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Assessing genomic technologies: do we need to overhaul the health economists' methodological toolbox?

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Genetic tests offered currently by the NHS are either targeted to specific genes of interest or can identify chromosomal rearrangements in the genome, including losses and gains of genetic material. However, genomic technologies are advancing rapidly, bringing unsurpassed genome-wide testing capability. Research studies suggest that these technologies allow disease stratification and individually tailored therapies, thus potentially reducing patient morbidity and avoiding costs of ineffective treatment. However, the NHS is slow to adopt genomic technologies, partly due to a lack of translational research evidence.

With expensive technologies such as whole genome sequencing emerging, health economists have a crucial role to play in the translational process but face several unanswered methodological questions, including which outcome measures and type of economic evaluation are most appropriate, and how to incorporate complex test effectiveness data into analyses. Is it time to overhaul our methodological toolbox and explore the most appropriate methods of economic assessment?

Here, we present initial findings from a PhD project investigating issues relating to the economic analysis of genomic technologies. Key methodological challenges are outlined, informed by a systematic review of genomic economic evaluation literature. Microarray testing, a genomic test close to implementation in leukaemia, is described. This test can identify patients with genomic complexity (multiple genetic changes) associated with poor prognosis and minimal (or no) response to chemotherapy. We use this as a case study to compare cost-effectiveness, cost-utility and cost-benefit analysis. We examine whether the choice of economic evaluation approach impacts upon the implementation decisions made by policymakers.

CONTENTS

1. INTRODUCTION

Genetic tests currently offered by the National Health Service (NHS) are either targeted to specific genes of interest or can identify chromosomal rearrangements in the genome, including losses and gains of genetic material. Common applications include the diagnosis of inherited disorders (e.g. newborn screening for cystic fibrosis [1]), or the generation of information on patient disease status (e.g. predictive testing for *BRCA1/2* in breast cancer [2]). However, there is increasing evidence to suggest that more detailed information on multiple genetic changes across an individual's whole genome can yield better disease stratification and permit individually tailored therapies [3]. Avoiding inappropriate treatment could benefit both patients (by reducing morbidity) and the NHS (by reducing the prescription of expensive treatments). However, the most commonly used genetic tests (e.g. karyotyping, to examine chromosomes in a sample of cells, or fluorescence *in situ* hybridisation (FISH), to detect the presence or absence of specific DNA sequences in chromosomes) are not sufficiently reliable or of good enough resolution to inform disease management.

New genomic diagnostic technologies have been developed that offer genome-wide testing capabilities, simultaneously scrutinising all of an individual's genes and their interrelationships in order to identify their combined influence. These technologies show promise in allowing disease management to be stratified [4]. Tests based on these technologies (e.g. microarrays or whole genome sequencing) may be particularly informative for multifactorial genetic diseases, for example, chronic diseases such as inflammatory bowel disease [5]), where individual gene mutations contribute, but are insufficient alone, to cause the disease.

The NHS has been slow to adopt genomic diagnostic technologies. One commonly cited explanation is the prohibitively high development costs of the tests [6]. However, a more substantial obstacle is the lack of high quality translational research evidence [7]. Economic evidence can make a substantial contribution to the translation of these genomic tests into clinical practice. However previous economic evaluations of genetic and genomic interventions have been mostly conducted in much the same way as those for non-genetic interventions [8]. As complex genome-wide testing approaches have become more common, many methodological challenges surrounding the economic evaluation of these tests have become apparent, such that standard health economic methods may not always be appropriate [9]. These challenges include the need to capture information on the non-health utility and disutility of genomic testing, including the value of testing information to patients, which may not be captured by commonly used outcome measures such as QALYs. As the choice of outcome measure dictates the type of economic evaluation conducted, this can have significant implications for decision making. In addition, it is important to evaluate carefully the cost impact of introducing such tests, and there is often a lack of robust generalisable evidence on effectiveness.

To date there is no consensus amongst health economists on how to address these issues, nor indeed on whether genetics is actually exceptional in any way to warrant any evaluation being undertaken different from other health care technologies from a health economics perspective [10,11]. Few of the genomic tests that have been translated into clinical practice are supported by robust economic evidence. Furthermore, more advanced genomic tests are emerging, such as whole genome sequencing. These tests will be expensive, and

their complexity will mean that robust evidence on effectiveness and cost-effectiveness is urgently required. Health economists clearly have an important role to play in the translational process but until agreement is reached on the most appropriate methods of economic assessment, the contribution of health economics to translational research will be limited.

This paper presents initial findings from a PhD project investigating issues relating to the economic analysis of genomic technologies. Key definitions are given, then the methodological issues associated with conducting economic evaluations of genomic interventions are outlined, informed by a systematic review of the genomic economic evaluation literature. A genomic test is then introduced as a case study. Microarray testing, which is close to implementation in chronic lymphocytic leukaemia (CLL), is described. This test can identify patients with genomic complexity (multiple genetic changes) associated with poor prognosis and minimal (or no) response to chemotherapy. We use this as a case study to illustrate the methodological issues identified in the literature review, consider some solutions to these problems, and more generally examine whether the choice of economic evaluation approach is likely to impact upon the implementation decisions made by policymakers.

