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Evidence used in model-based economic evaluations for evaluating pharmacogenetic and pharmacogenomic tests: a systematic review protocol

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ABSTRACT

Introduction: Decision models can be used to conduct economic evaluations of new pharmacogenetic and pharmacogenomic tests to ensure they offer value for money to healthcare systems. These models require a great deal of evidence, yet research suggests the evidence used is diverse and of uncertain quality. By conducting a systematic review, we aim to investigate the test-related evidence used to inform decision models developed for the economic evaluation of genetic tests.

Methods and analysis: We will search electronic databases including MEDLINE, EMBASE and NHS EEDs to identify model-based economic evaluations of pharmacogenetic and pharmacogenomic tests. The search will not be limited by language or date. Title and abstract screening will be conducted independently by 2 reviewers, with screening of full texts and data extraction conducted by 1 reviewer, and checked by another. Characteristics of the decision problem, the decision model and the test evidence used to inform the model will be extracted. Specifically, we will identify the reported evidence sources for the test-related evidence used, describe the study design and how the evidence was identified. A checklist developed specifically for decision analytic models will be used to critically appraise the models described in these studies. Variations in the test evidence used in the decision models will be explored across the included studies, and we will identify gaps in the evidence in terms of both quantity and quality.

Dissemination: The findings of this work will be disseminated via a peer-reviewed journal publication and at national and international conferences.

Strengths and limitations of this study

- The systematic review will extensively search decision models for evaluating pharmacogenetic and pharmacogenomic tests.
- Focusing on the test-related evidence used allows a thorough investigation into the quantity and quality of such evidence to inform these models.
- Obtaining the level of detail required to answer the systematic review questions may be limited by the amount of information reported in the included articles.

INTRODUCTION

Information from genetic and genomic tests is increasingly being used to inform patient management decisions in healthcare systems.[1] Examples include the identification of individuals likely to respond to treatment (eg, treatment with cetuximab in individuals with K-RAS wild-type colorectal cancer[2]), likely to have adverse treatment responses (eg, HLA-B*15:02 testing to predict Stevens-Johnson syndrome and toxic epidermal necrolysis when receiving carbamazopine)[3], or to inform treatment dose (eg, thiopurine *S*-methyltransferase testing prior to treatment with azathioprine)[4]. Such tests are commonly called pharmacogenetic or pharmacogenomic tests and are referred to collectively as pharmacogenomic tests hereafter. Economic evaluation of these tests is required to ensure that these interventions are providing value for money. Test-treatment randomised controlled trials capturing the health outcomes arising from the actions taken as a consequence of test results can be complex, time-consuming, costly[5] and have a strong potential for bias,[6] so are rare.[7 8] Decision analytic models are therefore advocated as the most systematic and transparent method for economic evaluation.[9 10] Decision analytic modelling allows the costs and benefits of strategies involving genomic testing to inform treatment response, and permits subsequent patient management decisions to be compared with standard approaches, providing insights into the trade-offs associated with the use of these strategies. However, evidence suggests that

relevant aspects of pharmacogenomic testing are not necessarily being captured in economic evaluations,[11] and there is a lack of standardisation in methods[12] and outcomes used.[13] A recent methodological review[14] highlighted additional issues in developing decision models for genomic testing strategies in general, including poor-quality effectiveness evidence and uncertainty concerning the appropriate analytical perspective, what resource and cost data to include, and how to measure outcomes and effectiveness.

A key issue with model-based economic evaluations of pharmacogenomic tests is that they generally contain many more parameters than decision models for economic evaluations of treatments. In addition to modelling the analytical and clinical validity and cost of the genomic testing, other aspects of testing that may be important in these evaluations include:

- The strength of relationship between the genetic information and clinical outcomes: the results of genomic tests do not themselves lead to improved outcomes. Links need to be made between the genomic test results, the treatment options available, the likely treatment response and the clinical outcomes for individuals.
- Estimates of the uptake of genomic testing by patients and clinicians: even if genomic testing has greater analytical and clinical validity than current practice, if individuals are less likely to agree to the genomic testing, it will have little clinical utility and may result in fewer clinical benefits compared with current practice.
- Consequences of false-positive and false-negative test results: depending on the context, the consequences of incorrect test results may have a large impact on the findings of the economic evaluation, for example, severe health impacts of experiencing an adverse drug reaction.
- Costs of sample collection: the costs associated with collecting the samples required for genomic testing should be accounted for.
- Costs of genetic counselling: it may be the case that additional resources are associated with a genomic testing strategy, so that details of the testing and the results can be communicated to, and understood by, those eligible for genomic testing.
- Test failures and/or repeated testing: it is possible that tests may not provide usable results and additional samples may need to be collected and/or tests repeated. Accounting for the costs of obtaining additional samples and/or the time impacts of any failures and repeat testing may be important in an economic evaluation.

