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Review

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Personalized Medicine

The use of the 'linked evidence approach' to guide policy on the reimbursement of personalized medicines

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It is uncommon to find published clinical trials that measure the health benefits of medical testing. As a consequence, policy makers often have to decide whether access to, or public funding of, medical tests is warranted without knowing the clinical impact of testing on the patient. In the situation where a policy maker is considering a companion genetic test and tailored drug therapy, deficiencies in the evidence base are exacerbated because two technologies need to be assessed and the proposed genetic biomarker needs to be validated. The Linked Evidence Approach (LEA) is a methodology that was developed in 2005 to cope with inadequacies in the evidence supporting medical test evaluations. In 2010 the approach was adapted to the evaluation of pharmacogenetic interventions. This article describes how LEA and similar analytic frameworks are used internationally, highlights particular challenges with the approach, and proposes ways that LEA might be applied to pharmacogenomic interventions.

Keywords: • biological markers • biomedical • diagnostic test approval • economics • health policy • health services accessibility/economics • individualized medicine • molecular targeted therapy • outcome assessment (health care)/economics • outcome assessment (health care)/methods • pharmaceutical • pharmacogenetics • technology assessment

Background

Tests are not perfect

In the past, tests have not received the same degree of scrutiny by policy makers, when formulating public funding decisions, as therapies have traditionally received. This could be because therapies have immediate and obvious impacts on patient health, whereas the consequences of testing are indirect and not immediately observable. However, tests are far from perfect and may result in immediate harm (associated with the procedure), or harm secondary to inaccurate information. Factors that can affect test accuracy include: poor communication and insufficient understanding of testing procedures; inappropriate test selection/ordering and interpretation of results; patient and/or specimen misidentification; inadequate specimen obtained for testing; specimen collection errors; and specimen contamination [1].

Advances in genetic testing have raised further quality challenges. A survey of all pathology laboratories in Australia, where test regulation and accreditation is fairly stringent, reported that genetic tests ranged considerably in their ability to correctly identify patients who have the target condition [2]. The estimated analytic sensitivities were largely concordant across the 52 laboratories surveyed (Table 1) and suggest that, in the most extreme example, up to 80% of patients with a condition could receive a false negative test result.

Even a small amount of imperfection in test accuracy can undermine the commercial viability and cost-effectiveness of a companion diagnostic and therapy [3]. For example, if a test has a high false positive rate, more patients would receive an inappropriate treatment resulting in an increase in treatment costs for no additional health

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Table 1. Range of genetic test methods offered by 52 Australian laboratories and their estimated analytic sensitivity[†].

Method	No. of types of tests based on method	No. of reports	Range of expected analytic sensitivity	No. of discordant reports[‡]
Diagnostic genetic tests (mutation identification)				
Mutation screening	48	48	60% to >94%	nil
Sequencing	146	174	20% to >94%	4
Sequencing plus MLPA	51	101	60% to >94%	2
Specific assays	108	177	<20% to >94%	2
FISH	25	47	60% to >94%	1
Somatic testing				
Mutation screening	2	2	80% to >94%	nil
Sequencing	3	3	80% to >94%	nil
Specific assays	29	66	40% to >94%	8
FISH	32	51	>94%	nil

[†] Data taken with permission from [2].
[‡]Expected analytic sensitivity for the same method and type of test varying by >20% in different laboratories.
FISH: Fluorescent *in situ* hybridisation; MLPA: Multiplex ligation-dependent probe amplification.

gain. The test/therapy combination would not be cost-effective and unlikely to receive government or insurance subsidization. The impact of test performance on the cost-effectiveness of therapies might have spurred the introduction of methods guidance in the UK [4,5], Europe [6] and the USA [7–9] (2008–2012) regarding the evaluation of tests for regulation and reimbursement purposes. Australia – perhaps because it had a policy mechanism specific to the evaluation of tests as part of a medical service – produced its guidance on medical test evaluation for reimbursement purposes in 2005 [10].

Evaluation of tests, when performed, is often restricted to test performance only (sensitivity, specificity etc) with little consideration given to the impact on patients of receiving a false negative result – leading to delayed treatment – or of a false positive result – leading to inappropriate treatment (no additional clinical benefit and additional harms from toxicity) [11]. This, in part, may be because many geneticists and laboratory scientists believe that the information from testing has value in and of itself [12]. However, it may also be due to the lack of direct trial evidence assessing the impact of testing on patient health outcomes.

Di Ruffano *et al.* (2012) conducted a capture-recapture analysis using two searches (broad and specific) from the Cochrane CENTRAL hand searched trial database to estimate the number of randomised controlled trials published on diagnostic tests between 2004–2007. Of the 23,888 randomized controlled trials retrieved, 135 were found to be diagnostic randomised controlled trials. The capture-recapture analysis estimated 37 diagnostic trials were published per year for the 4 years [13]. This is in contrast with the 5938 therapeutic trials per year that were known to have been published.

In general, if a test performs poorly in a diagnostic effectiveness trial, false positive and false negative test results will be reflected in the measured health outcomes of patients. However, as trial evidence of the impact of medical, including genetic, tests on the health outcomes of patients is often scarce, policy makers are faced with making decisions on access to, and reimbursement of, tests on the basis of incomplete and uncertain information.

