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Research Report

Cost-effectiveness analysis of genomic tests: what are the methods challenges?

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1. EXECUTIVE SUMMARY

The development of genomic tests has been rapid; however, the link between the identification of gene-mutations and long-term patient health is still developing. [1, 2] As a result, the clinical value of genomic tests is not always apparent, and very few tests have demonstrated cost-effectiveness. Cost-effectiveness analysis is used to inform resource allocation by assessing the health benefits and cost implications of new interventions. This approach is well established for considering investment in new technologies through the National Institute for Health and Care Excellence's (NICE) technology appraisals, and diagnostics assessment programme. However, the appropriateness of the current NICE approach for genomic tests has been questioned.

The main objective of this report is to determine whether the current principles and methods of cost-effectiveness analysis are appropriate for the assessment of genomic tests. First, a systematic literature review is undertaken to understand the challenges associated with applying the methods of economic evaluation to genomic tests, together with potential solutions previously identified. Second, the defining features, from an economic perspective, of genomic tests are established from the literature and used to define the key challenges associated with economic evaluation in genomic testing. Finally, the methods challenges associated with these defining features are identified. There are many practical issues remaining, however. Most are similar to problems faced in applying economic evaluation to other health technologies. We have discussed some practical issues commonly considered in the literature, such as the dearth of relevant evidence, but other general practical issues in economic evaluation have not been discussed in this report when they are covered in current methods guides.

Our review highlights two main differences between cost-effectiveness analysis of genomic tests and that of other technologies: the evaluation of tests for multiple disorders and the potential for infinite time horizons. In common with other diagnostic technologies, there is also a question of whether assessing health gain alone is sufficient to capture all the benefits of the intervention. Current methods for combining diagnostic evidence with treatment patterns and health consequences are well established. However, this could be difficult to implement with genomic tests given the large number of possible treatment disorders and treatment patterns. This report suggests three alternative approaches to economic evaluation to address this issue: an iterative approach, an aggregate approach or a pragmatic approach. The iterative approach suggests that the use of a genomic test would be considered independently in each disease area of potential use, this is the process used by the NICE Diagnostic Assessment Programme. The aggregate approach

suggests that all diseases for which the genomic test could be useful would be assessed in a combined analysis, where the costs and consequences of all diseases would be assessed at once. The pragmatic approach requires some upfront clinical decision guidance to determine which disease areas are most likely to drive the cost-effectiveness of the test, and then to undertake a more qualitative approach for determining the direction of bias for those disease areas not fully included in the analysis.

A further potential challenge of assessing the cost-effectiveness of genomic tests is the potential for an infinite time horizon. This is because it depends on whether the information could and would be shared in the future. Currently there is no national system for sharing genomic information so information sharing ultimately depends on the individual. The principle of economic evaluation is that all future costs and consequences should be considered. Current methods capture costs and consequences over the lifetime of a patient. However, there is a potential for the genomic information collected to have consequences for future generations. This issue is the same for other types of diagnostics, but is not currently considered by the NICE Diagnostic Assessment Programme in terms of formal analysis. This challenge suggests the need to understand the cost-effectiveness of a national system that could store and share genomic information.

As with other technologies, genomic tests are associated with many non-health consequences. This is a broader issue that requires decision makers to determine, firstly, whether non-health consequences should be considered and paid for by the NHS. Subsequently it would be important to determine how these non-health consequences should be traded-off against health and how to take account of non-health benefits in the opportunity costs.

Many of the issues in the genomics literature have been identified for other types of technologies including the addition of non-health benefits such as information value, the lack of relevant evidence, the quickly changing environment and the benefits to non-patient populations. Many of the features of conducting economic evaluation of genomic tests are the same as for more general diagnostic testing. The diagnostic nature of genomic tests implies the same common challenges, such as test error and the difficulty in establishing the added value of a test to the decision maker and patient populations. Solutions to many of these problems are well established, and the assessment of the cost-effectiveness of diagnostic tests is increasingly well practiced.

Many of the sections in this report refer to a lack of relevant evidence. This is invariably the case in economic evaluation and does not preclude the need to follow the methods given the available information. Many clinical questions remain regarding the use of genomic testing and particularly

whole genome sequencing. Economic evaluation will not provide additional clinical evidence but provides a framework in which to consider the implications of available clinical information and recommended treatment patterns. Economic evaluations that use model-based analyses also provide a framework for assessing the value of additional research to generate further evidence.

The commonalities and shared challenges with other health technologies suggest that the principles and methods of economic evaluation, in general, are appropriate for genomic tests. In terms of cost-effectiveness analysis, further methods research would be valuable on approaches for trading-off health and non-health consequences of tests, assessing the value of sharing genomic information across generations and for choosing among multiple disorders. This methodological research is needed to understand more fully whether current standard methods of cost-effectiveness analysis could be made more directly relevant to health system resource allocation decisions for genomic based diagnostics.

2. INTRODUCTION

Genomics is a branch of molecular biology concerned with the structure, function, evolution and mapping of genomes.[3] Genomic technologies are defined as any test, diagnosis, screen or treatment that involves the use of genomic information. This includes screening to identify people at risk of developing a disease, targeting of medicines and gene therapy. There are many potential applications of genomics that extend beyond the current remit of healthcare services and systems. This document discusses the implications for assessing the cost-effectiveness of genomic tests used to guide decisions in a collectively-funded health service (e.g. the UK NHS).

The delivery of genomic tests within the UK NHS falls into two broad services: (i) genomic-based diagnostic or predictive testing in the context of specialist medical genetics services; and (ii) genomic based technologies in the context of mainstream healthcare, which can then be divided into genomic-based testing and genomic-based treatments (for example gene therapy).

The function and availability of genomic tests has advanced rapidly in recent years motivated by the desire for the diagnosis of complex inherited conditions, the objective of diagnosing the cause of diseases more effectively and the attraction of making treatment decisions specific to individuals' characteristics ('personalized' medicine). Recently there has been a move from testing single genes to panels of genes. Ultimately this expansion will progress to clinical applications of whole exome/genome sequencing. Whilst development of genomic tests has been rapid,[1] establishing the link between the identification of gene-mutations and gains in long-term patient health is still lacking.[1, 2] As a result, the clinical value of such tests is not always apparent,[4] and the cost-effectiveness even less so.[5, 6]

The NHS faces a limited budget and, as a result, any new more costly service provided by the NHS must necessarily imply disinvestment in other areas of NHS care, resulting in some level of forgone health. Cost-effectiveness analysis is used to inform this resource allocation problem by i) determining the health consequences of interventions and programmes to patients and anyone else affected; ii) assessing the costs to the NHS, including any cost savings or ancillary costs as well as the acquisition costs of interventions; and iii) determining whether the new intervention is good value compared to how the resources could be used elsewhere in the health system[7] In the UK, this approach is well established for the consideration of investment in new technologies through, for example, the National Institute for Health and Care Excellence's (NICE) technology appraisals,[8] and diagnostics assessment programme in England and Wales.[9] However, the appropriateness of the current NICE approach in evaluating the value of genomic tests has been questioned.[10, 11]

This report identifies the methods challenges associated with the economic evaluation of genomic tests, discusses the limitations of existing methods to deal with these challenges, and considers potential solutions. First a systematic literature review was undertaken to understand the methods challenges and solutions previously identified. The methods for this systematic review are described in Section 3. In the methods section, Section 4, the defining features of genomic tests are derived from the literature and used to establish the key challenges associated with economic evaluation in genomic testing. In Section 5, key characteristics of genomic tests and methods challenges associated with each are identified. Finally, in Section 6 we compare the methods challenges of genomic tests to those for other types of health technologies, identifying similarities and areas for further consideration. The main objective of this report is to determine whether the current principles economic evaluation and methods of cost-effectiveness analysis are appropriate for the assessment of genomic tests.

3. SYSTEMATIC REVIEW METHODS

A systematic literature review was conducted to identify what authors have argued to be the key methods challenges associated with the economic evaluation of genomic tests, and to consider what potential solutions have been suggested.