2. DEFINITIONS

In the health economics literature, comprehensive definitions of 'genetic' and 'genomic' testing are rarely provided, which leads to some confusion over the exact nature of each type of test as the two terms are often used interchangeably. Furthermore, there is often no distinction made between tests that provide diagnostic vs. prognostic information, or tests that provide both - all are called genetic (or genomic) tests. In the non-health economics literature, more comprehensive definitions are usually provided but these can vary by organisation [12,13].

Historically, 'Genetics' is often used to refer to the study of single genes and their effects whereas 'Genomics' refers to the study not just of single genes, but of the functions and interactions of all the genes in the genome. However, in a clinical diagnostic environment, the distinction is not straightforward. Most tests are referred to as genetic tests, with scientists differentiating between tests that are either targeted to specific genes/DNA regions linked to certain well-defined conditions (e.g. predictive testing for *BRCA1/2* in breast cancer [2]), which represent a fraction of the conditions thought to have a genetic component, or genome-wide assays that are not targeted.

Genome-wide testing emerged many years ago in the form of karyotyping, which identified large changes in chromosomes involving many genes but was not able to detect the small chromosomal changes that might inform disease management. In the past decade, genome-wide testing capability has advanced significantly and microarrays (or 'chips') that have the ability to scan larger sections of the genome at a much higher resolution have become available. Arrays can identify single gene changes but are mostly applied to identify contiguous gene disorders and to consider interactions between certain genes or DNA sequences and a condition. They can also detect smaller, sub-microscopic, Copy Number Variants and Alterations (CNVs/CNAs) and combinations of these changes (e.g. allowing assessment of genomic complexity). However they still do

not assay every DNA sequence in the genome. The most recent technological advances in this field are next generation sequencing technologies such as whole genome sequencing (WGS). WGS has the theoretical potential to look at the whole genome at the highest resolution and can, within the same assay, identify changes within both the coding and non-coding sections of genes, including single nucleotide polymorphisms (SNPs) and CNVs/CNAs. Hence WGS could be said to have both genetic and genomic application.

Finally, this paper considers the methodological issues arising when conducting economic evaluations of genetic and genomic tests across all specialties, except evaluations of pre-implantation and prenatal genetic and genomic interventions for family planning purposes, which have been covered in detail elsewhere [11].

3. SYSTEMATIC LITERATURE REVIEW

As there is no consensus amongst health economists on the best approach to conducting economic evaluations of genomic interventions, a systematic review of the genomic economic evaluation literature was undertaken in order to critically assess the different economic evaluation approaches in this context and to summarise the methodological issues being debated. The literature review had two specific aims:

(1) To identify the methodological challenges faced within economic evaluations of genomic interventions;
(2) To classify these methodological issues into those where (a) there is some measure of consensus; (b) the best approach is currently under debate, and (c) further research is required.

It was anticipated that the papers identified were likely to fall into one of three categories, with search terms chosen accordingly:

(1) Health economics methods papers that evaluated the challenges associated with conducting economic evaluations of genetic or genomic technologies
(2) Applied health economics papers (economic evaluations, costing studies, outcomes research) that highlighted methodological issues when reporting the results of economic evaluations; or
(3) Non-health economics papers that reported research into genetic or genomic technologies and considered their translation into clinical practice, describing methodological issues that could arise in various disciplines, including health economics.

Although this paper focuses on genomic technologies, our review also considered papers related to genetic interventions, as they could provide insights relevant to evaluating genomic interventions. Literature searches were undertaken in Embase, Medline, Econlit, The NHS Economic Evaluation Database (NHS EED) and UK NHS Health Technology Assessments (both via the Centre for Reviews and Dissemination (CRD) database), and The Cochrane Library. The exact search syntax varied between the different databases and was designed to be inclusive (i.e. minimising false negatives). Keywords were identified by reviewing relevant papers in the literature, previous related literature reviews, and examining the Medical Subject Headings used by Embase and Medline. Copies of the search syntax are available on request. Searches were limited to full length papers

published in the English language (to enable in depth reviews to be carried out), studies published on or after January 1990 (to ensure that the results were applicable to the present setting), and studies in humans.

These searches were run in April and May 2012. Papers retrieved from the databases were manually reviewed and selected for further review if the paper title or abstract appeared to meet the inclusion criteria. These papers were retrieved in full and reviewed to identify those which actually satisfied the inclusion criteria. The references of these papers were reviewed to identify potentially relevant studies, and the entire publication record of authors known to be active in this field of research was also scrutinised. All papers were read by JB and relevant material was extracted from articles and entered into a proforma under one of 5 broad categories: Analytical Approach, Costs and Resource Use, Measuring Outcomes, Measuring Effectiveness, and Other. **Table 1** summarises the results of the literature search. Of the 1587 titles remaining after duplicates were removed, 24 met our inclusion criteria. 17 references were also included from other sources, leading to a total of 41 articles being included in the literature review. Most of these articles (39) were published since 2000, 30 of which since 2007.

4. METHODOLOGICAL ISSUES

The literature review identified articles that discussed methodological issues in all five of the aforementioned categories, as described below. **Table 2** summarises the key methodological issues identified.

4.1. Analytical Approach

4.1.1. Perspective

There remains some uncertainty over the correct perspective to use in economic evaluations of genetic and genomic interventions. One study reported that a health system perspective was used in 50% of studies, a societal perspective used in 27%, and in 23% of studies it was unstated [14]. Another reported that 57% of studies took a societal perspective [15]. Wider study perspectives may be beneficial as genetic and genomic testing can affect both healthcare and life decisions (spanning different public sectors): it may be worthwhile for future studies to consider the implications of multiple perspectives within economic evaluations (similar to the approach taken when evaluating public health programmes) [9]. Section 4.3 also discusses the importance of selecting the correct analytical perspective in the context of the measurement of utility.