The 'Linked Evidence Approach' (LEA)

To address this evidence gap, in 2005 a methodology was published that aimed to provide the maximum amount of information on test effectiveness and cost–effectiveness to Australian policy makers [10,14]. This 'linked evidence approach' (LEA) involves the narrative linking of evidence assessing components of a test-treatment pathway in order to predict the likely impact of testing on patient health outcomes. The method was informed by criteria developed by Fryback and Thornbury (1991) to assess the efficacy of diagnostic imaging tests [15]. These criteria include technical efficacy, diagnostic accuracy, diagnostic thinking (change in diagnosis), therapeutic efficacy (change in management) and patient outcome efficacy (change in health outcomes). The method was also informed by analytic frameworks pioneered by the US Preventive Services Task Force (USPSTF) to identify key questions that

guide clinical practice guideline development [16]. These frameworks address both the harms and benefits of medical testing on the patient [17–19].

The Guidelines on LEA [10] recommend the systematic review and narrative linking of evidence under certain conditions. This linking of evidence would occur in instances where direct trial evidence of the effect of testing on patient health outcomes is not available or inadequate for decision making purposes [10]. The evidence linkage is primarily undertaken as a methodological substitute for the ideal hypothetical trial that would be used to measure the health benefits of the test on patients (Figure 1) [14]. The trial design is broken down into its elements and used as a template for the decision analytic model which integrates the information and determines whether the new test is both effective and cost-effective [14]. Evidence addressing each element of the decision analytic model is systematically acquired and rigorously critiqued.

A systematic literature review of Australian health technology assessments (HTAs) [20] reported that the method had been applied to 85 patient indications for testing between 2005 and 2012. The method was used on tests for diagnostic, staging and screening purposes, as well as for genetic tests [21,22].

In the original Guidelines on LEA, it was noted that if there was evidence that the patients eligible for the new test are similar (transferable) to those patients currently receiving treatment for the condition, the findings of test accuracy studies could be considered sufficient to determine the clinical utility of the new test [10]. This means that the findings from studies that report the effect of the comparator (current) test on (i) the selection of treatment options for patients, and (ii) the flow-on effects of treatment on the health of these patients, could be used in a decision analytic model to simulate or predict the health benefits associated with the new test.

A key element of this transferability assumption is Fryback and Thornbury's criterion on change in management (see Figure 1). If the test, no matter how accurate, does not change the treatment options or management offered by the health professional to a patient, then there will be no impact of the test on the patient's health status. This means that there is no need to evaluate the safety and effectiveness of the treatment options in the linked test-treatment pathway. Put simply, the new test would create an additional cost for no additional patient health benefit and so would be considered cost-ineffective. A decision framework has been developed to assist those applying the linked evidence approach, including providing guidance on the type and extent of evidence needed in a linkage [20].

Staub *et al.* (2012) reviewed the methods used in English-language HTAs of medical tests to assist policy makers with regulation and reimbursement decisions [11]. The review encompassed the work of 18 HTA agencies in eight countries and found that 48% of the 149 HTAs reported only on test accuracy, 11% on test accuracy and the impact of treatment, 24% on test accuracy and impact on patient management, and 17% on all linked evidence elements. Of the 17 HTAs reporting the use of an analytic framework, Fryback and Thornbury's criteria was cited as the integrative framework in five HTAs, while the Australian linked evidence approach was cited in 12 HTAs.

The use of evidence linkage and integrative frameworks in medical test evaluation, in order to inform policy decisions, is increasing and is now recommended by many of the major technology assessment organizations internationally [5–7,10,23].

Genetic testing & methods of evaluation

According to a status report published in 2007, approximately 6.8 billion laboratory tests are performed annually in the USA [1]. The revenue, spending, and test volume of the clinical laboratory testing market has grown steadily. More than 4000 laboratory tests were available for clinical use in 2007, of which 1162 tests were reimbursed by US Medicare [1].

A key initiative developed specifically for the evaluation of genetic tests by the Centers for Disease Control and Prevention in 1997, was the creation of the Office of Public Health Genomics which in turn sponsored the ACCE Model project in 2000 [12]. The ACCE Model was the first publicly-available analytical process for specifically evaluating scientific evidence on emerging genetic tests. The model presents 44 questions that need to be addressed to determine the Analytic validity, Clinical validity, Clinical utility, and Ethical, legal, social implications (ACCE) of a genetic test [8]. It was applied to the assessment of several genetic testing technologies, including – in the first instance - an assessment of prenatal screening for cystic fibrosis via carrier testing for CFTR mutations [24], as well as in mini-reviews of genetic [25] and pharmacogenetic tests [26].

In 2004 the Office of Public Health Genomics established the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) initiative and, in 2005, a Working Group was created to develop an evidence-based process for assessing genetic tests and other clinical applications of genomic technology [27]. The EGAPP initiative commissions systematic reviews of genetic tests that address key questions that have been developed using USPSTF-style analytic frameworks, as well as using elements of the ACCE model.