Traditional methods of systematic searching were unlikely to identify all relevant literature within a reasonably manageable timeframe. Consequently, a "bidirectional citation searching"[12] technique was used to offer a more pragmatic approach to the identification of relevant papers. This involves identifying an initial set of relevant studies (pearls), which are then used to identify additional literature through the searching of their references and citations. This process is repeated until no new papers of relevance are discovered. The "initial pearls" were identified in consultation with other researchers working in this area, and are listed in **Appendix A-1.**

The literature pool was refined based on investigations of titles and abstracts where available. Literature was excluded if it did not contain some reference to methods challenges associated with the economic evaluation of genomic testing, either by identifying new issues or offering potential solutions to existing ones. Literature not specifically discussing genomics, but instead broader diagnostics, was excluded from the review. The full results of the pearl growing literature review are given in **Appendix A**. The final review contained 61 papers, the full list of which is available in **Appendix A-2**. These were derived from 2,527 hits identified through the iterative process presented in **Appendix A-3**. **Appendix A-4** presents an overview of the key points of each of the 61 papers reviews.

4. METHODS CHALLENGES

This section considers the issues associated with the economic evaluation of genomic testing, presenting the methods issues alongside possible solutions. The challenges and solutions are discussed in terms of the elements of health technology assessment identified in the NICE reference cases.[8, 9] A number of practical challenges were identified which we distinguish from methods challenges. Some of these practical challenges are considered in the discussion section due to their role as limiting factors in the conducting of economic evaluations.

The section is structured around the core considerations of any economic evaluation, namely: the definition of the decision problem, and the identification of the associated benefits and costs.

4.1.1. DECISION PROBLEM

Defining the decision problem provides a framework for an economic evaluation. When defining the decision problem NICE suggests it is important to consider:

- the disease or health condition and the population(s) for whom treatment with the technology is being appraised;
- the technology (and the setting for its use);
- the relevant potential comparator technologies (and the setting for their use if relevant)
- the principal health outcome measures appropriate for the analysis;
- the costs to be included;
- the time horizon over which health effects and costs will be assessed;
- consideration of patient subgroups for whom the technology might be particularly clinically and cost effective;
- issues relating to advancing equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and society as a whole;
- other special considerations and issues that are likely to affect the appraisal, for example, existing relevant NICE guidance and the innovative nature of the technology.

Here we discuss issues of particular interest for genomic tests. Firstly, the possible identification of multiple disorders is discussed; this has implications for defining the population as well as the comparators. Next the time horizon and discounting is considered. Finally the perspective of costs and benefits are discussed as previous literature has suggested alternatives for genomics from the current NICE recommendation for technologies.

4.1.2. IDENTIFICATION OF MULTIPLE DISORDERS

Unlike other diagnostic tests all genomic tests use two primary sources of information (a patient's genetic sequence or the genetic sequence within a tumour). As such the marginal costs of additional genomic investigations on a given sequence are likely to be relatively small. Once a patient's DNA has been collected the additional cost of further tests is negligible (note, however, there may be additional costs associated with reporting the test result and with subsequent care that are not small). This may be particularly useful for patients with non-specific symptoms, which might indicate several different diseases. Examples of such tests currently in development include the personal genome machine (PGM), which identifies multiple gene mutations.[13] This characteristic of genomic testing implies that the cost-effectiveness of performing multiple genomic tests at the same time is unlikely to be the same as undertaking them separately because of lower total costs and fewer detrimental health effects from being tested.

The review conducted found no literature directly considering the evaluation of tests that identify multiple disorders. This is expected to be due to the lack of such tests currently available in the NHS or more widely.

As a genomic test might identify multiple disorders and the same tests might be used in several different populations, it is important to specify how the population of interest will be identified. Identification of the population will include responses to previous diagnostic tests, symptoms, and possibly responses to previous genomic tests undertaken by family relations. The principle of identifying the population of interest does not differ from other types of technology appraisals, but since genomic tests can be used for a broad population covering multiple disorders narrowing the decision problem may take more consideration.

Once the patient population has been identified then it will be possible to determine the other treatments or testing strategies that should be compared with the genomic test. As with all diagnostics, choosing comparators can be complicated as the number of possible strategies is increased by different test sequences, and the frequency and timing of follow-up. The further complication for genomic tests is that its capability to identify multiple disorders might require that it be compared with all the possible testing strategies for all the possible disorders, however this can be limited by specifying a more focused decision problem.

Finally, the identification of multiple disorders will potentially affect many different treatment pathways (i.e. subsequent strategies for positive or negative diagnostic results), each of which must be identified when determining the decision problem. In principle researchers could specify the

decision problem to a single disorder and then consider each additional disorder iteratively. It is important to note that the cost-effectiveness of testing for one disorder, evaluated independently, does not guarantee the cost-effectiveness of the test for other disorders, as the identification of additional disorders may be associated with significant cost implications and/or negative health benefits. If a test is found to be cost-effective for a single disorder and the test is implemented for that single disorder, then further decisions that could be made from the test results for additional disorders may not need to include all the costs of the test in the cost-effectiveness analysis of the additional disorders. However, attributing the costs of the test to a single disorder may result in the test not being cost-effective. Alternatively researchers could conduct an economic evaluation for multiple disorders that could be investigated using the same genetic test. Under such a solution, each disorder, within the set to be evaluated, would have the incremental costs and benefits estimated i.e. the costs and benefits resulting from the genetic test and the subsequent treatment pathways followed. The incremental costs and benefits from each disorder would be aggregated along with the cost of undertaking the genomic test and used to estimate a single incremental cost-effectiveness ratio (ICER) for the full set of disorders.

A related consideration to testing for multiple disorders is the issue of incidental findings which refer to the possibility of finding potential abnormalities that are unrelated to the clinical question for which the test was initiated. These have also been called unsolicited findings or secondary findings. To fulfill the principles of economic evaluation, the consequences of all findings or possible findings of a test should be included in the analysis. The consequences of incidental findings will be determined by the clinical judgments made on the basis of the result. If clinical practice is to ignore incidental findings then there is no need to include them in the economic evaluation. If clinical practice is to follow-up on some or all incidental findings, incurring resource costs and potential therapeutic decisions with consequences for patients, then this should be reflected in the economic evaluation along with the probability of the incidental findings and reflected by a clear description of the health technology under evaluation. For inclusion of the incidental findings in the economic evaluation, the methods discussed for multiple disorders are applicable. Whether iterative or aggregate approaches are taken, a full economic analysis of each disorder being tested is required before a decision can be made about the cost-effectiveness of the test. These evaluative approaches are likely to be costly, time consuming and require a large amount of evidence and may reach the same decision as a more pragmatic approach. Under a pragmatic approach, an *a priori* judgment could be made as to which disorders are expected to be associated with the greatest net health effects, and full economic evaluations only applied to these areas. In some instances there may be no quantifiable health effects of a genome-based diagnostic such as when used as a

diagnostic tool for rare inherited disorders for which no treatments are available. All other disorders for which the test might be used should be subject to a more qualitative evaluation to ensure that there are no significant additional costs or detrimental effects. In this way the direction of bias from not including all possible disorders might be better understood. When beginning an economic evaluation of a genomic test it must be determined whether there are multiple disorders to consider.

4.1.3. INFINITE TIME HORIZONS

As with other technology assessments the time horizon should cover all downstream costs and effects of treatments over the period for which differences are expected. Genomic tests may provide information for not only the proband (the individual being tested) but also for genetic relations which may include future generations. This suggests costs and effects may be possible over many generations (infinitely) as the treatment effects are not only accrued over the life time of the proband as is the case in most other types of technologies. Similar issues arise in assessing the value of other health interventions such as immunizing infectious diseases where future generations benefit from the eradication of disease. Methodologically, there is no difference from cost-effectiveness analyses of other technologies, but practically there may be difficulty in understanding the potential future treatment practices, costs and benefits.

