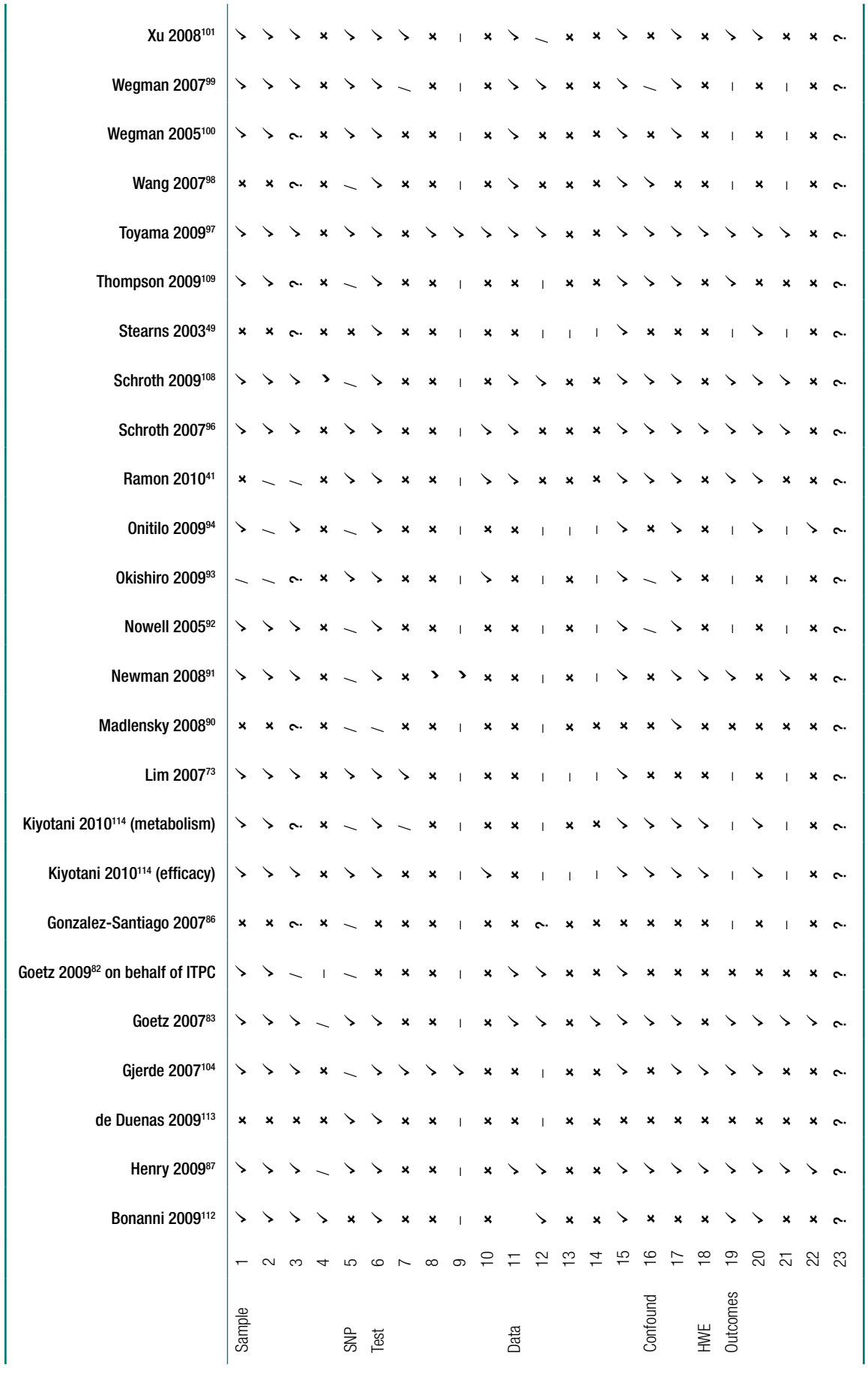
16. Are potential confounders described?
17. Are potential confounders adjusted for?

Hardy–Weinberg Equilibrium (see 'HWE', table below)

18. Was a test presented to check for HWE?

Choice and definition of outcomes (see 'Outcomes', table below)

19. Does the paper clearly define the phenotypes?
20. Does the paper clearly define all outcomes investigated?
21. Is justification provided for the choice of phenotypes?
22. Is justification provided for the choice of outcomes?
23. Were the outcomes assessed blindly (i.e. did the assessor know the genotype/phenotype in relation to this?)



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