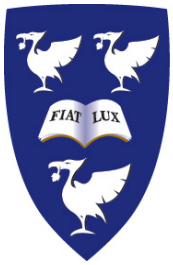
NETSCC, HTA

9th November 2009

Research Project: 08/83/01

The clinical and cost effectiveness of genotyping for CYP2D6 for the management of women with breast cancer

CONTENTS:



UNIVERSITY OF LIVERPOOL

Liverpool Reviews & Implementation Group

1. Title of project

The clinical and cost effectiveness of genotyping for CYP2D6 for the management of women with breast cancer

2. TAR team

Liverpool Reviews and Implementation Group (LR*i*G), University of Liverpool

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For details of expertise within the TAR team, see section 7

3. Plain English summary

Treatment for breast cancer takes two main forms: surgical treatment to remove the cancer locally (within the breast and related lymph nodes) and adjuvant treatment after surgical removal of the primary cancer, to reduce the risk that the cancer will reappear. Adjuvant treatment is commonly based on hormonal drug therapy, often using tamoxifen and/or aromatase inhibitors to block the cancer-promoting effect of naturally-occurring oestrogen.

How patients respond to hormonal therapy is highly unpredictable; some patients experience unpleasant side effects, and others do not respond at all to standard doses of the drugs. Some of this unpredictability may be due to differences in each patient's genetic makeup and therefore how they may respond to drug treatment. A group of enzymes know as the cytochrome P450 enzyme system has been found to play a major role in the way patients respond to tamoxifen, particularly the cytochrome P450 2D6 (CYP2D6) enzyme. It is possible that testing for genetic differences in how patients metabolise tamoxifen may help in tailoring drug therapy to suit individual patients better, when planning hormonal therapy.

This review aims to assess whether testing for genetic differences related to CYP2D6 is clinically useful when considering hormonal therapy. If suitable data are available, the review will also investigate if the use of cytochrome P450 testing would be a good use of NHS resources.

4. Decision problem

Clarification of research question and scope

CYP2D6 is a polymorphic enzyme which belongs to the cytochrome P450 (CYP450) enzyme system. The aim of this report is to assess whether genotyping for CYP2D6 is of clinical value when providing adjuvant hormonal therapy (tamoxifen and/or aromatase inhibitors) for postmenopausal women with early oestrogen receptor positive breast cancer and in the broadest sense, whether doing so would be cost effective.

Background

Breast cancer is the uncontrolled, abnormal growth of malignant breast tissue affecting predominantly women. Treatment can broadly 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, hormone therapy or molecular targeted therapy. Chemotherapy is usually given to oestrogen receptor negative (ER-) patients (i.e. those whose tumours are not oestrogen sensitive) but it is also considered useful for some women that are premenopausal oestrogen receptor positive (ER+).[1] However most women who have been diagnosed with ER+ breast cancer tumours receive hormonal therapy.

Hormonal therapy typically comprises tamoxifen and/or aromatatase inhibitors (AIs) to block the cancer-promoting effect of oestrogen.[2] In the UK, five years of tamoxifen therapy has become standard adjuvant hormonal treatment for postmenopausal women with early ER+ breast cancer. The long-term use of tamoxifen may be associated with vaginal bleeding, endometrial thickening, and increased risk of endometrial cancer and thromboembolic events; AIs have been reported to improve clinical outcomes when compared with tamoxifen and result in fewer hot flashes but are also associated with increased joint pain and bone fractures and may also be associated with increased cardiovascular risk.[3] Under the conservative assumption that benefits gained by AIs during the treatment period are gradually lost over the following 10 years, the cost per quality-adjusted life-year (QALY) for AIs compared with tamoxifen has been estimated to be between £21,000 and £32,000 in the primary adjuvant setting.[3]

The National Institute for Health and Clinical Excellence (NICE) guidance on hormonal therapy[2] has provided flexibility in decision making for clinicians. In reaching their decision, NICE was advised by clinical experts that the use of AIs as primary adjuvant treatment may have maximum benefit amongst women at highest risk of early recurrence. Therefore an AI might be preferable to tamoxifen on the basis of cost effectiveness in women in whom the risk of early recurrence is particularly high. However, because of the lack of definitive evidence on the relative clinical and cost effectiveness of the use of the AIs in different risk groups,[3] guidance was not issued on the relative cost effectiveness of the AIs for the different subgroups. Thus NICE agreed that the choice of treatment should be made after discussion between the responsible clinician and the woman about the risks and benefits of the options available. Consideration of the treatment to be adopted should include whether the woman has already received tamoxifen, the licensed indications of the individual drugs, the side-effect profiles of the individual drugs and, in particular, the assessed risk of recurrence.