When considering the future use of genomic information the analyst must consider the long-term costs. These will include the cost of storing information and making it accessible to future clinical decision makers. In the NHS, the 100,000 Genomes Project will adopt a dynamic reporting system which aims to report back to clinicians at least every year.[14] Currently no national infrastructure is available in the NHS for this type of storage and sharing, so the analyst will have to consider the probability that this information would be passed along or used in the future if the patient is responsible for sharing this information. The analyst must also consider the long-term consequences of the future use of the genomic information. More work is needed to understand how genomic information from a relative could be used in clinical practice and to quantify these potential long-term consequences. This is not a conceptual challenge for an evaluation, but is likely to present problems in terms of identifying relevant evidence. A decision to implement a national storage and sharing system will be important because of the potentially high budget impact and the irreversible nature of the fixed and variable costs. An assessment of the long-term costs and consequences of storing genomic information would be useful for all subsequent assessments of genomic tests.

As with public health initiatives and screening technologies, the expected benefits of genomic tests may occur well into the future. To appropriately consider future costs and benefits the trade-off between present and future costs and benefits needs to be understood. The UK Treasury recommends that future costs and benefits of public sector goods are discounted at an annual rate of 3.5%.[15] The Treasury defines this discount rate as "the value society attaches to present, as opposed to future, consumption". The discount rate may be considered to comprise three elements: a catastrophic risk premium; a rate of pure time preference; and the diminishing marginal utility of future consumption when per capita consumption is expected to increase over time.[16] The way to think about discounting is that it represents the opportunity cost of funding an intervention today to generate health outcomes in the future. Resources used today to generate health outcomes at some future time-point are effectively forgoing short-term productive opportunities (e.g. they could be deposited in a bank at a positive real rate of interest), and the growth in value of those resources over time could be used to generate greater health outcomes in the future. Discounting allows the analyst to express the *present value* of future improvements in health outcomes generated by an intervention in such a way as to reflect those lost investment opportunities if the intervention is funded. Using a discount rate suggests that current health benefits and future costs are more valuable. Benefits of a genomic test that occur in the distant future, possibly to a genetic relative of the proband, must be weighed against the decision to expend health care resources that could have more immediate benefits. Discount rates may vary over time and the relative importance of future consequences depend on the discount rate. Given current discount rates[8, 9] health benefits to the genetic family are unlikely to add substantially to the value of a treatment as their relative weight will be small.

When determining the time horizon and discount rates for the analysis of a genomic test the same principles should be followed as with other types of treatments. Genomic tests are slightly different from other technologies in that the tests for hereditary diseases may provide benefits and costs to the genetic family for many years. Following the principle that the time horizon should cover all downstream costs and effects of treatments over the period for which differences are expected may justify an infinite time horizon. However, when discounting is applied the very long-term differences will be minimal and at some time point will no longer affect the cost-effectiveness decision. It is important that the analyst justify the selected time horizon. The analyst should report the time horizon at which additional modelling no longer affects the decision and the direction of effect of increasing the time horizon.

4.1.4. PERSPECTIVE

The nature of genomic tests means that testing may result in benefits to the proband and all genetic relations, and the information provided by these tests may affect not only their health but potentially many other aspects of their lives, for example employment or reproductive decisions. Many authors have argued that economic models need to recognise benefits other than the health effects on the tested individual,[17-22] and others call for models to include the implication of the effect on birth decisions, insurance discrimination and privacy.[23] However, given the remit and budget constraints of the NHS, economic evaluations for new health technologies generally focus only on the implications to population health by limiting the perspective of the analysis.[8]

The perspective of an economic evaluation represents the analytical standpoint taken by the decision maker. In the case of the English NHS the budget constraint set by central government (this will vary in different international settings) implies the decision maker (e.g. NICE or NHS England) will seek to maximize population health (or broader measures of wellbeing in the case of social care) subject to this constraint, and will typically not explicitly consider the role of costs falling on other budget constrained sectors. The types of perspective that can be taken by the healthcare decision maker are typically defined as a healthcare perspective or a societal perspective.[24]

Under a healthcare perspective the decision maker seeks to maximize population health (or broader wellbeing) subject to the budget constraint faced by the heath sector, e.g. the NHS in England. A decision to invest in a new activity will be based on the comparison of any additional health gained from the new activity compared with health forgone due to additional costs falling on the healthcare budget and displacing existing activities. Under this perspective, as only the cost implications to the healthcare sector are considered, any additional implications of the activities funded by the healthcare sector on other areas of social welfare are excluded from the decision making process. These might include the non-health benefits or additional costs to employers or other public sectors.[24]

In contrast, a societal perspective seeks to account for these wider implications on costs and benefits as a result of investment in new activities. This would include all costs and benefits to society and should consider for example, changes in productivity, out of pocket transportation costs to patients attending clinics, additional costs and (dis)benefits associated with other public sector budgets such as criminal justice or education. It is important to note that any analysis seeking to take such a societal perspective must not only consider the wider costs and benefits of the new activity, but also the wider costs and benefits of comparators and the range of benefits of any activity that is displaced as a result of additional costs falling on budget constrained sectors.

Currently technology appraisal at NICE requires the adoption of the perspective of the healthcare provider (the NHS and personal social services (PSS)) in the consideration of costs, and that of health gains for outcomes in both their technological and diagnostic appraisals,[8, 9] consistent with a healthcare perspective. In contrast NICE guidance on the evaluation of public health interventions,[25] allows for a wider perspective to be considered in some topic areas.

There are some areas of difficulty that are raised in the literature as a result of adopting a societal perspective. Firstly, it is not clear, given how institutions are set up and budgets established, whether or how health resources should be used to meet other societal goals, such as improving productivity.[24] Trading population health against other outcomes such educational benefits is likely to be challenging for decision makers who are held accountable to the outcomes they achieve in health. Secondly, in order to conduct such a perspective fully it would be necessary to understand the full nature of trade-offs between health, consumption and other social arguments (i.e. defining a social welfare function), a highly complex task that over which social consensus is probably impossible. [24] Finally, as mentioned previously, when additional costs fall on budget constraints, forgone benefits must also be considered,[24, 26].

In the case of genomics, much of the cost-effectiveness literature on the evaluation of existing genetic-based tests takes a healthcare perspective or is unclear on its evaluative perspective.[27-29] Previous literature has called for evaluations to consider multiple perspectives to provide the most information to the decision maker and be clear about the perspective applied.[6] However, while a clear statement of the type of perspective being taken would be welcomed, the issue is much more fundamental. Primarily that there is no consensus on a range of requirements for the application of a societal perspective, such as the appropriate valuation of non-health metrics such as wellbeing and how to incorporate costs that fall outside of the NHS.[24] In order to overcome these issues significant methodological research is required. This research is required not only in the area of genomic tests but the evaluation of all medical technologies as any perspective applied by policy makers should be applied consistently across all evaluations. One pragmatic approach is for studies to identify costs and effects that fall outside a health care perspective, quantify them and assess their opportunity cost i.e. the non-health costs and effects of comparators and displaced treatments. This might be a sort of 'balance sheet' approach to looking at cross sectoral issues.