The EGAPP Working Group has reported difficulties in generating evidence-based recommendations

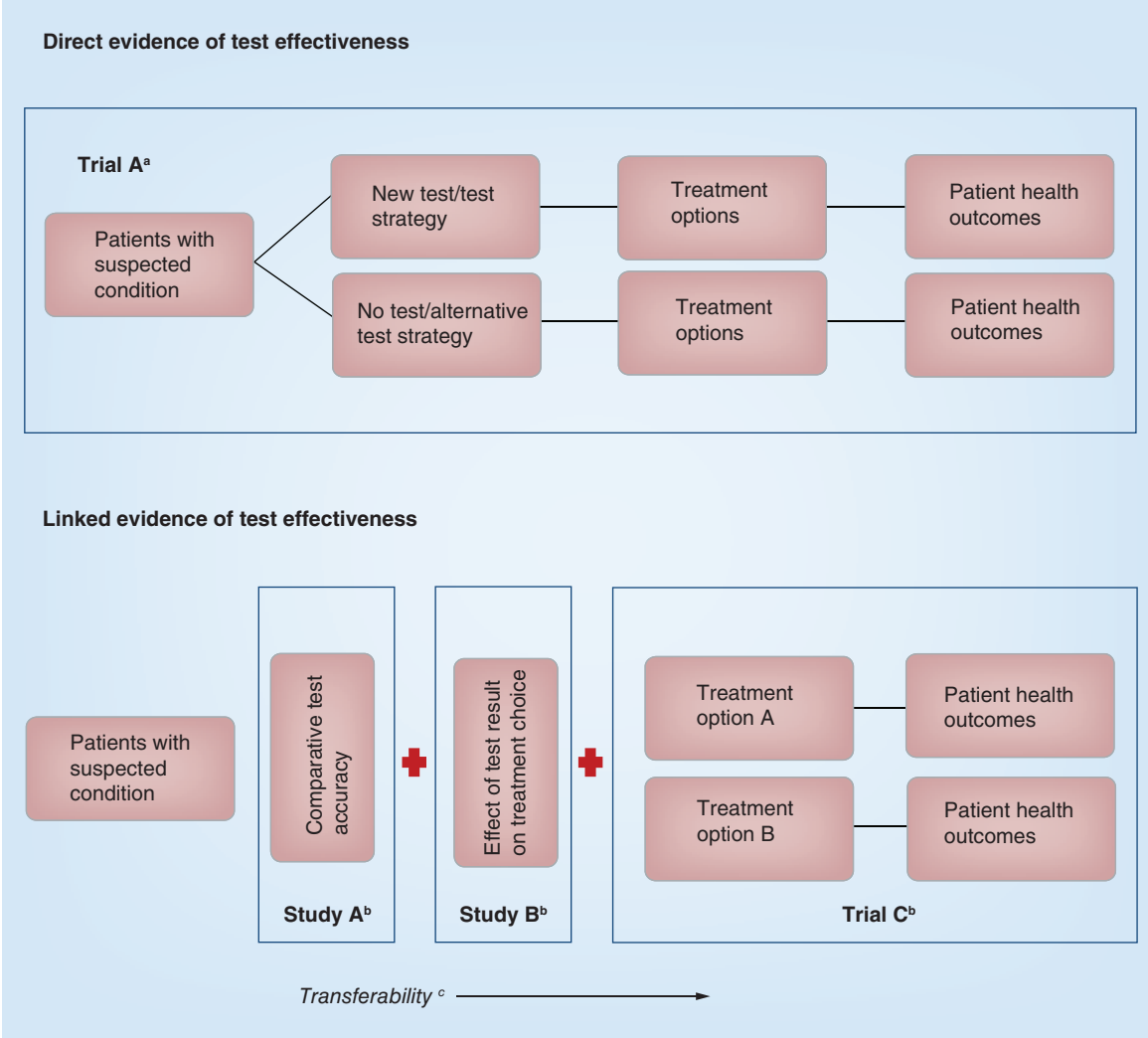

Figure 1. Estimating the clinical effectiveness of testing using the linked evidence approach.
[a] The results from one or more of these trials (including meta-analyses) would form the direct evidence base showing test impact on patient health outcomes.
[b] The results from one or more of each of these types of studies and trials (including meta-analyses) would form the linked (or indirect) evidence base predicting the test impact on patient health outcomes.
[c] Populations, tests and outcome definitions should be transferable (similar) across linkages.
Adapted from [10].

regarding the clinical utility of different genetic tests because of the scarcity of good quality evidence. The Working Group speculated that randomized controlled trials were lacking because of the constraints imposed by time, recruitment and resources when designing and implementing studies on testing for rare conditions or when the downstream effects of treatment involved relatively small effect sizes compared with usual care. The Working Group methods allow for the use of observational or nonrandomized evidence when high level evidence is not available [12,27].

This is very similar to the Linked Evidence Approach whereby different hierarchies of evidence and appropriate critical appraisal techniques are used to address different types of questions in the linkage [10]. The evidence hierarchy that is used addresses questions on diagnostic accuracy, interventions (relevant for direct evidence of diagnostic effectiveness and change in management studies), aetiology, prognosis and screening. It was originally produced to assist with clinical practice guideline development [28].

The synthesis of evidence supplied to the EGAPP Working Group is used to formulate recommendations on the use of genetic and genomic tests in clinical practice [29,30]. EGAPP information is disseminated to various stakeholders but the EGAPP initiative is not directly responsible for the regulation or reimbursement of genetic tests [27].