4.1.2. Timeframe of analysis

Genomic tests can have health and nonhealth impacts which have important long-term implications for both individuals and families, impacts that are not observed when non-genetic interventions are evaluated (e.g. with respect to reproductive choices). Studies that focus on short-term costs and consequences run the risk of misestimating the cumulative costs and effects of an intervention over time [9,11,15-18]. Given that a long timeframe is required in economic evaluations of genomic technologies, discounting is crucial [12,19]: it is important to carefully select a discount rate and consider how variations in this rate impact on study results [15].

4.1.3. Timing of analysis

The substance and context of genomic testing changes continually, and commercial and market forces affect both prices and practices [15,20,21]. Genomic tests are complex dynamic technologies and test accuracy can improve considerably over time, as costs fall simultaneously. Costs, efficacy and benefits are particularly poorly defined for newer interventions [12]: the earlier a genomic test is in product development, the more modelling assumptions must be made when conducting economic evaluations (potentially leading to misleading conclusions) [16]. A further consequence of the dynamic nature of these tests is that the categorisation of patients can also vary over time. As more is learnt about a test, it may be possible to identify additional subgroups of patients, with implications for individualised treatment [19,22,23]. A final challenge with timing economic assessments is that many genomic tests do not enter the healthcare system formally (via regulators). Instead they gradually emerge into clinical practice after previously being offered on a research basis [9]. This makes it difficult to compare economic evaluations conducted for a specific intervention at different points in time [15,20,21].

Despite these issues, evidence from economic evaluations is valued by decision makers at all stages in the translational process, and could be particularly important in the early stages of product development, when decisions about prioritisation of research funding are being made [16]. Rather than delaying economic analyses until better data are available, decision makers may find it more useful for economic evaluations to be undertaken in an iterative manner. Analyses should be rerun when new evidence becomes available and this should be built into study designs [12,19,22,23]. It should also be standard practice to engage in realistic simulations and sensitivity analyses to account for potential changes at each stage of product development and as new evidence becomes available [15,20].

4.1.4. Study design

An appropriate study design should be chosen for the economic evaluation, with particular attention paid to the choice of comparator. Standard genomic testing practice often does not exist, with laboratories using different test combinations in different regions. In the UK, preimplantation genetic diagnosis (including both genome-wide array CGH tests as well as targeted gene tests) to identify genetic disorders in embryos is only available in selected regions [24]. Where appropriate, analyses should therefore assess both genomic testing against nongenetic testing, and also genomic testing in addition to nongenetic testing [25,26]. Furthermore, it is unclear whether expensive yet specific genomic tests should be used in isolation, or whether they should be combined with cheaper less specific non-molecular screening tests. The latter approach may ultimately be more cost-effective [27-29]. Study designs should also take into account subsequent therapeutic decisions in determining the clinical impact of a test [21]. A genetic test for Duchenne muscular dystrophy has recently been developed which can detect mutations across 79 genetic regions. Treatment must be targeted to the specific faulty region, hence 30 different therapies are required in total, costing different amounts. Some exons are more frequently mutated than others: the most commonly prescribed therapy is used by 10% of patients, while the least common is only used by 0.3% of patients. In this scenario it is insufficient to only

conduct an economic evaluation of the genomic test - the cost-effectiveness of testing and individualised treatment will vary considerably, depending on the putative mutation [30].

In summary, genomic test performance can only be evaluated in the context of a specific clinical scenario and target population. Genetic tests often have multiple purposes and varied contexts and it can be difficult to synthesise results across multiple published analyses [18,27]. Study design must be carefully considered at the outset of an economic evaluation of a genomic test.

4.2. Costs and Resource Use

4.2.1. Which costs should be included?

The costs associated with all aspects of testing must be included, beginning with the costs of recruiting patients (in the case of a screening test) [11,15], collecting the necessary information or samples, and completing the various laboratory test procedures [15]. The next step is to cost the analysis of the results (i.e. including informatics solutions, data libraries, and quality assessment tools) [12] and the communication of test results to patients [15].

The costs associated with actions taken on the basis of testing results must also be included e.g. treatment, management of adverse drug reactions, genetic counselling, follow up testing, and any treatments and tests avoided due to having a highly discriminating genomic test [11,15,31,32]. The avoidance of multiple tests can be especially important when there are no clear cut clinical outcomes from a study and the main value of a test is the provision of information to parents to reduce diagnostic odysseys. For example, in a study examining the use of microarrays for idiopathic learning disability in the NHS, the cost of a single microarray (aCGH) test was estimated to be £442, while the cost of karyotyping was estimated to be £117 per test. From a single test perspective aCGH appears to be more expensive than karyotyping. However, the aCGH route was expected to yield 10-15% more diagnoses than the karyotyping route. Furthermore, 92% of cases tested by karyotyping required further diagnostic tests. When all tests were included in the analysis, and the improved diagnostic yield from aCGH was applied, the cost per diagnosis for karyotyping was £4,957, while that for aCGH was £3,118 at that time [6].