4.2. ASSESSMENT OF BENEFITS

The challenges associated with the complete assessment of the consequences of genomic testing are raised in much of the literature reviewed. The consequences and costs to be considered are informed by the evaluation perspective. The literature reviewed discusses the difficulties associated

with capturing the health and non-health consequences of a test. The value of a test can be to the proband or their genetic family and be positive or negative. An important determination for the economic evaluation is whether the genomic test will identify a hereditary disease. The main health related effects of genomic tests do not come directly from the test itself, but through the use of the information to impact treatment decisions. Genomic information may have a direct effect on a patient's anxiety but the time frame of this effect needs to be considered. It may be entirely relevant, and a normal response, for a patient to experience short-term anxiety but methods of evaluation should consider the relevant time-frame for anxiety. Anxiety that lasts over a long time can have substantial negative effects on a patient's health status. Non-health effects (that could be valued in terms of gains or losses) can have consequences for the proband and their family in terms of providing information to make life choices.[21]

4.2.1. HEALTH CONSEQUENCES

The different types of information collected from genomic tests (i.e. prognostic, diagnostic, etc.) result in different types of subsequent treatment choices and health related consequences, both positive and negative. The benefits include: increased certainty about diagnosis and mechanism of disease, improved estimation of patients risks of later outcomes which could influence treatment management, better prediction of response to therapy or drug metabolism rates or a reduced potential for adverse events, and improvement in the quality and cost-effectiveness of patient tailored treatment versus empirical approaches to prescribing.[30, 31]

Many of these consequences are difficult to assess due to their significant evidence requirements, an issue raised in much of the literature.[31] For example, a common challenge with the evaluation of any test which performs some diagnostic function is the strong correlation between the cost-effectiveness of the test and that of subsequent treatments.[32] The clinical and cost-effectiveness rely on the availability of effective treatments. It is also dependent on the next best alternative, sometimes called the fallback strategy. The fallback strategy refers to the treatment pathway if the test is not available. Given that a cost-effective treatment alternative exists, one of the main benefits of a test is its ability to avoid unnecessary treatment for true negatives. However, in situations where the most clinically effective treatment is not cost-effective, the test provides an opportunity to identify true positives. This may improve the cost-effectiveness of the treatment pathway, by identifying true positives as a sub-group who benefit from the treatment. To understand the possible consequences to be included in an economic evaluation one must determine whether an effective treatment exists for the genetic disorder or associated illness.

The NICE diagnostic assessment programme (DAP) reference case[9] (and the NICE technology assessment methods guide)[8] recommends that any analysis 'should include all relevant patient outcomes that change in the care pathway as a result of the diagnostic test or sequence of tests' (p.93). This demonstrates that this issue is not unique to the analysis of genomic tests, although suitable evidence may be harder to obtain in genomics,[6, 17] and existing evaluations have been poor in including all treatment implications to patient outcomes.[33]

The requirement to understand the health outcomes of a genomic test might suggest the need for a randomised controlled trial (RCT). However, it may be impractical to collect RCT data for genomic tests given the necessary length of follow-up and sample size. This is a common feature of diagnostic tests. In the absence of such data, NICE DAP recommends that test accuracy be linked to treatment pathways and the expected outcomes of those treatment pathways, for all patients, i.e. true positives, true negative, false positives and false negatives. This is often done using decision analytic modelling. In addition, a full evaluation of the consequences associated with a genomic test must consider the potential treatment implications to the rest of the genetic family including future generations.[30, 34] The hereditary nature of many of the conditions for which the proband is tested may imply some health gain to the family of the proband, if through diagnosis another family member is likely to seek medical treatment earlier. While data collection across generations may represent a challenge, by understanding the hereditary nature of a disease it is possible to consider the potential consequences of genomic information around particular indications to future generations through economic modelling. A further clinical complication is understanding the hereditary pattern of disease. If understood clinically, this can also be included in the economic modelling. This begins with the question, is the genomic information being collected for a disease that is hereditary?

The evaluation of pre-natal and pre-implantation genomic testing, where the proband is yet to be born, or any test that has implications to future generations, is more challenging due to the role of termination as an available decision, as well as the difficulty in quantifying the future health consequences of those who are yet to be born or even conceived. Clearly the potential long-term health consequences associated with a test, where an outcome could include termination of the foetus or embryo, must be dealt with carefully, as there are many factors which are being considered. As such, an important question when determining what types of consequences must be included in an economic evaluation is whether the proband is yet to be born.

The potential health consequences across unborn generations are not well served by the current NICE reference case[9] or the wider literature. While evaluative "best practice" tells us to include all

relevant health outcomes,[8, 35] typically potential health consequences of future generations are not included due to the difficulty in quantifying the impact. However, some economic evaluations have sought to include future health gains of unborn children.[36] The evaluation of pre-natal and pre-implantation cases occupies a grey area between these two extremes, as conception has occurred but the child is not yet born. Legal precedent might suggest the consideration of the legal limit of pre-natal termination (24 weeks gestation in the UK in compliance with the Abortion Act 1967) as the point beyond which outcomes should be included in an evaluation. Whilst there is consideration of these issues in the literature,[37] the legal, ethical and practical implications of this are vast. As discussed the ideal approach from an evaluative perspective would be to include all future health implications, appropriately discounted over time, to everyone affected by the initial test. However, a lack of sufficient evidence and broader policy concerns may necessitate a more pragmatic approach. Whatever approach is taken, a clear description of the assumptions made and their impact on the results of the analysis is vital, and the approach taken on the future consequences must be consistently applied to future costs. This is an area that future NICE evaluations of diagnostics, or any test or treatment with an impact on the health of future generations, should consider.

4.2.2. NON-HEALTH CONSEQUENCES

The consequences (positive and negative) of a genomic test may go beyond the direct medical benefits to the person tested.[10, 38, 39] Non-health consequences to the patient and their family include the value of informed decision making for the patient and relations; these can be in terms of, for example, reproductive or career decisions beyond the health implications discussed in the previous section.[10, 19, 34, 39-42]

The value of non-health consequences may be completely independent of the health effects of the test,[34] and, as such, may have a large effect on resource allocation if formally considered in decision making (discussed in Section 3.1.3). Literature states that there is little evidence that these have been included in existing economic evaluations.[22, 41, 43, 44]

The consideration of non-health consequences in any economic evaluation is associated with three challenges, as discussed in part in Section 3.1.3. Firstly, if, as with the NHS, the health care provider is budget constrained and compelled to focus on health outcomes, is it legitimate for disinvestment to occur in an area of health provision in the NHS to fund the accrual of non-health consequences? Secondly, if such reallocation is legitimate, how does an economic evaluation trade-off health and non-health outcomes? Finally, are such outcomes fully reflected in the consideration of opportunity costs, i.e. how do we fully reflect the non-health benefits of what must be disinvested?

The inclusion of non-health consequences is not reflected in the NICE guide for economic evaluation of diagnostic tests or technologies.[8, 9] The reasons for this exclusion are grounded in NICE's focus on population health, and is discussed in Section 3.1.3.

Further, many authors have emphasised that existing methods to quantify benefit, i.e. the QALY, do not represent an appropriate method for considering non-health consequences.[30, 31, 44, 45] This is not surprising given that the QALY is a measure of health status, although there is a literature which discusses its characteristics as a broader measure of individual utility.[46] Some have argued for the use of other methods such as willingness-to-pay, which would be consistent with using cost-benefit analysis rather than CEA as the method of economic evaluation.[43] In addition, some have argued it is feasible to keep within the extra-welfarist view that is consistent with using CEA but broaden beyond the current restrictive definition of health by using the capabilities approach, whereby the value of an intervention is considered to be its impact on individual (cognitive) capability that captures the value of informed decision making.[10, 43]

Not only is there a difficulty in identifying and quantifying non-health consequences, but their inclusion in any economic evaluation would require an understanding of how health and non-health should be traded-off.[24] As well as understanding how we reflect the non-health consequences of displaced treatments when existing practices are disinvested to fund new practices which add to system costs. As such it is a challenge to include non-health consequences into an economic evaluation to inform a funding decision. Further research is required not only on the suitability of the proposed methods aimed at estimating the non-health consequences but also the implications for their inclusion in a decision making process.

4.3. ASSESSMENT OF COSTS

The NICE DAP reference guide[9] considers costs in two parts: the cost to the NHS and PSS, and costs to other government bodies (no private sector or individual costs are considered unless they are reimbursed by the NHS or PSS). Costs to the NHS and PSS should include all costs associated with the diagnostic and comparators evaluated, as well as all costs related to the condition of interest and incurred for the rest of the period evaluated. Wider public sector costs are allowed in NICE diagnostic evaluations but only as a non-reference case analysis and should not be included in estimates of the ICER.

Most cost-effectiveness studies in genomic testing have been found to restrict costs to the direct costs of testing and any therapeutic or preventative interventions.[27] However, many authors have highlighted that the cost of a genomic test includes more than just the direct cost, such as additional

clinic visits, the cost of subsequent treatment, genetic counselling and further diagnostics.[47] In addition, Vegter *et al*[5, 48] has found substantial variations in the costs associated with the same genomic tests used to target treatments and Brown *et al*[49] that there is substantial uncertainty in the cost of screening and subsequent treatment.