Molecular testing has seen recent, rapid and escalating growth in developed economies, especially in the fields of infectious diseases and oncology [1,2]. This may, in part, be because these tests can identify particular genetic biomarkers that predict the therapeutic performance of specific drugs (pharmacogenetic application). Molecular testing methods identify specific sequences of human DNA or RNA to identify errors (mutations) that may or may not be associated with disease ie single nucleotide polymorphism, gene insertion, deletion or rearrangement. In Australia, requests for molecular tests increased 2.8-times from 2006 to 2011 [31]. Somatic genetic tests and diagnostic (mutation identification) tests each increased by 23% from 2006 to 2007, whereas pharmacogenetic tests increased by 101% [2]. Pharmacogenetic interventions involving a companion genetic test and tailored drug treatment have been emerging over the last decade and this has created challenges for existing regulation and reimbursement technology approval mechanisms.

Practical difficulties with the evaluation of pharmacogenetic interventions for policy decisions

There are some impediments to the evaluation of companion diagnostics and pharmaceuticals for reimbursement decisions. Terasawa *et al.* reported large differences in the way genetic factors are grouped and analyzed within pharmacogenetic studies, making it difficult to combine and interpret findings across studies [32]. Similarly, Laksman and Detsky (2011) noted that "the huge number of genes available for demonstrated associations and the wealth of information being churned out at an increasing pace leave some with the feeling that we are producing more data than we can analyze or understand" [33].

Perhaps this is the reason why Holmes *et al.*, when they conducted a systematic review of pharmacogenetic studies in 2009, found that the ratio of commentary/reviews to original research in the available evidence base (4674 papers spanning 1967–2007) was 25:1 [34]. Researchers and clinicians appear to be struggling to process all of the available information into a cohesive whole.

Holmes *et al.* also reported that of the original pharmacogenetic studies obtained, the majority focused on candidate genes rather than genome-wide analysis, were of inadequate sample size, provided suboptimal capture of genetic variation and were characterized by 'significance chasing' and reporting bias [34]. These problems lead to a failure to replicate and validate genetic associations [35,36].

Similarly, systematic literature reviews on selected pharmacogenetic tests for cancer treatment found problems with the evidence-base on *CYP2D6* for tamoxifen in breast cancer, *KRAS* for anti-EGFR antibodies in colorectal cancer, and *BCR-ABL1* for tyrosine kinase inhibitors in chronic myeloid leukemia [32]. Studies had small sample sizes and so could not reliably identify small treatment effects. Additional problems that were observed, irrespective of whether the genetic biomarker was a germline polymorphism (*CYP2D6)* or a somatic mutation (*KRAS*, *BCR-ABL*), included the lack of formal assessment for treatment-by-biomarker interactions (i.e., treatment effect modification) and the use of surrogate short term outcomes of treatment failure rather than patient-relevant outcomes such as overall survival or progression-free survival. Terasawa *et al.* noted that adjustments for potential confounding factors were often not based on sound epidemiological principles and that adjustments for multiple comparisons were often not documented. The other limiting factor in the evidence base was that multiple studies on each topic frequently originated from a limited number of specialized centers, meaning that populations could overlap and potentially threaten the generalizability of the findings [32].

There have been recent attempts to strengthen pharmacogenetic research, including conducting post hoc analyses of completed drug trials by genotyping prospectively banked tissue samples from patients prior to them being allocated to a treatment arm. Genotyping of tissue can be performed after the trial has ended, although the benefit of randomization in balancing confounding variables between trial arms is lost. An example of this approach is the pharmacogenetic *KRAS* and *CYP2D6* trials [37–39].

Despite some recent improvements in trial design, the overall evidence base available to inform policy makers on the safety, effectiveness and cost-effectiveness of pharmacogenetic interventions is poor, piecemeal and problematic to evaluate and synthesize.

Adapting LEA to pharmacogenetic interventions

Meckley and Neumann (2010) analyzed reimbursement decisions from NICE, AETNA, CIGNA, Premera (Blue Cross), and Centers for Medicare and Medicaid Services with regard to six case studies – namely, *HER2/neu* and trastuzumab; hepatitis C genotyping and ribavirin/pegylated interferon; Oncotype DX and chemotherapy; *UGT1A1* and irinotecan; *VKORC1/CYP2C9* and warfarin; *BRCA1/2* with prophylactic surgical measures; and OncotypeDX with chemotherapy. The authors observed that the strength of evidence available to support the clinical benefits/harms of use of a personalized medicine was the key determinant in predicting positive reimburse-

ment decisions [40]. Similarly, Faulkner *et al.* (2012) suggested that efforts to develop a coherent system of evaluation of medicines targeted to patients with specific genetic biomarkers have been hampered by the available evidence base which does not fit the established approaches to test and drug evaluation for reimbursement decisions [41]. This was a problem encountered by Terasawa *et al.* in their systematic reviews of selected pharmacogenetic tests [32]. The lack of a conceptual framework for integrating the disparate pieces of evidence meant that there were difficulties in developing a coherent picture from the mix of genetic association studies, predictive accuracy studies and trials showing treatment effects in patients with a biomarker. It would also be difficult to determine what key evidence, if any, was missing.

Evidence on companion tests and drugs presented for reimbursement decisions have typically concentrated on assessing the clinical benefit of the drug in patients with a particular genetic characteristic, with little attention being paid to: (1) whether the proposed test or combination of tests is accurate at identifying that specific genetic biomarker, or (2) isolating whether that particular genetic biomarker is the target (or effect modifier) for the drug, as opposed to being a consequence of other characteristics that may be defining or responsible for that particular patient group responding to the therapy. These other characteristics include determining whether the genetic biomarker is simply a prognostic factor that predicts improved patient health outcomes irrespective of the treatment offered, or whether the observed effect is due to measured (or unmeasured) confounding factors introduced through a non-randomized (or non-stratified) comparison by biomarker status.