A link between drug metabolism and drug response has been widely discussed in the literature and a significant proportion of this literature is focussed on the CYP450 enzyme system, which has been identified as a major metabolic pathway for many drugs and a source of inter-individual variability in patient response.[4, 5] In particular, tamoxifen is metabolised to its active metabolites N-desmethyl tamoxifen and 4-hydroxytamoxifen (4OHtam) by a number of CYP450 enzymes including CYP2D6, CYP3A4, CYP2C9, CYP2C19, and CYP2B6.[6] N-desmethyl tamoxifen is further metabolised to endoxifen by CYP2D6. Endoxifen, which is also formed via the action of CYP2D6,[7] is 30-100 fold more potent than tamoxifen in suppressing estrogen-dependent cell proliferation, and is considered an entity responsible for significant pharmacologic effects of tamoxifen.[8]

Genes are instructions that produce enzymes. The CYP2D6 enzyme is highly polymorphic - there are more than 60 different alleles of the *CYP2D6* gene (note the use of *italics* to denote genes and normal font to denote enzyme as is standard practice) which may be deficient or overactive in enzyme activity. It is the alleles that determine an individual's genotype and as can be seen from Table 1, there is also an association between genotype and the expected drug effects (i.e. the phenotype). For patients with normal enzyme activity (extensive metabolisers [EMs]), usual doses should result in expected drug concentrations and normal therapeutic response. Patients with deficient alleles (poor metabolisers [PMs] or intermediate [IMs]) are likely to have lower exposure to endoxifen and may have compromised clinical effects,[8] 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.[9] For example, patients treated with tamoxifen are commonly also prescribed selective serotonin reuptake inhibitors (SSRIs) to treat adverse events such as hot flashes but it has been reported that fluoxetine or paroxetine effectively changes the phenotype from EM to PM in some individuals.[10] Co-administration of such substances therefore needs to be taken into consideration.

Table 1: Effects of genetic polymorphisms of CYP2D6 enzyme*

Phenotype (metaboliser status)	Genotype	Expected drug effects from tamoxifen
Extensive metaboliser (EM)	Two copies of normal function alleles	Usual doses lead to expected drug concentrations and response
Poor metaboliser (PM)	Two copies of loss of function alleles	Usual doses may not lead to therapeutic drug concentration
Intermediate metaboliser (IM)	Two copies of reduced activity alleles or one copy of loss of function allele and one copy of decreased activity allele	Drug effects between those of EMs and PMs or possibly similar to those of PMs
Ultra-rapid metaboliser (UM)	Multiple copies of functional allele or of the whole gene itself (gene duplications)	Usual doses may lead to higher than expected drug concentrations

Adapted from Matchar 2006[11]

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

Since differences in response to tamoxifen may be a result of differences in the *CYP2D6* genotype, it is thought that CYP2D6 testing may play a role in optimising an individual's adjuvant hormonal treatment. However, a review published in 2008 by the Blue Cross and Blue Shield Association[9] reported there was a lack of evidence to support the clinical utility of CYP2D6 genotyping. This review did not consider cost effectiveness. In the current review, therefore, we propose to update the evidence base by searching for additional evidence for the clinical validity and clinical utility of CYP2D6 genotyping, and to consider the cost effectiveness of such tests and the associated costs of implementing their use in clinical practice.