Given these considerations, it is not always the case that analytical and clinical validity drive the economic evaluation of pharmacogenomic testing: the clinical utility of new strategies must also be considered.[5 15] It is therefore important that the evidence base to inform pharmacogenomic test parameters in decision models consists of the most relevant and unbiased evidence possible. However, research suggests that for many model-based economic evaluations in health technology assessment, this evidence base is often diverse and of uncertain quality, and that sufficient information is rarely provided on how evidence has been identified.[16] Although reviews of model-based economic evaluations of pharmacogenomics tests have been conducted,[11 12] they have not specifically evaluated the evidence base informing the decision models. In this review, we will systematically investigate the use of test-related evidence in economic evaluations of pharmacogenomic tests to inform treatment response and subsequent patient management decisions. Test-related evidence includes evidence on the analytical and clinical validity of the test, its clinical utility including the relation between genetic information and clinical outcomes, consequences of incorrect test results, test failures and repeats, costs of the test, sample collection and genetic counselling. We will also comment on the quality and quantity of this evidence. Understanding the current state of evidence used in decision models for pharmacogenomic tests will help identify what evidence is lacking and highlight areas where the collection of better quality evidence would be useful for future evaluations. This systematic review protocol has been reported according to the PRISMA-P reporting guidelines.[17]

The aim of this systematic review is to answer the following questions (1) What test-related evidence is being included in model-based economic evaluations of pharmacogenomic tests? (2) How is this evidence being identified? (3) What is the quality of this evidence? and (4) What is the general quality of these model-based economic evaluation?

METHODS AND ANALYSIS

Population: There will be no restrictions placed on the populations in which pharmacogenomic testing strategies are evaluated. For instance, individuals may be newly diagnosed with a condition and yet untreated, or may have received a number of previous treatments before being considered for pharmacogenomic testing.

Intervention: Any pharmacogenomic test used for predicting treatment response will be included. This will include targeted genetic tests as well as genomic tests, and may include next-generation sequencing.

Study design: Economic evaluations of pharmacogenomic tests using decision modelling will be sought regardless of the type of modelling used. Given that there are no restrictions on the outcomes used (see below), this could include cost-effectiveness, cost-utility, cost-benefit, cost-minimisation and cost-consequence analyses.

Measurement of outcomes: There will be no restrictions on the measurement of outcomes. The systematic review will capture all reported model outcomes, which may include quality-adjusted life years (QALYs) from

cost-utility analyses, cases detected from cost-effectiveness analyses, net monetary benefits from cost-benefit analyses, as well as other outcomes.

Search strategy: The search strategy will take the following form: (terms for genetic tests) AND (a bespoke methodological search filter to locate studies which use decision analytic models).

The search strategy, informed by the Centre for Reviews and Dissemination guidance[18] will be run in the following bibliographic databases:

- MEDLINE and MEDLINE in PROCESS (via OVID) 1946 to March 2015;
- EMBASE (via OVID) 1974 to March 2015 March;
- NHS EEDs via (The Cochrane Library, Wiley interface) 1994 to March 2015;
- Econlit (via EBSCO Host) 1886 to March 2015; and
- Web of Science (via ISI) 1900 to March 2015.

As NHS EED is no longer updated, we will be searching this resource as an archive. The HEED database closed in 2015 and it is no longer possible to search it, or access the archive. The annotated search strategy is provided in the online supplementary material. Reports produced by health technology assessment agencies will also be searched to identify relevant model-based economic evaluations that may not have been published. In particular, the online records of the National Institute for Health and Care Excellence in England, the Pharmaceutical Benefit Scheme in Australia and the Canadian Agency for Drugs and Technologies in Health will be searched.