However, , the complete estimation of costs is primarily not a methods issue, beyond the establishment of the correct perspective to be taken, discussed in Section 3.1.3. The majority of issues around the variation in the costing approaches could be solved by: adherence to the methods proposed in the NICE DAP reference case, and conducting more research to construct robust cost estimates relevant to genomic tests. Examples of such estimates elsewhere in the health sector include the BNF (for pharmaceutical product costs)[50], NHS Reference Costs (for NHS activities)[51] and PSSRU (for social services)[52]. The fundamental challenge is that, unlike pharmaceuticals, there is no national list of available genomic tests as each laboratory is free to set their own price (or charge) to clinicians requesting the test.

5. KEY EVALUATIVE CHARACTERISTICS

The systematic review, presented in the previous section, identified six characteristics that demonstrate the combination of challenges associated with the economic evaluation of genomic testing. Each of these characteristics is briefly detailed in this section, their role in determining the correct evaluative method being discussed.

Is the test for identity purposes?

One form of genetic testing is for identify purposes, for example in paternity testing. As these are not provided by the NHS and are not associated with potential health benefits their role in economic evaluation has not been discussed in this report.

Is the proband yet to be born?

A specific case may be made when genomic tests are used in situations where the proband is not yet born, such as pre-implantation and pre-natal tests as defined by Sequerios et al.[53] As discussed in Section 3 this characteristic raises many issues in the evaluation of termination decisions and forgone future health. Although these decisions might be a part of many genetic tests, the issues and treatment choices may be different if the proband is not yet born. Existing NICE guidance does not cover such methods issues for technology or diagnostic assessments;[8, 9] however, best-practice would indicate the inclusion of all future health care costs and health benefits, appropriately discounted.

Will the test identify multiple disorders?

In many cases an individual may undergo a test of multiple genetic disorders simultaneously to improve the speed and reduce the costs associated with multiple separate tests; for example, a pre-implantation test is likely to evaluate multiple potential conditions and abnormalities when considering the suitability of the embryos. Section 3 contended that any economic evaluation should take account of all costs and benefits. This could be done by assessing each disorder iteratively, aggregating assessments on each disorder, or by using a more pragmatic approach. Alternatively, an evaluation of a test with the capability of identifying multiple disorders may be limited by the decision problem; defining the decision problem clearly is a vital step when evaluating genomic tests.

Does an effective treatment exist for the genetic disorder or associated illness?

In many genomic tests the diagnosis of a condition may not lead to the direct provision of treatment, as any treatment may only be able to target an associated illness, not the underlying genetic disorder, or no treatment may yet be available. The lack of a clear treatment pathway subsequent to a diagnosis makes any economic evaluation problematic as a wide definition of the added value of the initial test must be used. The development of new treatments and treatment patterns over time will continually change the cost-effectiveness of genomic tests. One might expect that new cost-effective treatments would only make genomic testing more cost-effective, but for genomic tests which garner their value from avoiding costly less effective treatments i.e. improving false positive detection, the development of a new cost-effective treatment may mean the genomic test is no longer necessary. This demonstrates the need to re-assess the value of genomic tests when the treatment pathway is changed, as the interaction between treatments, or other aspects of the treatment pathway, and testing is not always obvious. This finding is not specific to genomic tests but is true of all diagnostics more generally.

Is the disorder hereditary?

While the majority of genetic conditions are hereditary, tests for those that are not, e.g. Down's syndrome (only 1% of cases are hereditary), are associated with different effects to the genetic family. Diagnosis of a non-hereditary condition does not provide information to the genetic family regarding their own risk of being a sufferer or carrier. This distinction highlights the different approaches to economic evaluation required for the wide range of genomic tests. While all costs and benefits through time should be included in all economic evaluations, the implications of this in the case of a hereditary condition (incorporating the proband's genetic family) are greatly different than those that are not (the proband alone).

Is the test seeking to identify a sufferer or a carrier?

Conducting a genomic test to identify the carrier of a disease implies that no treatment value will be gained by the proband who is by definition a carrier and hence largely asymptomatic. From a clinical viewpoint it is likely that the diagnosis of a carrier of a genetic disorder will lead to the invitation to testing of the wider genetic family and may result in health benefits beyond the proband. Any economic evaluation must reflect this distinction as, in the case of a proband being a carrier, all health benefits associated with the tests will be those accrued by the wider genetic family, not the proband.

These six key characteristics highlight that, despite the core method of any economic evaluation of a genomic test being consistent with that applied to other technologies, the answers to these additional questions may help researchers identify the areas of potential cost and health consequences outside those generally considered.

6. DISCUSSION

This report aimed to identify the key challenges in conducting cost-effectiveness analysis of genomic technologies, specifically focusing on genomic testing. The principles of economic evaluation were differentiated from the methods of cost-effectiveness analysis and the practicalities of implementing these principles and methods. The intention was to generate a view of the status quo of economic evaluation in genomic testing, which to date has focused on genetic-based tests, and illustrate where future methods research should best be targeted. In doing this a number of issues have emerged.

Our main conclusion is that the principles of economic evaluation are applicable for the assessment of genomic tests. There may, however, be some practical difficulties in implementing the principles and methods of cost-effectiveness analysis, although many of these are not unique to genomic tests. Further methods development in some areas specific to conducting cost-effectiveness analysis of genomic-based diagnostics will be useful.

Variation in the types of tests means that it is difficult to determine a one size fits all approach to economic evaluation for genomic tests which can range from single condition tests to whole genome sequencing. The focus so far in the literature has been on single gene tests. These are more straightforward to evaluate given existing methods, especially if there is a single condition relating to the faulty gene, for which a single treatment exists. However, the methods issues associated with whole genome and exome sequencing have not yet been covered in depth in the literature. With whole genome and exome sequencing there is the question of who to screen and the appropriate markers for referral. The issue of multiple disorders is a further complication, with the potential for a test to detect a vast number of conditions some with associated treatments. Whilst this may not change the appropriate methods of economic evaluation it will increase complexity, perhaps to a degree which makes complete evaluation of multiple disorders impractical. The solution in these circumstances could be the use of preliminary modelling to select which disorders are most likely to influence cost-effectiveness.

In moving towards whole genome and exome sequencing, there is a need to consider capacity issues. By widening the range of conditions to test and expanding patient populations, there is the potential for genomic testing potentially to become prohibitively expensive to fund, incurring significant opportunity costs. In addition, it is unlikely that current models of clinical genetics services will be sufficient and evaluations that identify and quantify the use of healthcare resources could usefully inform the impact of introducing whole genome sequencing on service capacity in

terms of whether current referral pathways and genetic counselling services can meet the induced demand as more patients and conditions are tested.

The current landscape for genomic testing in the UK NHS is complex and evolving. Genomic testing is currently offered by 23 regional clinical genetics services; however, there is a possibility that in the future genomics will move out of these specialist services to the front of the diagnostic pathway in primary and secondary care. This will present new practical challenges as well as potentially widening the population presenting for testing. By moving services into more mainstream care the potential to access genomic testing is likely to increase. It will then become more important to specify the populations in the decision scope and identifying which markers will be used to stratify patients for testing. It is likely that the cost-effectiveness of testing will depend on which markers have been used to identify patients in the first instance.

It is clear from reviewing the literature, that many of the features of conducting economic evaluation of genomic tests share commonalities with more general diagnostic testing and, as such, encounter many of the same challenges. The diagnostic nature of genomic tests implies the same evaluative hurdles, such as test error and the difficulty in establishing the added value of a test to the decision maker and patient populations. Solutions to many of these problems are well established,[9, 32, 54] and the assessment of the cost-effectiveness of diagnostic tests increasingly well practiced.[55] Valuing 'non-health' benefits and also 'process benefits' can be difficult from a practical point of view as they can be potentially independent from the health effects of the test and can be harder to quantify. This challenge is not exclusive to genomic testing. These trade-offs are particularly apparent in both public health interventions and in more patient centred interventions, such as patient decision aids. The issue of trading health and non-health benefits has been explored using discrete choice experiments (DCE),[56, 57] where individuals express their preferences regarding characteristics of competing treatments. This can include attributes relating to health and non-health benefits. These trade-offs can be used to generate marginal utilities and estimate the willingness to pay (WTP) for different attribute levels. However, DCE's are not without their challenges. Experiments can be complex to design in terms of identifying attributes and constraining these to a manageable amount. More manageable numbers of attributes can still be cognitively challenging and as such there can be issues of validity.[56, 57] It is also not clear how the process benefits of interventions and care should be reflected in terms of opportunity costs through the cost-effectiveness threshold.