It is also important to quantify the time and cost burden of monitoring disease progression and drug response, since this can impact on the cost-effectiveness of genomic tests. In cases where monitoring is cheap and easy to accomplish (e.g. testing for CYP2C9 mutations to direct warfarin therapy [32]), genomic tests to direct treatment may not be cost-effective. The most cost-effective tests are likely to be those for diseases where monitoring disease progression and drug response is difficult and expensive (for example, a hypothetical test for Alzheimer's disease) [32].

More generally, economic analyses should account for all of the training and infrastructure costs associated with a genomic test. Complex genomic tests often have multiple applications and a single test can act as a 'one stop shop' with several different applications, with cost savings arising from economies of scale. It is important

to account for these savings within an economic evaluation, but this can be difficult to achieve in practice [12]. Depending on the analytical perspective chosen (see sections 4.1.1 and 4.3) it may also be relevant to consider indirect costs accruing to patients, for example, productivity gains or losses. However few studies have incorporated these costs into their analyses in practice [10].

In summary, the main difference between costing a non-genetic intervention and a genomic test is that in the case of the latter, a much broader range of costs must be incorporated into an economic evaluation, even if a narrow perspective is taken which only considers the direct costs incurred by a healthcare provider.

4.2.2. How much does a genomic test cost?

In the UK there are no national pricing tariffs for genomic tests [9], and costs are highly likely to vary considerably between different laboratories as there is little standardisation across the NHS [12]. This is particularly problematic when conducting economic evaluations of these tests because NICE only uses nationally agreed prices within its technology appraisal process. Genomic testing costs can also vary considerably across countries, due to local price differences, variations in what constitutes a 'typical' test for a disorder, and differences in the extent to which patients themselves contribute directly to test costs. This will become increasingly problematic as more tests consider multiple genetic changes in a single assay, raising question marks about the generalisability of results across borders and suggesting a greater need for country-specific analyses [33].

4.2.3. When should cost data be collected?

Tests which measure genetic changes present from birth (i.e. in the germline genome) may only need to be performed once in a patient's lifetime, thus representing a one-time only cost [34]. In contrast, changes in tumour genomes tend to be acquired after birth and do not remain stable over time, so multiple genomic tests may be needed if the tumour is the target. Furthermore, some genomic tumour tests are packaged with an informatics solution which filters the data and permits more straightforward interpretation of results. These filters are updated over time when new research becomes available. Thus, data for a particular patient may need to be retrieved and re-analysed multiple times using updated filters, incurring additional costs. This means that many of the costs detailed in section 4.2.1 will need to be collected more than once within an economic evaluation [11,35]. As genomic testing progresses and whole genome sequencing enters widespread use, it may in the future be cheaper and easier to sequence a patient's entire genome multiple times, rather than retrieve and re-analyse data for new indications, presenting an additional cost complication.

4.3. Measuring Outcomes

4.3.1. Outcome measures used in cost effectiveness and cost utility analyses

Disease specific outcome measures (e.g. deaths prevented or complications avoided) are often measured within clinical studies, but they limit comparability and do not capture all relevant dimensions of outcomes. This is a particular problem for genomic tests which provide only diagnostic information. Such information may reduce anxiety or help patients to make future plans, but these non-clinical outcomes are not captured by

disease specific measures. Some authors note that no clinical instrument exists which can capture all relevant outcomes [11]. However, given the difficulties in translating outcomes into life years or QALYs, disease specific outcome measures can be informative in economic evaluations of genomic tests [31].

Preference based measures of health state utility (e.g. QALYs) are more comparable, but are beset by methodological problems, and relevant data is not always available for genomic interventions. QALYs measured using generic multiattribute instruments (e.g. the EQ-5D) do not include nonhealth outcomes (e.g. the ability to make informed decisions, the value to a patient of simply possessing diagnostic or prognostic information) [10-12,15,18,23,28,31,36]. They are typically only calculated for the affected individual and fail to capture family spillover effects (commonly observed in genomic interventions) [36]. Furthermore health state utilities are not available for all possible health states, including those specific to genomic mutations (e.g. living with the knowledge that you have a mutation, or choosing not to have a test and living with the uncertainty) [29]. A particular problem with QALYs is that some complex genomic interventions do not aim to improve health or extend life (e.g. microarray testing in learning disability). This means that differences in outcomes between genomic tests and comparators tend towards zero, which pushes ICERs towards infinity [37]. QALYs have additional limitations for prenatal testing: issues include how to measure the value of avoiding a delivery that would have resulted in the birth of a child with a genetic disorder [38,39], and which individuals' quality of life should be evaluated within the QALY measure [9,10,25,39].

4.3.2. Incorporating personal utility into economic evaluations of genomic tests

In many economic evaluations, a single dimension of utility (clinical utility) can often capture the main benefits of a test [11]. In the case of genomic tests, it is crucial to also consider personal utility (defined as "…those benefits or harms that [are accrued by patients but] are manifested primarily outside medical contexts" e.g. acquiring information that will help patients to make future plans) [40]. Personal genomic information returns large amounts of data about many genetic changes. While some of these are informative, many are of completely unknown significance – this makes the usual criterion of clinical validity less straightforward as a measure of utility [40]. Also there is evidence that health status as an outcome is not considered to be useful when evaluating a genetic test [37]. On the other hand, although personal genomic information lacks clinical utility it may offer other benefits (and harms) that could indirectly affect a patient's well-being [9,23,40]. For some individuals these effects are more profound than the clinical effects of testing [15].