Epidemiology

There were 45,947 new cases of breast cancer diagnosed in the UK in 2005 of which 45,660 were in women.[12] Despite being rare in those aged under 35, it is still the most commonly diagnosed cancer in women of all ages. Almost 1,500 women aged 35-39 are diagnosed with breast cancer each year.[12] Breast cancer incidence rates increase with age; around 80% of breast cancers occur in women older than 50 and women have a one in nine lifetime risk of developing breast cancer.[2] As the incidence of breast cancer is high, and five-year survival rates are over 75%,[12] the prevalence is also high, being around 172,000 women in the UK according to the most recently published data.[13]

The technology

Diagnostic genotyping tests for certain CYP450 enzymes are now available. Many tests are offered as in-house laboratory services, which do not require regulatory approval but which must meet general laboratory quality standards for high complexity testing. Before any genetic test is likely to

be accepted and incorporated into routine practice, it has been suggested that four components will need to be satisfied, as defined by the ACCE model (which takes its name from these components): **a**nalytic validity; **c**linical validity; **c**linical utility; **e**thical, legal and social implications.[14]

Analytic validity is in essence a measure of the accuracy and reliability of a particular test in relation to a gold standard (such as DNA sequencing) or another accepted test. Assuming there is analytic validity, assessment of clinical validity considers associations between clinical outcomes and genotype/phenotype. Clinical utility refers to the ability to use the information from analytic and clinical validity in clinical practice. Ethical, legal and social implications of testing also need to be considered, particularly in relation to clinical utility, e.g. if a patient possesses a particular phenotype, will it be acceptable to deny them a particular treatment, especially where alternatives are considered to be much less efficacious? Given ethnic differences in genetic make-up and thus metaboliser status, will this result in discrimination?

Currently the only pharmacogenetic test to be granted market approval in the USA[15] as well as in the European Union[16, 17] is the AmpliChip® which has been identified as having high sensitivity and specificity (analytic validity).[16] However, despite an FDA expert advisory panel announcing that the CYP2D6 gene was considered to be a predictor of tamoxifen efficacy (clinical validity), no consensus as to whether testing should be recommended or considered an option (clinical utility and ethical, legal and social implications) could be reached.[9]

Recent guidelines on the diagnosis and treatment of early and locally advanced and advanced breast cancer published by NICE in February 2009[18, 19] made no reference to pharmacogenetic testing for CYP2D6.

Costs

When considering the costs of integrating genetic testing into clinical practice it is necessary to consider issues well beyond the cost of conducting the genetic screening test. The introduction of what has come to be known as 'individualised patient prescribing' will require a significant shift in the manner and delivery of patient care. Therefore, in addition to reviewing the standard economic literature related the use of genetic screening in clinical practice this review will begin to identify the factors that will need to be integrated into future economic models that could be used to assist decision makers faced with the responsibility of integrating these new tests into clinical practice.

Objectives of the HTA project

The project will address two distinct but linked questions related to the use of genetic testing in practice – clinical validity and clinical utility. It will also examine the existing health economic evidence and through reviewing of the literature identify the key economic issues related to the integration of such testing in clinical practice. If suitable data are available, an economic model will be developed and populated to evaluate if the use of CYP2D6 testing before prescription of tamoxifen would be a good use of NHS resources.

Clinical validity

In patients treated with tamoxifen:

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

Clinical utility

4) Do women with breast cancer who are identified as EMs for CYP2D6 have similar or different clinical outcomes with tamoxifen compared to AIs?

Cost effectiveness

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

5. Methods for synthesising clinical effectiveness evidence

A systematic review methodology will be utilised to address each of the identified objectives.

Systematic review search strategy

The following databases will be searched for relevant published literature:

- CENTRAL (Cochrane Central Register of Controlled Trials)
- CDSR (Cochrane Database of Systematic Reviews)
- DARE (Database of Abstracts of Reviews of Effectiveness)
- EMBASE
- Health Technology Assessment (HTA) database
- ISI Web of Science
- MEDLINE
- NHS EED
- HuGENet Published Literature database (http://www.hugenavigator.net/HuGENavigator/startPagePubLit.do)
- Conference websites such as the American Society for Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO)

Because CYP2D6 genotyping is a relatively new area and because the earliest study[20] identified in the previous review of pharmacogenomics of tamoxifen treatment [9] was from 2003, searches will be limited to the years 2000 and onwards. Details of the search strategies that will be used to explore MEDLINE are presented in Appendix 1.