Many of the sections in this report refer to a lack of evidence. This is always the case in economic evaluation and does not preclude the need to follow the methods given the available information. When determining whether to fund additional research for genetics, or any other types of technologies, the opportunity costs of the additional evidence should be considered. This requires considering the trade-offs between funding genomic research, funding research for other technologies, or funding other health programmes. This can be done using value of information methods.

There are some practical challenges which must also be resolved. In particular, there would ideally be an improvement in the availability of evidence on both the costs associated with genomics and the benefits of the tests. National price lists of genomic test costs, similar to those instituted for other health interventions, would help avoid the currently reported variation in costs.[58] Data on clinical accuracy and an understanding of potential treatment pathways and fallback strategies are needed to support both clinical and cost-effectiveness.

Further research would be valuable on methods for trading-off health and non-health consequences of tests, assessing the value of storing and sharing genomic information and developing methods for choosing among multiple disorders for a more pragmatic cost-effectiveness approach.

7. REFERENCES

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8. APPENDIX A: PEARL GROWING RESULTS

Pearl growing literature search was conducted on the 13th November 2013.

8.1.1. APPENDIX A-1: INITIAL SET OF PEARLS

1. Assasi N, 2012[27]
2. Carlson JJ, 2005[59]
3. Djalalov S, 2011[28]
4. Fang C, 2011[40]
5. Faulkner E, 2012[30]
6. Griffith GL, 2005[41]
7. Grosse SD, 2008[43]
8. Jarrett J, 2006[60]
9. Payne K, 2008[31]
10. Payne K, 2009[39]
11. Payne K, In press[45]
12. Payne K, In press[10]
13. Payne K 2008[61]
14. Payne K, 2009[62]
15. Philips KA, 2004[63]
16. Rogowski W, 2006[29]
17. Rogowski W, 2007[64]
18. Sullivan W, 2012[44]
19. Veenstra DL, 2000[47]
20. Vegter S, 2008[48]
21. Wong WB, 2010[65]

8.1.2. APPENDIX A-2: ADDITIONAL PEARLS DISCOVERED

Step 1: initial pearl references

1. Asch D, 1990[66]
2. Brown M, 1995[67]
3. Brown M, 1996[49]
4. Col N, 2003[23]
5. Dervieux T, 2006 [68]
6. ECHRD, 2011 [69]
7. Edwards R, 2011 [17]
8. Epstein R, 2010 [70]
9. Faulkner E, 2010 [71]
10. Faulkner E, 2011 [72]
11. Flowers C, 2004 [73]

12. Garrison L, 2007 [18]
13. SACG, 2007 [74]
14. Hall J, 1998 [19]
15. Hubbard H, 2006 [75]
16. Neumann P, 2012 [34]
17. Paci D, 2009 [76]
18. Payne K, 2011 [77]
19. Payne K, 2010 [78]
20. Payne K, 2010 [11]
21. Phillips K, 2003a [79]
22. Phillips, 2003b [80]
23. Ramsey S, 2011 [81]

Step 2: initial pearl citations

1. Cohen J, 2013 [33]
2. Deverka P, 2010 [82]
3. Foster M, 2009 [20]
4. Grosse S, 2010 [83]
5. Grosse S, 2009 [84]

Step 3: first iteration pearl references

1. Bala M, 2004 [85]
2. Basu A, 2005 [21]
3. Conti R, 2010 [86]
4. Giacomini M, 2003 [87]
5. Murray T, 1994 [38]
6. Payne K, 2007 [88]
7. Shackley P, 1996 [89]
8. Van Bebber S, 2007 [90]
9. Vegter S, 2010 [5]

Step 4: first iteration pearl citations

1. Khoury M, 2006 [42]

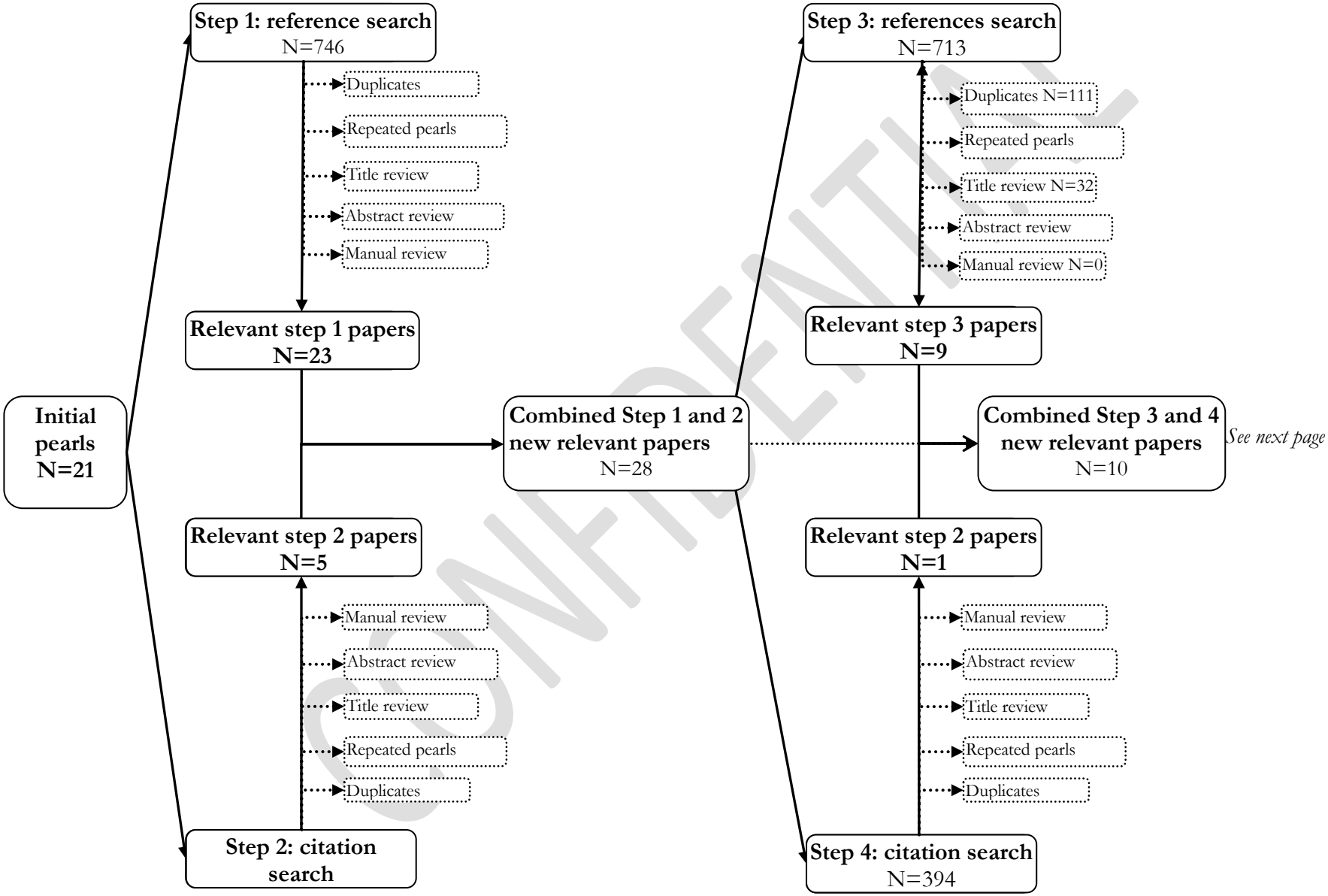
Step 5: second iteration pearl references