Factors that can have a positive effect on personal utility include the acquisition of information that will help with the understanding of disease diagnosis and prognosis, and widened therapeutic choice based on this information [41]. Accessing this information can enhance individuals' sense of choice and control, giving them greater personal accountability for health-related choices and informing a sense of self-identity and autonomy [11,40]. Furthermore, genomic testing information is valued for the reassurance and anxiety relief it can provide [16,27,38,42], and the fact that it helps patients to make future plans and lifestyle modifications [27,43]. Patients also value genomic risk information for their relatives and future generations [16,37].

Undergoing genomic testing can also have a negative impact on personal utility. It may increase anxiety if a test indicates that a patient should not receive a drug, but no alternative treatment is available [20,44], or if false positives, mutations of unknown significance, and other incidental findings are reported [10,11,37,40]. Family dynamics and reproductive decisions can be disrupted when genomic knowledge is attained [10,11,40], and genomic test results can lead to fear of discrimination and stigmatisation [18,36]. Finally, negative genetic test results can lead to complacency, encouraging unhealthy behaviours [36].

Although there is some merit to considering the personal utility of testing, this information is difficult to measure and incorporate into policy decisions – the metrics for measuring personal utility are not well established [21,27], and little practical advice has been provided on how to appropriately incorporate this information into economic evaluations. Reaching agreement on an acceptable construct and rigorous assessment of personal utility will be challenging [43]. Some authors have focused on particular concepts of personal utility and tried to develop outcome measures based on these (e.g. empowerment [37]), but several limitations of this approach have been noted [22].

The incorporation of personal utility into economic evaluations will depend largely on decision makers. For regulators deciding which tests should be available, it may be reasonable to consider personal utility along with the other dimensions of utility (a welfarist perspective). From a public health care provider (extra-welfarist) perspective with an overall aim of improving health, personal utility may not be relevant [16,36].

4.3.3. Cost benefit analysis

Given the challenges associated with disease specific or preference based outcomes measures, as well as the potential inclusion of information on personal utility within economic evaluations of genomic tests, a number of authors have considered whether cost benefit analysis might have a greater role to play in this context. Although only around 20% of genomic economic evaluations are currently cost benefit analyses, they are considered to be useful because they aim to determine whether social welfare, including both health and nonhealth outcomes and values, is maximised subject to social budget constraints [15,36].

Willingness to pay (WTP) instruments such as discrete choice experiments (DCEs) are considered to be better equipped to capture the wider impacts of genomic testing as they can be used to derive monetary valuations of outcomes that encompass both health and nonhealth factors [10,11,15,18,23,31,36,37]. DCEs in particular can capture the intangible costs of testing (e.g. emotional costs associated with pain, suffering as a result of information) [12]. However DCEs have rarely been used in genomics, or to inform CBAs [15,36]. This may be because people struggle to make hypothetical choices in unfamiliar contexts within DCEs: low public awareness of personalised genomics makes consideration of such testing an unfamiliar context for most people [43].

It has also been suggested that a cost-consequence or comparative effectiveness approach may be relevant for economic evaluations of genomic interventions in order to overcome the issues associated with measuring the

outcomes of a genomic diagnostic test [12]. One can extend this point to suggest that it might be prudent to consider several types of economic evaluation simultaneously to allow for more confidence in study conclusions, particularly in light of the shortage of good quality evidence [45].

4.3.4. Individual versus population outcomes

Finally, considering the outcomes of all patients together will yield information on average outcomes. This may be appropriate when conducting an economic evaluation of a drug which cannot be targeted only at responders. However, an average patient does not always exist when genomic tests are being evaluated [20,38,46]: there is likely to be significant individual variation (e.g. in risk perception) in how patients value an intervention [20,38,40]. Averaging individual outcomes across such a patient population may therefore not be appropriate. Pre-screening activities such as counselling may be able to identify individuals who are unlikely to value a test, and these should be incorporated into economic evaluations if appropriate [40]. More generally, subgroup analysis is crucial when evaluating genomic tests [26].

4.4. Measuring Effectiveness

4.4.1. Poor data quality

The quality of effectiveness data for genomic tests is often weaker than that which exists for non-genomic interventions, limiting the scope of economic evaluations. In part this is because many genetic conditions are uncommon, and large randomised controlled trials (RCTs) would be required, run over long time periods, at great expense, to generate sufficient power to detect clinically significant endpoints. Such trials are often not feasible, and may not provide relevant results at their conclusion, given the fast pace of medical technology evolution [11,12,17,19,20,27,28,35,46-48].

Consequently, regulators are increasingly open to the submission of data from observational studies, cohort studies and other long-term epidemiological investigations in support of genomic tests [20], although this data may also suffer from the problem of inadequate numbers [25,27] and these studies also cannot account for recent advances in treatment [17]. In some circumstances, expert opinion estimates of intervention effectiveness may have to be synthesised from different sources to inform economic evaluations. These issues may not be particularly problematic if the intervention in question is targeted at a small patient subgroup, if the budget impact is small, or if the information provided may result in little to no improvement in measurable health outcomes (see section 4.3.2 for further discussion about personal utility) [11]. However, some commentators have argued that if a genomic test is being used to screen otherwise healthy people: the burden of proof for effectiveness should be higher [11,22]. For low prevalent risk factors, evidence of a highly specific screening test is needed to avoid undue inconvenience to large numbers of people with false-positive test results [20]. Others have argued that as the potential risk and cost of tests rises, so should the level of evidence for effectiveness [20,23]. Tests could also be stratified by budget impact, although this depends on the analytical perspective selected [23].