In an attempt to address the deficiencies in the available evidence base for pharmacogenetic interventions and to provide a conceptual framework to incorporate the disparate pieces of evidence, we adapted the linked evidence approach used for test evaluation to personalized medicines [42]. The aim was to develop an approach that was flexible and adaptable to the different types of evidence generated in the research community and yet still provide robust evaluations of the safety, effectiveness and cost–effectiveness of both test and drug. Another key aim was to make areas of clinical risk and cost uncertainty transparent to policy makers.

The co-dependent technology evaluation framework

The framework for assessing pharmacogenetic interventions in Australia has been reported elsewhere [42]. In summary, the approach uses the hypothetical framework of a double randomized controlled trial as a template for determining what information elements are needed when linking evidence – this trial design is unlikely in practice but consists of all the elements needed to evaluate the test, drug and the interaction between the two. The use of a hypothetical framework had been suggested previously for undertaking test evaluations in LEA [14]. Consistent with this, our framework was informed by an awareness of the importance of maintaining transferability across evidence linkages and a need to define the likely biases if the transferability assumptions could not be fulfilled. Complementary to this approach, given the largely observational evidence base associated with pharmacogenetic interventions, elements suggested by Bradford-Hill to determine causation [43] were incorporated within the framework. This included a biological plausibility (or 'rationale') criterion to justify, using molecular biological or pharmacological principles, the plausibility of treatment effect modification (or interaction) between the biomarker itself and the drug, or alternatively between the drug and another factor for which the biomarker is a proxy. A criterion was also included to ascertain whether there is any other validated biomarker which predicts variation in the comparative treatment effect (between using the drug and not using the drug) (Additional File 1 of [42]).

In addition, information was requested to ascertain whether the proposed genetic biomarker is a prognostic factor or a treatment effect modifier and to determine the strength of any treatment effect modification (Additional File 1 and Additional File 3 of [42]).

The end product in 2010 was 79 information requests that have been incorporated into Government guidance for applicants seeking reimbursement of companion tests and drugs (Additional File 1 of [42]). The optimal study designs needed to address some of the 79 items and methods for presenting information and reducing bias were also outlined, often with reference to current methodological norms. Key information requested as part of this evaluation framework is outlined in Figure 2, as it relates to a simple decision analytic model.

One of the advantages of the adaption of LEA to pharmacogenetic applications as described in Figure 2, is that the clinical evidence is systematically acquired and critically appraised for internal and external validity. This occurs prior to use as inputs and transition probabilities in the decision analytic modeling underpinning the economic evaluation [44]. Cost–effectiveness estimates are therefore likely to be more realistic and arguably less biased and sensitivity analyses can be used to vary key clinical (e.g., harms from inappropriate treatment) and cost inputs over which there is uncertainty.