Bibliographies of previous reviews and retrieved articles will be searched for further studies. Data deposited in the Pharmacogenetics and Pharmacogenomics Database[21] and made available via the International Tamoxifen Pharmacogenomics Consortium[22] will be searched and used where appropriate to supplement the review. Attempts will also be made to obtain individual patient data from patients genotyped for CYP2D6 in tamoxifen studies by contacting principal investigators. Relevant data and on-going studies involving the AmpliChip® will be sought by contacting the manufacturer (Roche Molecular Diagnostics).

Study selection

For each review objective, the citations identified by the search strategy will be assessed for inclusion through two stages. Firstly, two reviewers will independently scan all the titles and abstracts identified by the searching exercise to isolate the potentially relevant articles to be retrieved. Full text copies of the selected studies will subsequently be obtained and assessed independently by two reviewers for inclusion using the inclusion and exclusion criteria outlined below. Any disagreements will be resolved by discussion at each stage, and if necessary a third reviewer will be consulted.

1) Clinical validity: Do women with breast cancer identified as EMs for CYP2D6 have similar or different clinical outcomes to those identified as PMs, IMs or UMs?

Inclusion:

- Women with early ER+ breast cancer treated with tamoxifen and genotyped for CYP2D6
- Any study design other than single case reports
- One or more of the following relevant clinical outcomes:
    - overall survival, defined as hazard of death from any cause after any follow-up, or the time to death from any cause expressed in months
    - disease-free survival, however defined
    - local and distant recurrence, however defined
    - adverse events, however defined
    - health-related quality of life, however defined

Exclusion:

- Editorials, opinions and reviews

2) Clinical validity: Is there a relationship between CYP2D6 status and endoxifen levels?

Inclusion:

- Women with early ER+ breast cancer treated with tamoxifen and genotyped for CYP2D6
- Any study design other than single case reports
- Relevant outcomes include plasma concentrations of endoxifen

Exclusion:

- Editorials, opinions and reviews

3) Clinical validity: Are endoxifen levels related to clinical outcomes?

Inclusion:

- Women with early ER+ breast cancer and treated with tamoxifen in whom endoxifen levels have been measured
- Any study design other than single case reports
- One or more of the following relevant clinical outcomes:
    - overall survival, defined as hazard of death from any cause after any follow-up, or the time to death from any cause expressed in months
    - disease-free survival, however defined
    - local and distant recurrence, however defined
    - adverse events, however defined
    - health-related quality of life, however defined

Exclusion:

- Editorials, opinions and reviews

4) Clinical utility: Do women with breast cancer who are identified as EMs for CYP2D6 have similar or different clinical outcomes with tamoxifen compared to AIs?

Inclusion:

- Women with early ER+ breast cancer treated with tamoxifen and/or AIs and genotyped for CYP2D6
- Any study design other than single case reports
- One or more of the following relevant clinical outcomes:
    - overall survival, defined (as in the review of hormonal therapies for breast cancer[3]) as hazard of death from any cause after any follow-up, or the time to death from any cause expressed in months
    - disease-free survival, however defined
    - local and distant recurrence, however defined
    - adverse events, however defined
    - health-related quality of life, however defined

Exclusion:

- Editorials, opinions and reviews

Data extraction and quality assessment strategy

Data from identified studies will be extracted to tables and summarised. The types of data extracted will include, but not be limited to, those listed in Appendix 2.