Noninferiority trials have been suggested as an alternative source of evidence for genomic tests. However, they have several limitations, such as the fact that genomic tests are associated with both additional costs and additional benefits, so supplement rather than replace existing practice. Also, noninferiority trials may need to be larger than RCTs that are designed to show superiority [44]. An additional problem for genomic testing is the personalised nature of test results. To capture the true effects of personalised treatment, there is a need to focus on patients who are outliers [34]. A more individualistic approach to the measurement of effectiveness may be required, similar to N-of-1 clinical trials [12]. However, it is not easy to conduct prospective well-controlled studies of these patients [34].

In summary, the appropriate evidentiary framework for genomic testing is yet to be clearly defined, which means that economic evaluations of such interventions are often based on weak effectiveness data [9,21,23]. 'Wait and see' policy conclusions may become increasingly common in these economic evaluations as decisions are delayed until better evidence emerges (discussed further in section 4.2.3) [12].

4.2.2. Unpredictable patient behaviour

Genomic interventions may only be cost-effective if a percentage of patients behave in a certain way (e.g. undergo appropriate treatment), hence information on behavioural probabilities should be sought and used as an input into economic evaluations of these tests [11,16,20,38,42]. However, little data on behaviour is available [20]. Those studies that do exist are unclear on whether all patients will want to be tested [49] or whether patients will adjust their behaviour to fully adhere to genomic testing advice (e.g. participate in increased medical surveillance) [17,18]. Conti et al. describe the case of genetic testing to inform dose adjustment when patients are experiencing bleeding events due to Warfarin treatment: a lack of information concerning physician behaviour in response to the results of these tests means that evaluating the cost-effectiveness of this intervention is challenging [20].

4.2.3. Post-implementation analysis and evaluation

Given that (a) the quality of effectiveness data in economic evaluations of genomic tests is often poor, and (b) patients may not fully adhere to genomic testing advice, leading to different outcomes, basing implementation decisions on economic evaluations which use evidence generated prior to implementation may be problematic. Compounding these issues is the fact that it has been reported that tests used in routine clinical practice often do not perform as well as in research programmes [25]. Furthermore, in the absence of good quality effectiveness data there is a greater role for economic modelling, which has a greater reliance on assumptions and expert opinion, and is sometimes characterised by significant uncertainty. The combination of these factors suggests that one potential solution to filling this evidence gap might be to collect more practice-based evidence by undertaking comprehensive post-implementation economic analyses and evaluations [42,44]. More pragmatic trials could provide the evidence of effectiveness that cannot be generated using RCTs [47,50]. For genomic tests already in clinical practice there may also be advantages to using large administrative healthcare databases to access routinely collected data and linking this to genomic data to provide evidence for the clinical utility of testing (e.g. Biobank data): the large population size allows

study of infrequent events, and these databases are also representative of routine care so provide real-world effectiveness data [21,47,50].

4.2.4. Data complexity

It is becoming increasingly clear that the information provided by genomic tests is challenging to evaluate due to its complexity. Outcomes are likely to be influenced by multiple genes, and each gene can influence multiple outcomes. The influence of a genetic variant on a given outcome can also vary across individuals [20]. Testing for the *CYP2D6* gene (to indicate tamoxifen resistance) is a good illustration of testing complexity – there are over 130 documented variations of this gene, and it remains unclear which mutations are most clinically relevant [34].

Association studies performed to detect these mutations are commonly underpowered, so the probability of detecting a true signal is tiny [51]. Consequently associations between genotypes detected by genomic tests and phenotypes related with disease are frequently weak and potentially overestimated [11]. Other methodological problems that arise when analysing effectiveness data for genomic tests include issues such as multiple testing (how to properly control the false positive rate) and the 'winner's curse' (the likelihood that the effect of a newly identified mutation is overestimated in initial studies versus later replication studies) [21].

The complexity of the testing process therefore also contributes to the lack of good quality effectiveness data available to inform economic evaluations of genomic interventions. Very large samples (in the tens of thousands) are likely to be needed to provide sufficient power to allow appropriate statistics to be calculated and analyses to be undertaken, given this complexity [51].

Some solutions to these problems have been suggested. For example, polygenic risk scores can combine and thus make the most efficient use of all available genotypic data. This PhD project is examining the use of genomic complexity in CLL tumours as a summary measure. Genomic complexity is defined in one publication as "the presence of three or more CNAs at least 20kb in size, and/or Copy Neutral Loss of Heterozygosity regions (cnLOHs) at least 2Mb in size" [52]. However, these risk scores may require large sample sizes before statistical significance is reached [51]. Also, two separate studies each attempting to design a polygenic risk scoring tool for use in clinical practice for a particular disorder will seldom develop the same scoring tool. Therefore, it will be difficult for decision makers to find replications of single studies or to synthesise multiple studies [15].

4.5. Other

4.5.1. Service delivery

Genomic tests usually fall into one of two categories - those developed in house and provided through accredited clinical laboratories, and those for which a product licence has been granted and commercially marketed genetic testing kits exist [9,31]. In both cases, it is common for there to be a range of laboratories offering sample analysis for a particular disorder, with varying performance standards. For some disorders (e.g.