Search limit: Where possible, the search will be limited to human-only population groups. The search will not be limited by language or date. Owing to the level of information required from each article in this review, only studies reporting full details of the decision model will be included. Therefore, conference abstracts will be excluded at the screening stage.

Search recording: EndNote V.7.3 (Thompson Reuters).

Study selection: There will be two stages to the screening. Following de-duplication, title and abstract screening to identify model-based economic evaluations of pharmacogenomic tests will be completed by two reviewers using defined inclusion and exclusion criteria (see table 1). Pilot screening of 100 hits has shown a very high level of agreement between these two reviewers (κ statistic of 0.93). Screening of full-text articles will be completed by one reviewer (but in discussion with a second researcher should there be uncertainties regarding the inclusion of an article).

Data extraction: A data extraction form will be developed and piloted. Details to be collected will include:

- Characteristics of the decision problem, such as disease/condition, gene(s), setting, perspective, purpose of the test (eg, to predict a treatment response, aid dose setting, predict adverse drug reactions), type of test (eg, fluorescence in situ hybridisation testing, Sanger sequencing, microarray testing, whole genome sequencing).
- Characteristics of the decision model, such as the model structure (eg, decision tree plus Markov model), discount rate, time horizon, outcome measures used (eg, QALYs, cases detected), whether probabilistic analyses were done.
- Which aspects of the pharmacogenomic testing strategy reflect clinical utility/benefit above current practice (eg, improved clinical validity, less invasive testing). We will use the checklist developed by Ferrante di Ruffano *et al*[15] to help identify the clinical utility of the new pharmacogenomic test(s).
- Characteristics of the test evidence used to inform the model, including those stated in the introduction. The evidence source used, its study design, how the evidence was identified (eg, by a systematic review, not reported), whether an assessment of the quality of the evidence was reported to have been done. The evidence hierarchy used by Cooper *et al*[16] will be used to help assess these characteristics.
- Whether sensitivity analyses have captured uncertainty in the genomic test evidence.
- Whether authors have reported the use of good practice guidelines to conduct their analyses and/or report their model and results, such as the Modelling Good Practice Guidelines[19] or the Consolidated Health Economic Evaluations Reporting Standards (CHEERS) statement.[20]

The first 20% of included articles will have data extracted by one reviewer and checked by another. If there are any disagreements or inaccuracies in the data

Table 1 Inclusion and exclusion criteria

	Included	Excluded
Study type	Model-based economic evaluations, including cost-effectiveness analyses, cost-utility analyses, cost-benefit analyses, cost-consequence analyses, cost-minimisation analyses	Any non-model-based economic evaluation Any decision model not including measurement of costs
Population	Any	–
Disease/condition	Any	–
Purpose of testing	Genetic or genomic testing to predict treatment response	Any genomic or genetic testing used for screening, diagnosis, prognosis or prediction of current or future disease status

extraction, these will be discussed. Once these disagreements or inaccuracies have been addressed, one reviewer will extract data from the remaining included articles, in discussion with another reviewer in the case of uncertainties.

Study quality: A modified version of the Philips *et al*[21] checklist for the quality of economic evaluations will be piloted before use. A copy of the checklist is given in the appendix but may change after piloting. The Phillips checklist is a suggested list of items for critical appraisal of decision analytic models in health technology assessment and will reflect a number of decision model characteristics that will be extracted.

Data synthesis: Characteristics of the decision models will be tabulated and summarised, drawing together similarities and highlighting differences in approach and/or quality. Variations in the test evidence used in the decision models will be explored, and we will identify gaps in the evidence in terms of both quantity and quality.

Reporting: The systematic review will be reported in line with the PRISMA reporting guidelines.[22]

Discussion: The systematic review will help to characterise the state of decision models evaluating pharmacogenomic testing strategies. It will focus primarily on the evidence used in the decision models to inform the pharmacogenomic testing aspects of the evaluation; however, it is acknowledged that the detail required may be limited by the extent of reporting in included articles (any evidence of this effect will also be noted). Understanding the extent to which genetic test evidence is incorporated into decision models, with particular attention paid to the identification of this evidence, its type and quality, will highlight evidence gaps and areas where better quality evidence is needed.