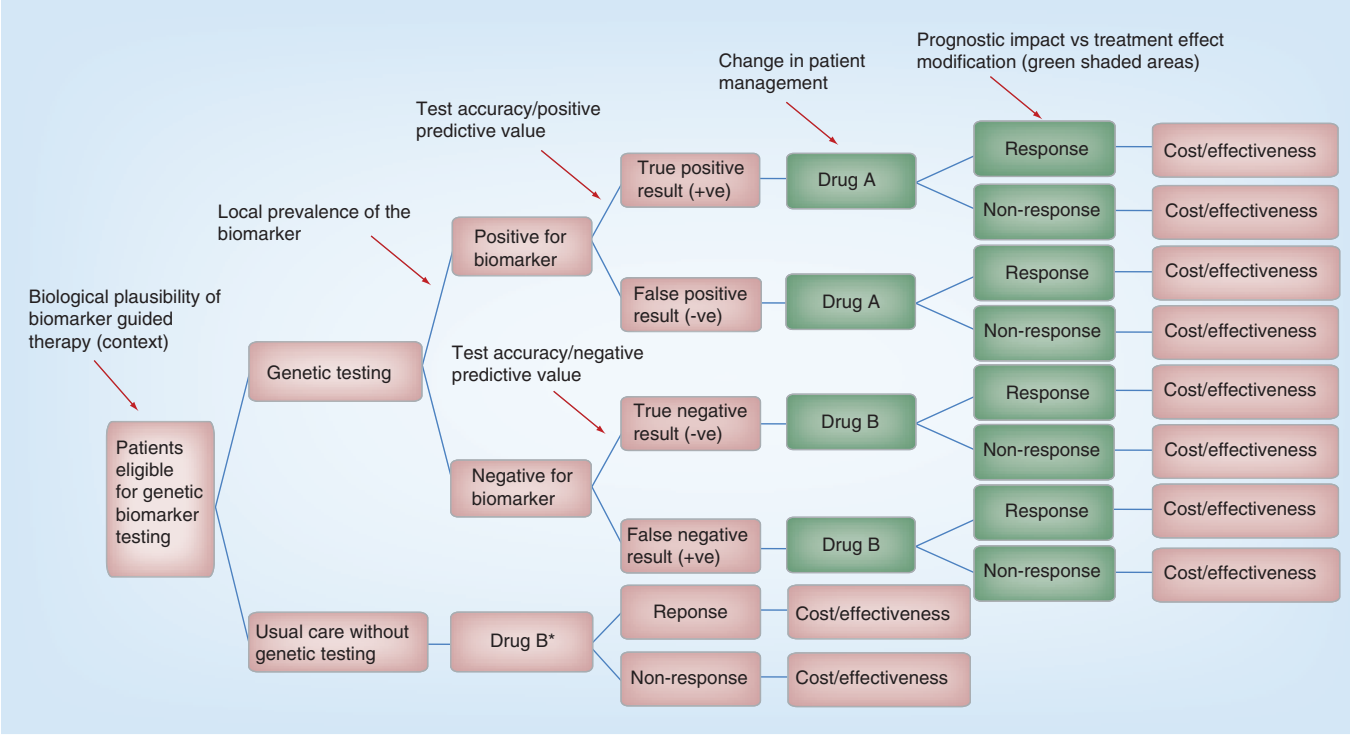

Figure 2. Using the results from linked evidence as inputs in a simple decision analytic model to estimate the comparative costs and effectiveness of a pharmacogenetic intervention.

*Drug B is usual care (e.g., one or more drugs) but a scenario could be tested whereby this could be Drug A (the proposed pharmacogenetic drug) without the use of a companion genetic test

Note: Inputs used for different pathways in the model can be extracted from different types of studies (preferably with a low risk of bias) but there needs to be clinically sensible transferability between the linkages.

International experience

The method used by the Expert Working Group of EGAPP when evaluating genetic tests – including pharmacogenetics [45–48] - and developing practice recommendations, involves the synthesis of a chain of evidence, along with consideration of ACCE model criteria [12,27]. As of February 2014, EGAPP had recommended 36 tier 1 pharmacogenetic interventions – 30 of which are used to guide cancer treatment - with a base of synthesized evidence supporting implementation into clinical practice [72]. In 2013, the Working Group started investigating basic modeling techniques to deal with the lack of available evidence on genetic tests [12]. The Working Group supports the need for additional approaches and methods for evidence generation and innovative modeling strategies. They also recognize that basing recommendations on evidence from poorer quality studies (risk of bias) will require accepting a higher risk of providing no net health benefit or introducing patient harms. As such, consistent with the Australian approach, they indicate that there needs to be a careful consideration of the risk of harm balanced with the opportunity for benefit when considering a genetic test, and to develop a plan for addressing evidence gaps [12].

The evaluation of pharmacogenetics in Europe is lagging a little behind other major developed health systems and part of the reason relates to structural impediments. In the United Kingdom, the National Institute of Health and Care Excellence (NICE) is making some headway in evaluating products that have dissimilar regulatory evidence requirements, such as CE-marked and in-house laboratory tests, as well as pharmaceuticals. Other European countries, however, often have completely unlinked processes, which makes it particularly difficult to evaluate both the test and the drug in a coherent manner [49]. Health technology assessments conducted in Europe again exemplify the learning curve associated with identifying evidence that can properly populate economic models to inform policy makers of the cost–effectiveness of pharmacogenetic interventions [50].

To date, NICE has completed one pharmacogenetic test appraisal under their new diagnostic assessment program [51], with a further four underway. Although several pharmacogenetic interventions have been evaluated using the NICE Technology Appraisal process, the required evidence base mainly pertains to the clinical effectiveness and cost–effectiveness of the drug component of the technology rather than determin-

ing whether the genetic test is effective in identifying the eligible patient population [50]. This means that until recently there has been minimal scrutiny as to whether the drug is being appropriately targeted and/or inappropriately replacing effective treatments as a consequence of incorrect test results.

The NICE diagnostic test assessment program recognizes the utility of the linked evidence approach when modeling the effects of testing. The methods manual states "If data on the final patient outcomes of a diagnostic technology are not available, it may be necessary to combine the evidence from different parts of the care pathway. In this case the linkages between diagnosis, treatment and final outcomes need to be specified, and relevant data about those linkages needs to be obtained and reviewed. Data about test accuracy and the nature of the care pathway and its outcomes can be used to create an assessment comparing the effect of different testing approaches." [5]

The experience in Australia of assessing companion test-drug combinations for reimbursement decisions has accelerated since the introduction of the co-dependent technology evaluation framework. Apart from the five pharmacogenetic interventions that were used as case studies for the development of the framework in late 2010, there have been a further nine companion test-drug evaluations conducted since the evaluation framework was finalized. Five of these interventions were reimbursed, two were rejected and two have been deferred (as of March 2014, see Table 2). The evaluation framework appears to be working well in terms of the technical requirements being met and evaluated in a fairly timely way. Given the lack of available direct evidence, many of the applications have had to provide linked evidence to address many of the 79 information requests [42]. Areas of uncertainty are made clear and the use of specific inputs in the models can be critically appraised. This has allowed Government to negotiate reduced prices as a consequence of the uncertainties identified [52–54]. It has also allowed subsidized market access for products that would not previously have been considered as having an acceptable evidence base because of the lack of direct evidence [42], and perhaps rejected for public funding.

Table 2. Pharmacogenetic interventions submitted for a reimbursement decision in Australia after introduction of the co-dependent evaluation framework.