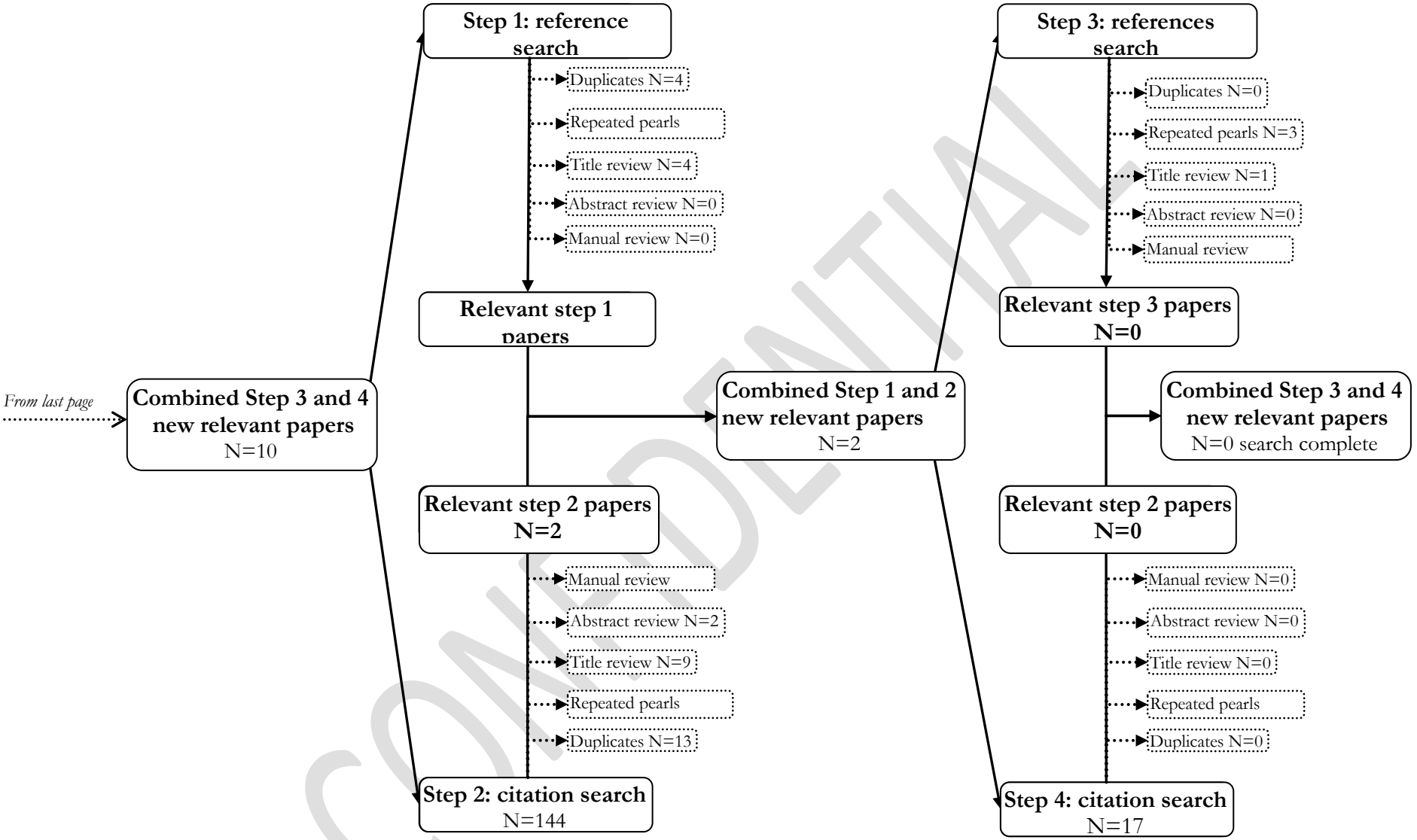
No relevant references discovered

Step 6: second iteration pearl citations

1. Caughey A, 2005 [22]
2. La Caze A, 2005 [91]

8.1.3. APPENDIX A-3: PEARL GROWING EXCLUSION PROCESS





8.1.4. APPENDIX A-4: KEY POINTS OF SYSTEMATIC REVIEW

Author/Year	Key points
Initial Pearls	
Assasi 2012[27]	• Two-thirds of studies reviews adopted a third party payer perspective. • Most studies failed to consider costs beyond initial testing and therapy costs. • More than half of the HTAs had a moderate to low score in methodological and reporting quality. • Identifies several areas of evaluative challenge including perspective, inclusion of wider costs and outcomes, long-term medical and non-medical impacts of genetic tests, and dealing with uncertainty.
Carlson 2005[59]	• Analyses should include uniform measures of outcome that are familiar to decision makers who use the literature. • International guidelines on how to conduct evaluations would be useful. • The number of studies of genetic testing has slowly increased over time.
Djalalov 2011[28]	• Terms genetics and genomics are very broad and include a wide field of biomedical research. • Health care perspective most frequently used in the literature, very few used a societal perspective. • Only outcomes in terms of QALYs are considered in most of the literature.
Fang 2011[40]	• Tests may provide information that does not change a treatment decision. • Test information may also induce harms unrelated to treatment consequences, such as increased anxiety over the test results.
Faulkner 2012[30]	• There are a wide range of potential benefits of pharmacogenetics tests. • There is a lack of guidance on best evaluative practice. • Unclear is QALY is the best metric for diagnostics where it is often difficult to demonstrate clinical utility of standalone test. • Challenges of evaluation include: appropriateness of HTA evaluative framework, poor evidence base, and difficulty in assessing benefit. • Expert elicitation methods maybe required to fill the significant evidence gaps. • Unclear how genetic tests will be valued under VBP.
Griffith 2004[41]	• Literature uses a range of CBA outcomes as well as QALYs. • Future evaluations should include: the value of information, the effects of choice and regret, the feelings of vulnerability, guilt, blame and continuous watching for early signs, discrimination, equality of access to technology, social pressure on choice and social expression of altruism and sympathy.
Grosse 2008[43]	• CV and DCE could be used to measure intergenerational and psychosocial impacts. CBA could be used to measure benefits of information. • The information value of predictive testing has not been incorporated into economic models.
Jarrett 2006[60]	• Found that the economic evaluation papers did not seem to tackle any of the problems discussed in the methodological

	papers. • Argue better skills and guidance in health economics is needed in this area to correctly evaluate genomics
Payne 2008[31]	• QALYs may not reflect all of the potential benefits. Focussing on improved health status alone may miss key benefits, such as ability to make an informed decision. CBA can be used to assess these non-health and process attributes, possibly using WTP methods. • There is a need to consider longer term benefits of tests, such as deaths averted or HRQoL. • The cost of introducing a pharmacogenetic test includes more than just the cost of the test.
Payne 2009[39]	• Genetic testing has three roles: 1. To inform or predict disease diagnosis or carrier status for single-gene disorders and, to a lesser extent, for multifactorial conditions 2. To help predict disease prognosis 3. To target the selection of medicines. • 'Spill over effects' to other family members should be considered. • The results of a test may effect marriage and reproductive decisions. • Genetic tests do not have unique evaluation issues, but current evaluative frameworks may not be directly applicable. • Issues include: wide study perspective, lengthy time horizon, difficulty in focusing on QALY gains, potential need to consider supplementary cost-consequences analysis and limited availability of weak research evidence.
Payne 2013[45]	• The extra knowledge provided by a test result is unlikely to be captured by the EQ5D. • Stated preference methods such as WTP could be used as well as the concept of capability. • There are currently no trial-based economic evaluations of pharmacogenomic technologies.
Payne 2013[10]	• WTP recommended by UK treasury for non-health, QALY not deemed appropriate to measure non-health benefits. • Patients in clinical genetics are not just one individual but include other family members who are healthy but at risk of developing or transmitting a condition.
Payne 2008[61]	• Defines genetic services as offering diagnosis of genetic conditions: information about genetic conditions including information about inheritance and risks to family members; genetic testing; and supportive counselling to help the family make decisions and cope better with the genetic condition in their family. • Traditional approaches to outcome measurement may be inappropriate. • There are various genetics specific outcomes measures available, these focus primarily on process/non-health outcomes.
Payne 2009[62]	• Found most modelled input parameters were based on expert opinion due to a sparsity of available data.
Phillips 2004[63]	• Found 11 studies on the cost-effectiveness of pharmacogenetics, finding most interventions cost-effective.
Rogowski 2006[29]	• Perspective was not specified in many of the studies reviewed.
Rogowski 2007[64]	• Distinguishes between "healthcare consisting of gene technology" and "healthcare enabled by gene technology" the latter being more encompassing and intertwined with treatment rather than e.g. in vitro diagnostics for hereditary disease.
Sullivan 2012[44]	• Concern that QALYs cannot capture the full potential benefits such as familial and non-health effects. • A key challenge is how to generate data on the resource use for care pathways.