ETHICS AND DISSEMINATION

As this is secondary research, ethical approval is not required. Disseminating this work to developers of genetic and genomic tests will be important to highlight current evidence gaps as future research priorities. The findings of this work will also be very relevant to researchers undertaking decision modelling to help consider the type of test-related evidence that might be included in future models, and also provide insight on how to identify such evidence. Dissemination will be undertaken via a peer-reviewed journal publication and at national and international conferences.

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Contributions JLP conceived the original idea and contributed to the development of the search strategy. JLP and CC designed the protocol and drafted the manuscript. CC developed and ran the search strategy. JB advised on study design and critically revised drafts of the manuscript and the search strategy. JLP is the guarantor for the review.

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Disclaimer The views expressed are those of the authors and not necessarily of the NHS, the NIHR or the Department of Health.

Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

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Online Supplementary Material

Title: **Evidence used in model based economic evaluations for evaluating pharmacogenetic and pharmacogenomic tests: a systematic review protocol**

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Literature Searching

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)
Host: OVID
Data Parameters: 1946 to Present
Date Searched: 05/03/2015
Searcher: CC Press Checked: JP
Hits: 4034
Search Strategy:

	Search Strategy	Notes (# refers to line)
Intervention	1 Genetic Testing/ (27360) 2 ((gene$ or genom$) adj3 test$).ti,ab,kw,ot. (47181) 3 ((gene$ or genom$) adj3 screen$).ti,ab,kw,ot. (28598) 4 ((gen$ variant$ or gen$ variation$) and (test$ or screen$)).ti,ab,kw,ot. (13508) 5 (DNA adj5 (test$ or screen$)).ti,ab,kw,ot. (21814) 6 *DNA/ and (test$ or screen$).ti,ab,kw,ot. (11567) 7 exp Pharmacogenetics/ (9577) 8 (pharmacogenetic$ or pharmacogenomic$).ti,ab,kw,ot. (10846) 9 *Genotype/ (6096) 10 (genotype or genotyping).ti,ab,kw,ot. (146862) 11 or/1-10 (279529)	1. MeSH term. No explosion available; 2. Truncation to capture genes and genome or genomic; 6. The MeSH term has been focused here (indicated by the * symbol). Focused MeSH terms are studies in which the focused MeSH term represents a core topic for the study. The MeSH term is then further focused by free text; 7. Pharmacogenetics has been exploded to capture Toxicogenetics; 9. The MeSH term has been focused here; and 11. Lines 1-10 are combined using OR, meaning that all of the lines are to be searched. The free-text lines are being searched on: title (ti), abstract (ab), author assigned keyword (kw) and original title (ot)
Search Filter	12 exp *decision support techniques/ (18297) 13 ((economic adj3 evaluat$) or (cost$ adj3 (utility or decision or benefit or consequence or model or effect$ or minimisation or minimization)) or (CBA or CEA or CUA) or DAM or (decision adj3 (model$ or analytic or tree)) or (model based or model-based) or Pharmacoeconomics).ti,ab,kw,ot. (168759) 14 12 or 13 (185150)	12. This line has been exploded to capture the MeSH, 'data interpretation, statistical.' The MeSH term has been focused. 13. This free-text line is used to locate studies that might have models or modelling data as a part of their analysis. It looks for cost effectiveness, cost utility, cost benefit and cost minimisation (UK and US variants) as well as cost

		consequence. It also employs the use of acronyms for these types of analysis, such as: CBA (cost benefit analysis), Cost effectiveness analysis (CEA) and Cost utility analysis (CUA).
Search logic	15 11 and 14 (5020)	15. This line combines the intervention set (lines 1-10: being combined at line 11) AND the search filter (lines 12 or 13: being combined at line 14).
Search limits	16 (letter or editorial or historical article).pt. (1539038) 17 15 not 16 (4961) 18 exp animals/ not humans.sh. (4003797) 19 17 not 18 (4187) 20 (rat or rats or mouse or mice or hamster or hamsters or animal or animals or dog or dogs or cat or cats or bovine or sheep or primate or primates).ti,ab,kw. (3022018) 21 19 not 20 (4034)	16. This line removes the listed publication types from the search. This takes the total search (at line 15) and removes the listed publication types at line 17. 18. This study is only interested in human populations so line 18 seeks to remove studies conducted on (or indexing) animals. It does this using the same Boolean NOT connecter as at line 16, and it uses the Cochrane limit to remove these studies[1].