Condition	Genetic test/ biomarker	Drug	Current status (March 2014)
Locally advanced or metastatic melanoma	*BRAF* V600 mutation test	Dabrafenib	Funding of test and drug recommended. Prospective data collection on test utilization to be undertaken to inform the risk-share arrangement [52,59]
HIV infection	Genotype test for HIV tropism	Maraviroc	Funding of test rejected on basis of insufficient evidence that test adequately distinguishes between HIV-infected individuals who should and should not receive Maraviroc [60,61]
Gastric cancer	*HER2* gene amplification	Trastuzumab	Recommendation deferred as further consolidation of information required between committees assessing test and drug [62,63]
Locally advanced or metastatic NSCLC	*EGFR* mutation test	Gefitinib	Funding of test and drug recommended [53,64]
Locally advanced or metastatic melanoma	*BRAF* V600 mutation test	Vemurafenib	Not considered cost-effective. Recommendation deferred pending further negotiation with the sponsor. Sponsor indicated it is unlikely to re-submit an application [65,66]
Locally advanced or metastatic NSCLC	*EGFR* mutation test	Erlotinib	Funding of test and drug recommended [54,67]
Breast cancer	*HER2* IHC test	Neoadjuvant trastuzumab	Funding of test and drug recommended [68,69]
NSCLC	*ALK* test	Crizotinib	Recommendation deferred. Acceptable comparative effectiveness. Unacceptable cost-effectiveness and so negotiation with sponsor commenced. Awaiting decision by other committee with regard to test listing [70]
Metastatic colorectal cancer	*KRAS* testing	Panitumumab	Funding of drug recommended. Test currently listed but additional information being sought with regard to role of wider RAS testing [71]

IHC: Immunohistochemistry; NSCLC: non-small cell lung cancer.

There have, however, been lengthy delays in some instances because of the need to coordinate policy processes – perhaps similar to the European situation. As Australia has independent committees evaluating each of the test and drug [55], there have been several deferrals in order to seek advice from the other Committee and so there have been delays before coordinated advice could be provided to Government.

Limitations of LEA

One of the limitations of LEA is finding evidence to support all areas of the linkage. This does not mean that the companion test and drug are not beneficial, only that there is insufficient evidence to make a determination either way. The main area of difficulty is identifying evidence of the likely treatment effect of the co-dependent pharmaceutical in patients without the biomarker or in an untested population.

Some researchers suggest that in the biomarker development phase, once a specific treatment is established, it is unethical to randomize patients to a control arm of no therapy until there are sufficient data on the biomarker's clinical validity [56]. Industry researchers have also suggested that if a pharmaceutical has been developed to target a particular biomarker it would be unethical to randomize patients without the biomarker to receive that pharmaceutical. Studies are less likely to be mounted when there is a risk of harm.

Either way, when there is a lack of information to support those aspects of the linkage, modeling can be undertaken to determine whether the conservative assumptions of clinical benefit/harm that necessarily need to be made are likely to have an impact on the overall clinical and cost–effectiveness of the pharmacogenetic intervention. However, modeling cannot substitute for good trial data and trials should be performed when there is equipoise regarding likely benefits and harms; such that even if a pharmaceutical has been developed to address a particular biomarker it needs to be confirmed through robust trial evidence that the biomarker is relevant. There have been instances in the past where researchers have wrongly attributed a clinical benefit or harm to an interaction between a genetic biomarker and drug [27,56].

An example of the limitations associated with LEA can be drawn from the first pharmacogenetic test evaluation conducted by an external assessment group commissioned by NICE under the diagnostic assessment program [51]. Three modeling methods were provided to estimate the cost–effectiveness of different EGFR tyrosine kinase tests in adults with locally advanced or metastatic lung cancer experience. These included: 1) a 'comparative effectiveness' analysis which only used direct evidence of testing on final health outcomes; 2) a 'linked evidence' analysis which included evidence of test accuracy for predicting response to tyrosine kinase inhibitors, according to EGFR mutation status, and the clinical effect was estimated from other trials; 3) and an 'assumption of equal prognostic value' analysis when no data were available on either the comparative effectiveness or the accuracy of EGFR mutation tests for predicting response to tyrosine kinase inhibitors. The incremental cost effectiveness ratio (ICER) produced using either the direct or linked evidence approaches were very similar (the ICER for the prognostic value analysis could not be calculated). However, the test accuracy estimates used in the linked evidence model were considered unreliable as they were sampled from different populations, using different test methods and different definitions of resistance mutations. As a consequence of this, the cost–effectiveness analysis was not considered robust by NICE. Despite these uncertainties, a decision was made to recommend EGFR testing with Sanger sequencing based methods, the Cobas EGFR mutation test and the TheraScreen EGFR PCR kit [51].

This example highlights how, even using linkage methods to extract the most out of the pharmacogenetic data available, it is critical to ensure that the evidence used to derive inputs for modeling is internally consistent, clinically meaningful and *transferable* across the linkages ie similar populations, tests, biomarker definitions and outcome criteria are used.

Future perspective

Despite the difficulties associated with the evaluation of a test to identify a single genetic biomarker that could guide treatment with a single pharmaceutical (sometimes over a background of usual care), pharmacogenetics is actually a simple example of a personalized (or stratified) medicine. Reimbursement consideration of the use of genome testing paired with targeted prophylactic and symptomatic treatment raises further complexities – technical, legal, ethical and social.

The *genome* is the entirety of an organism's hereditary information. The introduction of DNA microarray platforms and projects like IT Future Of Medicine (ITFOM) [73] – a consortium of partners whose role it is to construct computational models of the molecular and anatomical biological processes that occur in every human – means that integrated maps of human genomes across diverse populations are being developed and can be used to predict and validate genome wide association studies [57]. In the future, genomic regions associated with human disease will be able to be isolated and both prophylactic and symptomatic treatments will be able to be targeted to each individual's genomic profile [33].