All included studies resulting from our search will be assessed for methodological quality in accordance with principles consistent with those in the HuGENet handbook for gene-disease association studies.[23] The general study design and conduct of studies will be based on general accepted criteria for assessing the methodological quality of studies[24] and using a tool based on a checklist developed to assess the methodological quality of pharmacogenetic studies.[25]

Methods of analysis/synthesis

Individual study data and quality assessment will be summarised in structured tables and as a narrative description. If appropriate, meta-analytic guidelines set out in the HuGENet handbook [23] for undertaking meta-analyses of genetic association studies will be adapted as appropriate to suit the pharmacogenetic setting of the current review. Forest plots will be produced for binary outcomes comparing odds ratios (ORs) and for continuous outcomes by comparing differences in means. An assessment of heterogeneity between studies will be conducted by visually inspecting the forest plots and by calculating the I^2 statistic[26] which measures the proportion of variation across studies that is due to genuine differences rather than due to random error. If heterogeneity is detected, summary effects will be estimated using a random-effects approach; otherwise a fixed effects approach is to be taken. Where studies differ in terms of study design and/or the ethnicity of included patients, separate effect estimates will be calculated for each study type and ethnic group.

6. Methods for synthesising cost effectiveness evidence

The review of economic literature will be done in two parts. The first will include a standard review and evaluation of the published economic evaluations. The second will examine the issues related to the implementation of testing in clinical practice and if appropriate, and data are available, include the development of an economic model.

Systematic review of published economic literature

The search strategies detailed in section 5 will be adapted accordingly to identify studies examining the cost effectiveness of CYP2D6 testing for the management of breast cancer patients. Other searching activities, including electronic searching of online health economic journals and contacting experts in the field will also be undertaken. Full details of the search process will be presented in the final report.

Titles and abstracts will be examined for inclusion by two reviewers independently. Potentially relevant studies will then be obtained in full text and examined more carefully by two independent reviewers using a pre-specified inclusion / exclusion criteria, details of which will be described in the final report. Any disagreement will be resolved by consensus, and if necessary a third reviewer will be consulted.

Only full economic evaluations (assessing both outcomes and benefits) of CYP2D6 testing will be included in the initial review (see below). To supplement these findings, additional information on resource use, costs and patient outcomes will be collated and discussed narratively. The aim of these supplementary findings is to understand the economic impact of the CYP2D6 test as a diagnostic tool to identify women at risk of poor response from tamoxifen who are more likely to benefit from treatment with an AI. Therefore, this review will begin to describe the potential clinical pathways that women with breast cancer could follow if offered CYP2D6 testing with tamoxifen or treatment with an AI. If appropriate, this information will be used to inform the development of a *de novo* model structure and identify the key parameters required in the model. Key parameters are likely to be: sensitivity and specificity of the CYP2D6; cost of the CYP2D6 test; population-stratification based on probability of response and typical treatment strategies with or without the CYP2D6 test.

Inclusion:

- Full economic evaluations (assessing both outcomes and benefits)

Exclusion:

- Women not diagnosed as having breast cancer
- Women not taking tamoxifen or AIs

Data from the full economic evaluations meeting the inclusion criteria will be extracted into structured tables and will include, but not be limited to, the criteria set out in Appendix 3. The quality of the included studies will be assessed using the critical appraisal checklist for economic evaluations proposed by Drummond and colleagues.[27]

Development of a de novo economic model

If suitable data relating to clinical validity and clinical utility are available, an economic model will be developed. The model will assume a lifetime horizon and the NHS perspective for costs and will be constructed to represent the options of CYP2D6 testing plus tamoxifen compared to treatment with AIs. An expert panel (comprising clinicians from the TAR team) will be used to further refine the modelling structure and identify the key parameters.

The target study population for this model will be women with breast cancer. The model will use clinical data from our review of CYP2D6 genotyping in the management of patients with breast cancer to determine if CYP2D6 testing is a cost effective strategy when considering hormonal therapy. However, data additional to information on test accuracy will be required and obtained from the systematic review. This supplementary information is necessary to understand the opportunity cost of introducing the CYP2D6 test before the prescription of tamoxifen. To be useful for decision-makers, it is necessary for the model to describe how the test affects the referral of patients to care pathways, subsequent services and treatments. The primary outcome of interest is likely to be the impact on life-expectancy that will be extrapolated from data on clinical outcome with CYP2D6 plus tamoxifen and AIs. The literature will also be reviewed to identify any available utility data to quantify the impact of health-related quality of life and calculate QALYs.