Notes: N/A
File Name: MEDLINE RIS 4034.txt

Database: EMBASE
Host: OVID
Data Parameters: 1974 to 2015 April 03
Date Searched: 05/03/2015
Searcher: CC
Hits: 5496
Search Strategy:

	Search Strategy	Notes (# refers to line)
Intervention	1 genetic screening/ (49977) 2 ((gene$ or genom$) adj3 test$).ti,ab,kw,ot. (62763) 3 ((gene$ or genom$) adj3 screen$).ti,ab,kw,ot. (36107)	1. This is the EMTREE term for the MEDLINE MeSH term genetic testing. There was no explosion available, as with the MEDLINE search;

	4 ((gen$ variant$ or gen$ variation$) and (test$ or screen$)).ti,ab,kw,ot. (18152) 5 (DNA adj5 (test$ or screen$)).ti,ab,kw,ot. (27287) 6 *DNA/ and (test$ or screen$).ti,ab,kw,ot. (13586) 7 exp pharmacogenetics/ (22746) 8 (pharmacogenetic$ or pharmacogenomic$).ti,ab,kw,ot. (18005) 9 *genotype/ (20957) 10 (genotype or genotyping).ti,ab,kw,ot. (194302) 11 or/1-10 (374521)	2. Truncation to capture genes and genome or genomic; 6. The MeSH term has been focused here (indicated by the * symbol) and free text terms are used to further focus the controlled indexing term for specificity; 7. Pharmacogenetics has been exploded to capture pharmacogenomics and toxicogenetics; 9. The MeSH term has been focused here (indicated by the * symbol); and 11. Lines 1-10 are combined using OR, meaning that they are all to be searched. The free-text lines are being searched on: title (ti), abstract (ab), author assigned keyword (kw) and original title (ot)
Search Filter	12 exp *decision support techniques/ (7483) 13 ((economic adj3 evaluat$) or (cost$ adj3 (utility or decision or benefit or consequence or model or effect$ or minimisation or minimization)) or (CBA or CEA or CUA) or DAM or (decision adj3 (model$ or analytic or tree)) or (model based or model-based) or Pharmacoeconomics).ti,ab,kw,ot. (223720) 14 12 or 13 (230319)	13. This free-text line is used to locate studies, which might have models or modelling data as a part of their analysis. It looks for cost effectiveness, cost utility, cost benefit and cost minimisation (UK and US variants). It also employs the use of acronyms for these types of analysis, such as: CBA (cost benefit analysis), Cost effectiveness analysis (CEA) and Cost utility analysis (CUA).
Search logic	15 11 and 14 (6562)	15. This line combines the intervention set (lines 1-10: being combined at line 11) AND the search filter (lines 12 or 13: being combined at line 14).
Search limits	16 (letter or editorial).pt. (1350686) 17 15 not 16 (6527) 18 exp animals/ not exp humans/ (4319013) 19 17 not 18 (5694) 20 (rat or rats or mouse or mice or hamster	16. This line removes the listed publication types from the search. This takes the total search (at line 15) and removes the listed publication types at line 17. The

	or hamsters or animal or animals or dog or dogs or cat or cats or bovine or sheep or primate or primates).ti,ab,kw. (3496419) 21 19 not 20 (5496)	publication type, historical article, is not listed as an EMBASE publication type as it is in MEDLINE. 18. This search is only interested in human populations so line 18 seeks to remove studies conducted on (or indexing) animals. It does this using the same Boolean NOT connecter as at line 16, and it uses the Cochrane limit to remove these studies[1].