Proponents of this type of research have indicated that in these circumstances randomized controlled trials will become obsolete and that n-of-1 trials would be the only possible alternative for determining the clinical benefits and harms of individualized therapies. However, it is unlikely that payers would subsidize population-based testing and treatments solely on the basis of n-of-1 studies [58]. An alternative could be the

Executive Summary

Tests are not perfect

- Inaccurate tests can lead to delayed, inappropriate or harmful treatment.
- Trial evidence of the direct impact of medical tests on the health outcomes of patients is scarce.

The 'Linked Evidence Approach' (LEA)

- The 'linked evidence approach' (LEA) is an integrative framework, developed in Australia, that narratively links evidence addressing key elements of the test-treatment pathway. The framework used to link the disparate pieces of evidence is a hypothetical randomized controlled trial designed to determine the diagnostic effectiveness of the new test. As direct trial evidence is often absent, this linkage approach maximizes the available information for policy makers so that the likely impact of the new test on patient health outcomes can be determined.
- The findings from these evidence linkages can be used as inputs in decision analytic modeling to predict whether the new test provides good value for money when compared to existing diagnostic approaches.
- LEA was informed by methods pioneered by the United States Preventive Services Task Force (USPSTF) and the efficacy criteria proposed by Fryback and Thornbury (1991).

Genetic testing & methods of evaluation

- The Office of Public Health Genomics in the USA has produced two key programs for the evaluation of emerging genetic tests – the ACCE Model Project and the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) initiative.
- Pharmacogenetic interventions involving a companion genetic test and tailored drug treatment have been emerging over the last decade and this has created challenges for existing technology approval mechanisms.

Adapting LEA to pharmacogenetic interventions for policy decisions

- Pharmacogenetic interventions often have a poorer evidence base than other testing interventions. However, research suggests that the strength of evidence available to support the clinical benefits/harms of these interventions is the key predictor of positive reimbursement decisions.
- In order to address the deficiencies in the typical evidence base for pharmacogenetic interventions, an evaluation framework to inform reimbursement decisions was developed using an adaptation of LEA.

The co-dependent technology evaluation framework

- The approach uses the hypothetical framework of a double randomized controlled trial as a template for determining what information elements are needed for the evaluation. Information is also elicited on the biological plausibility of the genetic biomarker, as well as whether the biomarker is a prognostic factor or an effect modifier for the accompanying drug therapy. All of this information is linked narratively and then the findings are integrated using decision analytic modeling.
- The framework includes 79 information requests and these have been incorporated into Government guidance for applicants seeking reimbursement of these companion tests and drugs.

International experience

- Methods of linking evidence to inform test reimbursement decisions is gaining momentum but the largest application to pharmacogenetic interventions is in Australia. Since 2011, nine pharmacogenetic test-drug evaluations have been conducted. Five of these personalized medicines were publicly funded, two were rejected and two have been deferred. To date, the National Institute of Health and Care Excellence (NICE), UK, has evaluated one pharmacogenetic intervention but has a further four underway.

Limitations of LEA

- The main limitation of LEA is finding evidence to support all areas of the linkage and to ensure that there is transferability of populations, genetic tests, biomarker definitions and outcome criteria between each linked piece of evidence, particularly when used in economic modeling.

Future perspective

- Regulatory and reimbursement consideration of the use of genome testing to guide targeted prophylactic and symptomatic treatments raises further complexities – technical, legal, ethical and social.
- The suggestion that the current evidence-based paradigm is too inflexible to address individualized medicine – through genomics – is premature. Complementary assessment methods can be used, including the use of LEA to inform genomic prediction models and then the validation of genomic prediction models to guide therapies using standard empirical methods.

use of complementary evaluation processes. Linked evidence approaches addressing stratified personalized medicines (pharmacogenetics) could be used to inform policy making and at the same time inform the prediction models that have been developed for individualized medicines using synthesised n-of-1 data. The rigorous approaches used to inform reimbursement decisions would mean that there is some assurance that the genetic association underpinning a stratified personalized medicine is valid. The individualized risk prediction models could then be assessed in studies that compare treatment/prophylaxis guided by ITFOM (or other) genome risk prediction models versus treatment guided by clinical judgment (or a previous version of a risk prediction model). Randomized controlled trials could be used to assess short term benefits/harms of the two types of treatment targeting models and/or prospective cohort studies, registries or comparative effectiveness research [56] could be used to assess long-term benefits/harms. The risk prediction models would likely need review and re-specification on an ongoing basis as new developments and understandings occur in the personalized medicine evidence base.

Conclusion

Momentum is gaining in the use of linked evidence approaches to identify relevant data on pharmacogenetic interventions and to synthesize the findings in a robust and yet flexible manner for reimbursement decisions. However, the approach should be used and appraised cautiously as the body of accumulated evidence needs to maintain internal clinical coherence. The approach is meant to be a proxy for an ideal trial design, it is not meant to be a 'Frankenstein creation' for incorporating disparate or biased pieces of evidence. The approach, if used well, can explicate the patient risks and benefits from pharmacogenetic interventions, enable value for money determinations to be made, and assist policy makers to formulate informed reimbursement decisions.

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