Resource use measures and unit costs will be drawn from recent UK sources wherever possible in order to reflect current NHS clinical practice. However, it may be necessary to carry out additional searching of published and unpublished sources to remedy deficiencies in available economic data necessary to populate the model effectively.

Where possible, the results will be presented as incremental cost per QALY ratios. If sufficient data are not available to construct these measures with reasonable precision incremental cost effectiveness analysis will be undertaken employing appropriate primary and intermediate measures of patient benefit, or failing this a narrative discussion will be presented in place of a formal economic model.

Appropriate sensitivity analyses will be undertaken in order to assess the robustness of model results to realistic variations in the levels of the underlying data. Where the overall results are sensitive to a particular variable, the sensitivity analysis will analyse the nature and impact of variations.

Threshold analysis will also be undertaken to determine the threshold of effectiveness required for a genotyping technology to be cost effective.

Imprecision in the principal model cost effectiveness results with respect to key parameter values will be assessed by use of techniques compatible with the modelling methodology deemed appropriate to the research question (e.g. multi-way sensitivity analysis, cost effectiveness acceptability curves, etc).

If development of a full economic model is not possible, a careful examination of all relevant research and methodological issues will be carried out and reported in the form of recommendations for further research and data collection.

7. Expertise in this TAR team

The LRiG team is a multi-disciplinary group of researchers with skills in mathematical modelling (Professor Adrian Bagust and Dr Carlos Martin Saborido), health economics (Bagust, Martin Saborido and Ms Claire McLeod) and systematic reviewing (Ms Rumona Dickson, Dr Yenal Dundar, Mr Nigel Fleeman). LRiG is well practised in undertaking HTAs, recently completing a Health Technology Assessment (HTA) examining the evidence for the clinical and cost effectiveness of testing for cytochrome P450 polymorphisms in patients treated with antipsychotics. Also involved in this review were other members of the current TAR team: Dr Katherine Payne, a Senior Research Fellow in Health Economics with a specialist interest in the economic evaluation of genetic technologies; Professor Munir Pirmohamed, a clinical pharmacologist and the NHS Department of Health Chair in Pharmacogenetics; and Professor Tom Walley, a clinical pharmacologist. As with previous HTAs, the team will be strengthened through collaboration with the Centre for Medical Statistics and Health Evaluation at the University of Liverpool. For the current HTA, the TAR team will be joined by Dr Bill Newman, a Senior Clinical Lecturer at the Academic Unit of Medical Genetics in Manchester who has been involved with studies of CYP2D6 genotyping in tamoxifen. It is anticipated that the TAR team will be completed by Dr Ana Fernández Santander from the Universidad Europea de Madrid who is currently involved with three studies of CYP2D6 genotyping in tamoxifen in Spain.

8. Timetable/milestones

Dates (estimated)	Activity
1st August 2009	Begin review
August – September 2009	Literature searching and assessment of papers for inclusion in the review Contacting authors/manufacturer for data*
September – November 2009	Data extraction and quality assessment
October - December 2009	Data synthesis and economic modelling
January 2010	Draft report for internal and external advisors
Mid February 2010	Full report produced

*delays in receipt of data from the researchers or the manufacturers may limit the ability of the team to meet the established timelines