Notes: N/A
File Name: N/A

Database: NHS EEDs
Host: Wiley Interface
Data Parameters: Issue 1 of 4, January 2015 (see notes)
Date Searched: 05/03/2015
Searcher: CC
Hits: 1822
Search Strategy:

	Search Strategy	Notes (# refers to line)
Intervention	ID Search Hits #1 MeSH descriptor: [Genetic Testing] this term only 513 #2 ((gene* or genom*) near/3 test*) 2512 #3 ((gene* or genom*) near/3 screen*) 914 #4 ((gen* variant* or gen* variation*) and (test* or screen*)) 8066 #5 (DNA near/5 (test* or screen*)) 598 #6 MeSH descriptor: [DNA] this term only 428 #7 (test* or screen*) 202901 #8 #6 and #7 136 #9 MeSH descriptor: [Pharmacogenetics] explode all trees 277 #10 (pharmacogenetic* or pharmacogenomic*) 966 #11 MeSH descriptor: [Genotype] this	1. MeSH term. No explosion available; 2. Truncation to capture genes and genome or genomic; 9. Pharmacogenetics has been exploded to capture Toxicogenetics; 13. Lines 1-12 are combined as an OR, meaning that they are all to be searched. This search is run on the following fields: Title, Abstract and Keywords This search was completed by down-loading the returns from NHS EEDs only, therefore the search filter was not used.

	term only 2695 #12 (genotype or genotyping) 6488 #13 #1 or #2 or #3 or #4 or #5 or #8 or #9 or #10 or #11 or #12 17179	

Notes: NHS EEDs is no longer updated as a bibliographic resource so the data parameters are 1994 to Jan 2015
File Name: N/A

Database: Econlit
Host: Ebsco Host
Data Parameters: 1886-Current
Date Searched: 05/03/2015
Searcher: CC
Hits: 145
Search Strategy:

	Query	Limiters/Expanders	Last Run Via	Results
S9	S7 and S8	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit	145
S8	TI (((economic N2 evaluat*) or (cost* N2 (utility or decision or benefit or consequence or model or effect* or minimisation or minimization)) or (CBA or CEA or CUA) or DAM or (decision N2 (model* or analytic or tree)) or (model based or model-based) or Pharmacoeconomics)) OR AB (((economic N2 evaluat*) or (cost* N2 (utility or decision or benefit or consequence or model or effect* or minimisation or minimization)) or (CBA or CEA or CUA) or DAM or	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit	39,843

	(decision N2 (model* or analytic or tree)) or (model based or model-based) or Pharmacoeconomics))			
S7	(S1 OR S2 OR S3 OR S4 OR S5 OR S6)	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit	1,609
S6	TI ((genotype or genotyping)) OR AB ((genotype or genotyping))	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit	117
S5	TI ((pharmacogenetic* or pharmacogenomic*)) OR AB ((pharmacogenetic* or pharmacogenomic*))	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit	7
S4	TI (((DNA N4 (test* or screen*))) OR AB ((DNA N4 (test* or screen*)) and (test* or screen*)))	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit	20
S3	TI (((gen* variant* or gen* variation*) and (test* or screen*))) OR AB (((gen*	Search modes - Boolean/Phrase	Interface - EBSCOhost Research	106

	variant* or gen* variation*) and (test* or screen*)))		Databases Search Screen - Advanced Search Database - EconLit	
S2	TI (((gene* or genom*) N2 screen*)) OR AB (((gene* or genom*) N2 screen*))	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit	51
S1	TI (((gene* or genom*) N2 test*)) OR AB (((gene* or genom*) N2 test*))	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit	1,333

Notes: N/A
File Name: N/A

Database: Web of Science (Conference Proceedings Citation Index- Science (CPCI-S) and Conference Proceedings Citation Index- Social Science & Humanities (CPCI-SSH) --1990-present
Host: ISI
Data Parameters: 1900-2015-02-24
Date Searched: 05/03/2015
Searcher: CC
Hits: 568
Search Strategy:

	Search Strategy	Notes (# refers to line)
Intervention	# 1 2,302 TOPIC: ((((gene or genes or genetic or genom*) near/2 test*))) NOT TOPIC: ((((animal or animals or rat	The search lines here have been run on the TOPIC search field. This searches: title, abstract, author

	or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys or fish or fishes)))) Indexes=CPCI-S, CPCI-SSH Timespan=All years	keyword, and keyword plus. There is no controlled syntax in this database so we have used a pragmatic search string to remove animal studies.
	# 12 1,601 TOPIC: ((((gene or genes or genetic or genom*) near/2 screen*))) NOT TOPIC: ((((animal or animals or rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys or fish or fishes)))) Indexes=CPCI-S, CPCI-SSH Timespan=All years	
	# 13 8,209 TOPIC: (((gen* variant* or gen* variation*) and (test* or screen*))) NOT TOPIC: ((((animal or animals or rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys or fish or fishes)))) Indexes=CPCI-S, CPCI-SSH Timespan=All years	
	# 14 572 TOPIC: (((gene or genes or genetic or genom*) near/2 (variant* or variation*) and (test*))) NOT TOPIC: ((((animal or animals or rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or	

	pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys or fish or fishes)))) Indexes=CPCI-S, CPCI-SSH Timespan=All years	
# 5	1,288 TOPIC: (((DNA near/4 (test* or screen*)))) NOT TOPIC: ((((animal or animals or rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys or fish or fishes)))) Indexes=CPCI-S, CPCI-SSH Timespan=All years	
# 6	1,784 TOPIC: (((pharmacogenetic* or pharmacogenomic*))) NOT TOPIC: ((((animal or animals or rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys or fish or fishes)))) Indexes=CPCI-S, CPCI-SSH Timespan=All years	
# 7	18,645 TOPIC: (((genotype or genotyping))) NOT TOPIC: ((((animal or animals or rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or	

	cow or bovine or sheep or ovine or monkey or monkeys or fish or fishes)))) Indexes=CPCI-S, CPCI-SSH Timespan=All years	
Search Filter	# 8 120,700 TOPIC: ((((economic near/2 evaluat*) or (cost* near/2 (utility or decision or benefit or consequence or model or effect* or minimisation or minimization)) or (CBA or CEA or CUA) or DAM or (decision near/2 (model* or analytic or tree)) or ("model based" or "model-based") or Pharmacoeconomics))) NOT TOPIC: ((((animal or animals or rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys or fish or fishes)))) Indexes=CPCI-S, CPCI-SSH Timespan=All years	
Search logic	# 9 32,180 #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1 Indexes=CPCI-S, CPCI-SSH Timespan=All years # 10 568 #9 AND #8 Indexes=CPCI-S, CPCI-SSH Timespan=All years	

Notes: N/A
File Name: N/A

1. Lefebvre C, Manheimer E, Glanville J. Searching for studies. In: Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions Version 510 (updated March 2011): The Cochrane Collaboration, 2011.

Online Supplementary Material

Title: **Evidence used in model based economic evaluations for evaluating pharmacogenetic and pharmacogenomic tests: a systematic review protocol**

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Modified Phillips checklist for the quality of decision models in health technology assessment

	Comments
Is there a clear statement of the decision problem?	
Is the primary decision-maker specified?	
Are the model inputs consistent with the stated perspective?	
Has the scope of the model been stated and justified?	
Is the structure of the model consistent with a coherent theory of the health condition under evaluation?	
Are the sources of the data used to develop the structure of the model specified?	
Are the structural assumptions transparent and justified?	
Is there a clear definition of the options under evaluation?	
Have all feasible and practical options been evaluated?	
Is there justification for the exclusion of feasible options?	
Is the time horizon of the model sufficient to reflect all important differences between the options?	
Do the disease states (state transition model) or the pathways (decision tree model) reflect the underlying biological process of the disease in question and the impact of interventions?	
Is the cycle length defined and justified in terms of the natural history of disease?	
Are the data identification methods transparent and appropriate given the objectives of the model?	
Where choices have been made between data sources, are these justified appropriately?	
Has the quality of the data been assessed appropriately?	
Where expert opinion has been used are the methods described and justified?	
Is the choice of baseline data described and justified?	
Are transition probabilities calculated appropriately?	
Has a half-cycle correction been applied to both costs and outcomes?	
If not, has the omission been justified?	
Have the methods and assumptions used to extrapolate short-term results to final outcomes been documented and justified?	
Are the costs incorporated into the model justified?	
Has the source for all costs been described?	
Have discount rates been described and justified given the target decision-maker?	
Are the utilities incorporated into the model appropriate?	
Is the source of utility weights referenced?	
Have all data incorporated into the model been described and referenced in sufficient detail?	
Have methodological uncertainties been addressed by running alternative versions of the model with different methodological assumptions?	
Is there evidence that structural uncertainties have been addressed via sensitivity analysis?	
Has heterogeneity been dealt with by running the model separately for different subgroups?	
Are the methods of assessment of parameter uncertainty appropriate?	
Have the results been compared with those of previous models and any differences in results explained?	