HER2 testing in breast cancer patients) laboratories with lower testing volumes are more likely to report incorrect findings, which can make the interpretation of results challenging and suggests the need for a model of service delivery focused around specialist regional testing hubs [21,47,49]. The choice of service delivery model within an analysis should therefore be carefully considered as model selection can have a direct impact on economic evaluation results: a genomic testing service organised around regional testing hubs may report fewer incorrect findings but it may take longer to return results to patients, delaying actions based on these results [35]. This provides further support for the more widespread use of post-implementation analysis and evaluation (as discussed in section 4.2.3).

4.5.2. Prioritisation of research

A number of authors have suggested that there may be a greater role for the value of information (VOI) approach in genomics [18,21]. VOI techniques are increasingly widely used within health economics to compare the expected benefits from possessing additional information for a decision maker with the expected costs of undertaking the studies required to acquire this information, to assist with prioritising further research. The pace of innovation in genomics suggests that there is indeed a need to prioritise investment in expensive comparative studies [21]. Furthermore, if evidence of effectiveness remains weak, there is a need to carefully consider the costs and consequences of collecting additional data to better inform translational research [18]. Two recent papers have argued that VOI analysis should be used more widely following economic evaluations of genomic technologies, given the potential impact of these interventions on patients [20,53]. However, with the exception of a single study these techniques have not been applied in this context [53]. This may be due to the fact that there is some uncertainty concerning how useful VOI analysis is if the option of conducting a large RCT to gather additional effectiveness data is not available [54].

5. CASE STUDY INTERVENTION

Given the existence of the methodological issues identified in section 4, a PhD project has been designed to investigate a number of these challenges within the setting of a genomic test in cancer. An Oxford University based study is developing a novel genomic test to diagnose and direct therapy in haematological cancers, along with an informatics solution to enable the successful translation of this test into clinical practice. This study focuses on CLL, a chronic leukaemia which occurs mainly in individuals over the age of 60, is incurable, and is characterised by a chronic relapsing course, requiring regular treatment and thus representing a significant healthcare burden. Genomic imbalances can provide important information concerning response to chemotherapy in CLL patients. Morbidity from the effects of chemotherapy is high, and two-thirds of patients die from complications and develop resistance to available treatments. However, current cytogenetic tests such as karyotyping and FISH testing have limited resolution to detect these genomic changes. A microarray-based test has been proposed with the potential to better facilitate treatment stratification by detecting more of these genomic changes, as well as additional changes such as CNLOH and copy number variant regions.

A health economics PhD project has been designed to run alongside this study. Within this project data will be collected to allow the costs, effectiveness and outcomes of current (karyotyping and FISH) and proposed

(microarray) testing strategies to be estimated and compared. Three types of economic evaluation will be conducted using this data: cost effectiveness analysis, cost utility analysis and cost benefit analysis. The results will be compared to explore the implications of the different approaches for decision-making.

This PhD project can contribute to a number of the methodological debates outlined in section 4. Data will be collected to allow both health system and societal perspectives to be considered so that the implications of multiple perspectives for decision making can be explored. Given that CLL patients can accrue more genetic changes over time, a long timeframe is likely to be required for the analysis, so the impact of different discount rates will be assessed. The informatics solution packaged with the test will be updated at regular intervals to take advantage of new genomic discoveries in this field. Hence the study will be designed so that an iterative analytical approach is possible when new evidence becomes available.

The proposed test will be compared with different combinations of karyotyping and FISH testing to allow for the fact that standard testing practice for CLL does not exist across the UK, and different service delivery models may need to be considered. Following on from this, a full micro-costing of the test will be undertaken to avoid relying on often absent national pricing tariffs. As the project is being undertaken alongside a clinical study, this provides a good opportunity to collect data on costs in most of the categories outlined in section 4.2.1, with particular attention paid to likely training and infrastructure costs in different centres. The microarray test is carried out on genetic material extracted from a patient's tumour, so the test will also need to be rerun multiple times.

Data on both disease specific (e.g. complications avoided) and preference based outcome measures (e.g. the EQ-5D and the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life instruments) will be collected to enable cost effectiveness and cost utility analyses to be undertaken. To incorporate information on personal utility into the analysis and allow a cost benefit analysis to be undertaken, a DCE will be carried out amongst approximately 1000 CLL patients across the UK.

Effectiveness data will be extracted from the clinical study, which is using a combination of UK Biobank data and data extracted from administrative datasets. Information on likely patient behaviour will also be collected by using the DCE to explore patient attitudes towards, and experience of, both genetic testing and cancer treatment. The use of a polygenic risk score (genomic complexity) as a summary measure will be examined, and value of information techniques will be applied to consider the costs and consequences of collecting additional data to resolve any evidence gaps that may be identified.

Most importantly, the results of the PhD project will provide information on the implications of taking different economic evaluation approaches when analysing a genomic test. It is not currently clear what decision makers should do if different types of economic evaluation form different conclusions about the relative costs and benefits of a genomic diagnostic technology. This PhD project will explore the different options available for decision makers in this scenario.

6. CONCLUSIONS

New genomic diagnostic technologies are showing considerable promise in terms of yielding information to allow disease management to be stratified, but a significant obstacle to their more widespread use in the NHS is the lack of high quality translational research evidence. Economic evidence can contribute to this translational research but there are many methodological challenges surrounding the economic evaluation of these tests. This paper presented a systematic literature review which summarised this methodological debate and identified issues where there is consensus over potential solutions, and issues where there is uncertainty and further research is required. A case study genomic test (microarray testing in CLL) was described and used to illustrate some of these methodological issues and consider some potential solutions.