9. References

1. Cancer Research UK. Breast Cancer symptoms and treatment. 2004 [cited 03/09/2008]; Available from: http://info.cancerresearchuk.org/cancerstats/types/breast/symptomsandtreatment/?a=5441#source20.
2. NICE. Hormonal therapies for the adjuvant treatment of early oestrogen-receptor-positive breast cancer. Technology Appraisal TA112. London: NICE 2006.
3. Hind D, Ward S, De Nigris E, Simpson E, Carroll C, Wyld L. Hormonal therapies for early breast cancer: systematic review and economic evaluation. Health Technol Assess. 2007; 11(26).
4. de Leon J, Susce M, Pan R, Koch W, Wedlund P. Polymorphic variations in GSTM1, GSTT1, PgP, CYP2D6, CYP3A5, and Dopamine D_2 and D_3 receptors and their association with Tardive Dyskinesia in severe mental illness. J Clin Psychopharmacol. 2005; 25(5):448-56.
5. Pirmohamed M, Park BK. Cytochrome P450 enzyme polymorphisms and adverse drug reactions. Toxicology. 2003; 192:23-32.
6. Nolvadex (Tamoxfien Citrate) label. 9-27-2005. Wilmington D, AstraZeneca Pharmaceuticals LP.
7. Stebbing J, Stearns V, Davidson NE. Role of CYP2D6 testing in selection of endocrine therapy for breast cancer. Pharmacogenomics. 2007; 8(1):1-3.
8. US Food and Drug Administration. Sally's Tamoxifen Review (Draft 9/15/06). 2006 [cited 09/10/2008]; Available from: www.fda.gov/OHRMS/DOCKETS/AC/06/briefing/2006-4248B1-01-FDA-Tamoxifen%20Background%20Summary%20Final.pdf
9. Piper MA. CYP2D6 pharmacogenomics of tamoxifen treatment. Washington DC: Blue Cross Blue Shield Association 2008.
10. Alfaro CL, Lam YW, Simpson J, Ereshefsky L. CYP2D6 inhibition by fluoxetine, paroxetine, sertraline, and venlafaxine in a crossover study: intraindividual variability and plasma concentration correlations. J Clin Pharmacol. 2000; 40(1):58-66.
11. Matchar D, Thakur M, Grossman I, McCroy D, Orlando L, Steffens D, et al. Testing for cytochrome P450 polymorphisms in adults with non-psychotic depression treated with SSRIs: Agency for Healthcare and Research Quality 2006. Technology Assessment No. 146.
12. Cancer Research UK. UK breast cancer incidence statistics. 2008 [updated August 2008; cited 03/09/2008]; Available from: http://info.cancerresearchuk.org/cancerstats/types/breast/incidence/.
13. Micheli A, Mugno E, Krogh V, Quinn MJ, Coleman M, Hakulinen T, et al. Cancer prevalence in European registry areas. Ann Oncol. 2002; 13(6):840-65.
14. Palomaki G, McClain M, Haddow J. ACCE Reviews of Genetic Tests: BRC1, BRC2, and CFTR In: Gwinn M, Bedrosian B, Ottmann D, Khoury M, editors. Genomics and Population Health. Atlanta (GA): Centers for Disease Control and Prevention, Office of Genomics and Disease Prevention; 2005. p. 27-33.
15. Roche Molecular Systems Inc. U.S. Food and Drug Administration. 510(k) Substantial Equivalence Determination Decision Summary for Roche AmpliChip CYP450 microarray for identifying CYP2C19 genotype (510(k) Number k043576). 2005 [updated 19 April 2006; cited 21/04/2008]; Available from: www.fda.gov/cdrh/reviews/k043576.pdf. .
16. Roche Molecular Systems Inc. U.S. Food and Drug Administration. 510(k) Substantial Equivalence Determination Decision Summary for Roche AmpliChip CYP450 microarray for identifying CYP2D6 genotype (510(k) Number k042259). 2004 [updated 19 April 2006; cited 21/04/2008]; Available from: www.fda.gov/cdrh/reviews/k042259.pdf. .
17. Roche's AmpliChip test gets EU approval. Pharmacogenomics. 2004; 5(7):763.
18. NICE. Early and locally advanced breast cancer: diagnosis and treatment. 2009 [cited 11/03/2009]; Available from: http://www.nice.org.uk/Guidance/CG80.
19. NICE. Advanced breast cancer: diagnosis and treatment. 2009 [cited 11/03/2009]; Available from: http://www.nice.org.uk/Guidance/CG81.