	• Significant costs and benefits of testing occur after the test, as a result of the test outcome.
Veenstra 2000[47]	• Strategies may reduce unnecessary drug expenditures by providing treatment to those that would not have otherwise been treated. • The cost of a genetic test includes more than just the cost of the test itself. • In general interventions with a onetime cost that offer long-term benefits are often cost.
Vegter 2008[48]	• Substantial variation in the reported costs.
Wong 2010[65]	• Clinical implementation is limited by a lack of understanding of value for money.
Cycle 1 references	
Asch 1990[66]	• Models of diagnostics should not be limited to the outcomes of withhold, test and treat but include test but withhold anyway and test but treat anyway.
Brown 1995[67]	• Highlighted the need for a better understanding of the costs of genetic testing and subsequent concealing. • Argues that many of the principles of CE for screening tests apply to genetic tests.
Brown 1996[49]	• Finds significant uncertainty as to the costs and benefits of screening and subsequent treatment. • Determination of the cost-effectiveness of genetic screening is dependent on the estimate of underlying prevalence of relevant gene mutation, which is always associated with significant uncertainty.
Col 2003[23]	• Models need to recognise that genetic testing has far reaching implications on family members, birth decisions, insurance discrimination, privacy, and health infrastructure. • Evaluations need to take account of all of the downstream costs and effects. • Availability of genetic tests appears to be driven more by technical feasibility and commercial potential rather than evidence based medicine.
Dervieux 2006[68]	• All CEAs in pharmacogenetics so far are exploratory and argues that analysis using prospective randomised clinical trials is needed.
Edwards 2001[17]	• Discusses the uncertainty the NHS faces in evaluating value and perspective. • Only in a small proportion of all disease areas for which patients are referred for genetic tests are costs and outcomes easy to identify.
Epstein 2010[70]	• Argues that comparative effectiveness research has an important role in personalized medicine but will require the embracing of new data sources and analytical approaches.
Flowers 2004[73]	• Argue for a pragmatic approach to considering the likely dominance of a new test in all cases before formal CEA is conducted.
Garrison 2007[18]	• Argues that the current perspective and repayment environment is suboptimal to incentivise investment into genetic testing.
Hubbard 2006[75]	• Calls for a better understanding of the costs and benefits of infant screening.
Neumann 2012[34]	• Conventional cost-effectiveness analyses may underestimate the value of testing. • Patients may value information from a test even when it does not affect treatment.

Paci 2009[76]	
Payne 2011[77]	• Patient preference was found to be for timely and accurate information on the reason for the test and the meaning of the results, whereas professions focus was on the predictive accuracy and waiting time for the result.
Payne 2010[78]	• Important to understand uncertainty of genetic tests. • Need to generate evidence of predictive value to populate economic models.
Payne 2010[11]	• Need to improve the quality of the evidence base. Currently no prospective economic evaluations of pharmacogenomics. • More complex methods may be required to reflect the number of potential treatment pathways resulting from a multiple gene pharmacogenomic test.
Phillips 2003[79]	• synthesise information on forthcoming technologies to ensure evaluations take place before new technologies adopted.
Phillips 2003[80]	
Ramsey 2011[81]	• Many genomics are introduced without sufficient evidence as to their benefit risk or impact on costs.
SACGHS 2007[92]	• The current health information infrastructure is not well-suited for developing pharmacogenomic technologies and supporting informed practice at the site of care.
ECHRD 2011[93]	• Highlights issue that personalised medicine is likely to stratify patients into smaller and smaller groups, in this way leading to many of the same issues as orphan medicines.
Faulkner 2011[72]	• Need to know if testing solves an unmet need, will the test change practice, is the test correlated with treatment outcomes, who to test, when do you test, how should economic models incorporate the test.
Faulkner 2010[71]	• States that NICE diagnostics panel takes unique attributes into consideration. Issue of how value is recognised. Regulator systems may need to change.
Hall 1998[19]	• The opportunity costs of genetic tests are the same as other health technologies and that taking account of the full range of costs benefits and risks represents significant methodological difficulty. • Information has value to the patient, their family and to society (effecting social interactions such as insurance).
Cycle 1 citations	
Cohen 2013[33]	• A lack of evidence linking diagnostic tests to health outcomes has caused payers to be sceptical about the clinical usefulness of tests.
Deverka 2010[82]	• The biggest barrier to their implementation is the lack of evidence that clinical benefit (let alone cost) occurs through their use. • Lack of investment in funding evidence base required.
Foster 2009[20]	• Argues that the perspective is vital to an evaluation as the utility estimate depends on why the question is being asked.
Grosse 2010[83]	• For economic evaluation to consider benefit fully it must address all three forms of value of a genomic test (analytical and clinical validity and clinical utility).
Grosse 2009[84]	• Reaching agreement on an acceptable contract that fully represents both quality of life & personal utility will be challenging.

Cycle 2 references	
Bala 2004[85]	• Argue that as personalised medicine becomes a reality economic evaluation should be conducted at an individual level to maximize societal welfare.
Basu 2005[21]	• Argues that a societal perspective should take into account the additional costs and benefits to the family of a patient treated. • To take account of the costs and benefits to those other than the patient may be impossible due to huge evidence requirements and raises the equity concerns that their inclusion would entail.
Conti 2010[86]	• The identification of the economic cost of a genetic testing strategy as a challenge. • The lack of data on patient and clinician behaviour as a result of tests results is the most important limiting factor in economic evaluation in genetics.
Giacomini 2003[87]	• To perform economic evaluation first decision makers must inform economic researchers about the aims, context and value system against which to consider the tests.
Murray 1994[38]	• Genetic tests reveal information relevant to others in addition to the person tested. • Ethical considerations of what treatment provision can be stratified ethically by genetic indicators, and that a focus on genetics emphasises racial and ethnic differences that may result in treatment inequality. • Opportunity cost of genetic testing maybe large as more and more genetic 'diseases' can be tested for.
Payne 2007[88]	• Explores patient/professionals' views on the most appropriate outcome domains, many beyond quality of life were identified.
Shackley 1996[89]	• More sophisticated measures of benefit should be incorporated into economic evaluations of prenatal diagnoses.
Van Bebber 2007[90]	• CEA does not capture the full range of outcomes of genetic testing that are important to decision makers and consumers, they recommend decision makers include the value of information and other non-health attributes in considerations.
Vegter 2010[5]	• Substantial variation exists in the reported cost of pharmacogenetic tests for the same polymorphisms, expected to be due to estimates including only material costs versus personnel costs.
Cycle 2 citations	
Khoury 2006[42]	• Highlights the importance of a population perspective on genetic tests. • Highlights the need to quantify the baseline case against which to compare the genetic test.
Cycle 3 citations	
Caughey 2005[22]	• Raises methodological issue of whether/how CEA should include impact to those other than the patient. • Screening in prenatal disease may both reassure and cause anxiety depending on the result. • Raises issue in prenatal diagnosis of how termination should be evaluated under CEA.
La Caze 2005[91]	• Contends that pharmacogenetics challenges the fundamental principles underlying allocation decisions in healthcare, bringing into focus the conflict between equality and utility. • Raises issue that genetic tests may lead to withdrawal of treatment from some patients, disincentivising the test.