A consensus is yet to be reached amongst health economists on how to solve the vast majority of the methodological issues identified in this paper, and as a result many of the genomic tests that have been translated into clinical practice are not supported by robust economic evidence. More generally, health economists are also yet to reach consensus on a more fundamental question: does 'genetic exceptionalism' (the belief that genetic information is special and must therefore be treated differently from other types of medical information) exist from a health economics perspective i.e. are new methods needed to analyse genomic technologies, or are existing methods sufficient?

Those favouring existing methods argue that genomic tests share many characteristics with other screening or diagnostic technologies e.g. long term health outcomes depend on treatment and patient adherence and are uncertain [11]. It could therefore be argued that many of the issues identified in this paper are present in any form of diagnostic or prognostic testing, genetic or nongenetic. Some authors have previously commented that "the 'new genetics' does not pose new problems for health economics, but it highlights aspects of evaluation that have been neglected in previous economic evaluation research" [10]. This may also be true of research into stratified medicine using genomic interventions.

However, there are several issues that need to be resolved before we can conclude that this is the case with any certainty. Crucially, several authors have argued that the value of genomic tests cannot be adequately assessed using standard methods, and these tests are similar to other complex interventions which may need to take account of both health and non-health benefits [11]. Such complex interventions may not be well suited to current appraisal mechanisms, which assume that the various components can be evaluated separately in different processes, with the benefits subsequently summed to quantify the benefit for the whole service. This assumption does not necessarily hold for complex interventions [37,49]. Systems are being designed to better evaluate these interventions e.g. the NICE Diagnostics Assessment Programme (DAP). However 99% of genetic and genomic tests in the UK cannot be considered by the DAP as they are not formally licensed. In addition the current methods guide for diagnostics remains unclear about how to measure outcomes [37].

Future health economics work in this area should focus on two lines of research. Firstly, papers which consider possible solutions to the various unresolved methodological issues identified in this paper would make a welcome contribution to the literature in this area. Secondly, research is required into a more fundamental question: what type of economic evaluation is most relevant when conducting an economic appraisal of a genomic test? Both methodological research (comparing and contrasting different approaches) and applied research (testing the conclusions of the methodological papers with real world data) are required. This PhD project will contribute to both lines of research, with a particular focus on comparing and contrasting the different types of economic evaluation using real world data for a genomic test. By the end of the project, we will be in a better position to decide whether we need to overhaul the health economists' methodological toolbox for assessing genomic technologies.

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7. TABLES

Table 1: Systematic literature review: results

Database	References identified	After removing duplicates	After reviewing titles	After reviewing abstracts	Papers meeting inclusion criteria
Embase	1253	1052	205	69	16
Medline	878	290	46	13	3
Econlit	44	43	4	2	2
Cochrane Library	193	190	87	65	3
CRD	15	12	6	6	0
Other [a]	-	-	-	-	17
References retained	**2383**	**1587**	**348**	**155**	**41**

[a] Includes articles identified by (a) reviewing the references of included studies, (b) searching the publication records of key authors, and (c) articles that were already known to the authors

Table 2: Summary of methodological issues

Category	Issue
1. Analytical Approach	1.1. The correct perspective to use in economic evaluations of genomic tests remains uncertain, and future studies should consider multiple perspectives.
	1.2. The appropriate timeframe for an economic evaluation of a genomic test can be many years in length. Consequently the discount rate should be carefully selected.
	1.3. The timing of an economic evaluation of a genomic test is crucial. Analyses should be undertaken in an iterative manner and rerun multiple times if possible.
	1.4. The choice of comparator is crucial. Study designs must also take into account all subsequent therapeutic decisions.
2. Costs and Resource Use	2.1. A much broader range of costs must be included when conducting an economic evaluation of a genomic intervention, as compared to a study of a non-genetic test.
	2.2. There are no national pricing tariffs for genomic tests, and costs vary considerably both between laboratories and also between different countries.
	2.3. Cost data may need to be collected on multiple occasions when conducting an economic evaluation of a genomic test.
3. Measuring Outcomes	3.1. It is problematic to use either disease specific or preference based outcomes measures within economic evaluations of genomic tests.
	3.2. Capturing information on personal utility may be important, depending on the analytical perspective chosen, but the metrics for measuring personal utility are not well established.
	3.3. Cost benefit analyses might be particularly appropriate for the evaluation of genomic tests than cost effectiveness or cost utility analyses.
	3.4. Individual outcomes may be more important than population outcomes when evaluating a genomic test. Subgroup analysis is crucial.
4. Measuring Effectiveness	4.1. Data quality is weak. RCTs are infrequent, impractical and expensive, and other conventional study designs are also limited. The individualistic nature of treatment should feed through to study design.
	4.2. Unpredictable patient behaviour means that evaluating the cost-effectiveness of genomic interventions is challenging.
	4.3. There is a greater need for post-implementation economic analyses and evaluations, based on pragmatic trials.
	4.4. Effectiveness data for genomic interventions, when available, is complex and challenging to incorporate into standard health economic analyses.
5. Other	5.1. It is crucial to consider all possible models of service delivery within an economic evaluation of a genomic test.
	5.2. There is likely to be a greater role for value of information analysis in genomics than other clinical areas.

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