20. Stearns V, Johnson MD, Rae JM, Morocho A, Novielli A, Bhargava P, et al. Active Tamoxifen Metabolite Plasma Concentrations After Coadministration of Tamoxifen and the Selective Serotonin Reuptake Inhibitor Paroxetine. J Natl Cancer Inst. 2003; 95(23):1758-64.
21. Pharmacogenetics and Pharmacogenomics Database (PharmGKB). Available from: http://www.pharmgkb.org.
22. International Tamoxifen Pharmacogenomics Consortium. ITPC Profile. 2009 [cited 11/03/2009]; Available from: http://www.pharmgkb.org/views/project.jsp?pId=63.
23. Little J, Higgins J, editors. The HuGENet HUGE Review Handbook, version 1.0 2006 [cited 30/06/2008]; Available from: http://www.genesens.net/_intranet/doc_nouvelles/HuGE%20Review%20Handbook%20v11.pdf.
24. Khan K, Ter Riet G, Glanville J, Sowdon A, Kleijnen J. Undertaking systematic reviews of research on effectiveness. CRD's guidance for carrying out or commissioning reviews. CRD Report Number 4 (2nd Edition). York: Centre for Reviews and Dissemination, University of York 2001.
25. Jorgensen AL, Williamson PR. Methodological quality of pharmacogenetic studies: Issues of concern. Stat Med. 2008; 27(30):6547-69.
26. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analysis. Br Med J. 2003; 327:557-60.
27. Drummond M, Jefferson T. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working. Br Med J. 1996; 313(7052):275-83.

10. Appendices

Appendix I Details of MEDLINE clinical search strategies

1) Clinical validity: Do women with breast cancer identified as EMs for CYP2D6 have similar or different clinical outcomes to those identified as PMs, IMs or UMs?

2) Clinical validity: Is there a relationship between CYP2D6 status and endoxifen levels?

4) Clinical utility: Do women with breast cancer who are identified as EMs for CYP2D6 have similar or different clinical outcomes with tamoxifen compared to AIs**?**

1	exp Genotype/
2	exp Phenotype/
3	(genotype$ or phenotype$).tw.
4	exp Cytochrome P-450 Enzyme System/
5	(CYP2D6 or CYP 2D6).mp.
6	amplichip$.tw.
7	or/1-6
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.
9	exp Tamoxifen/
10	exp Aromatase Inhibitors/
11	or/8-10
12	exp Breast Neoplasms/
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.
14	or/12-13
15	7 and 11 and 14
16	animals/ not (animals/ and humans/)
17	15 not 16
18	limit 17 to (yr="2000 - 2009")

3) Clinical validity: Are endoxifen levels related to clinical outcomes?

1	(tamoxifen or endoxifen or 4-hydroxy-N-desmethyl-tamoxifen).af. or exp Tamoxifen/
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.
3	1 and 2
4	animals/ not (animals/ and humans/)
5	3 not 4
6	limit 5 to yr="2000 - 2009"
7	limit 6 to english language

Appendix 2 Details of clinical data extraction and quality assessment

Data extraction will include but may not be limited to:

- Size of study population
- Aim/Primary outcome
- Study design
- Patients
- Location
- Dose
- Duration
- Follow-up
- Study accounted for CYP2D6 inhibitors?
- Alleles tested
- Method(s) of CYP testing
- Comparisons
- Outcomes measured
- Ethnicity
- Age
- Findings

Studies of CYP2D6 will be assessed for quality using the following criteria, which is based on the checklist developed by Jorgensen:[25]

- Sample size
- Genes/SNPs genotyped
- Genotype procedure and reliability
- Missing genotype data
- Population stratification
- Hardy-Weinberg Equilibrium
- Choice and definition of outcomes

Appendix 3 Details of economic data extraction and quality assessment

Cost effectiveness data extraction will include, but not be limited to:

- Type of evaluation and synthesis
- Intervention
- Study population/disease
- Time period of study
- Cost items
- Cost data sources
- Country, currency year
- Range of outcomes
- Efficiency data sources
- Modelling method and data sources
- Probabilities and assumptions of models
- Cost effectiveness ratios
- Subgroup analysis and results
- Sensitivity analysis and results
- Authors conclusions

Studies of cost effectiveness will be assessed for quality using the following criteria, which is an updated version of the checklist developed by Drummond:[27]

- Study question
- Selection of alternatives
- Form of evaluation
- Effectiveness data
- Costs
- Benefit measurement and valuation
- Decision modelling
- Discounting
- Allowance for uncertainty
- Presentation and generalisability of results