How Are We Evaluating the Cost-Effectiveness of Companion Biomarkers for Targeted Cancer Therapies? A Systematic Review

Mikyung Kelly Seo (mk.seo@imperial.ac.uk)
Imperial College London
John Cairns
London School of Hygiene & Tropical Medicine

Research Article

Keywords: Biomarker, companion diagnostic, precision medicine, targeted therapy, oncology, cancer, economic evaluation, health economics, cost-effectiveness, systematic review.

DOI: https://doi.org/10.21203/rs.3.rs-139157/v1

Abstract

Background Despite the increasing economic assessment of biomarker-guided therapies, no clear agreement exists whether existing methods are sufficient or whether different methods might produce different cost-effectiveness results. This study aims to examine current practices of modeling companion biomarkers when assessing the cost-effectiveness of targeted cancer therapies. It highlights the challenges in methods and data requirements faced in the evaluation of biomarker tests which do not necessarily arise with the evaluation of pharmaceutical drugs.

Methods A literature search was performed using Medline, Embase, EconLit, Cochrane library. Articles published from 2014 to 2018 were searched. Economic evaluations on biomarker-guided therapies with companion diagnostics in cancer were searched. Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA) guidelines followed. Studies were selected by pre-specified eligibility criteria using PICO framework. To make studies more comparable, data were synthesized under ten categories of key areas of methods where consensus deemed lacking.

Results Eighteen papers were included in this review. Three out of eighteen studies found to be of good quality regarding incorporating the characteristics of companion biomarkers in economic evaluations. However, many evaluations focused on a pre-selected patient group with a specific biomarker status instead of including all patients with a disease regardless of their biomarker status. Companion biomarker characteristics captured in evaluations were often limited to the cost or the accuracy of the test. Often, only the costs of biomarker testing were modelled. Clinical outcomes or utilities were often difficult to include due to the limited data generated by clinical trials. We found that no consistency and consensus existed to the methods of existing economic evaluations of companion cancer biomarkers for targeted therapies. It was also shown that conflicting cost-effectiveness results were likely depending on what comparator arm was chosen and what comparison structure was designed in the model.

Conclusion We found that there was no consistent approach applied in assessing the value of biomarkers and including the characteristics of biomarkers in an economic evaluation of targeted oncology therapies. Currently, many EEs fail to capture the full value of companion biomarkers beyond sensitivity/specificity and cost related to biomarker testing.

Introduction

Economic evaluations (EEs) are increasingly used to inform market access, reimbursement and coverage of new medical technologies including biomarker diagnostics for targeted therapies. Companion biomarkers are used to select and guide the best treatment options for patients prior to the administration of a corresponding therapy. However, no agreement exists whether existing methods are sufficient to evaluate the health economic impact of biomarkers, or whether different methodological approaches might produce conflicting results with regard to the cost-effectiveness of biomarkers or biomarker-guided therapies.

This study focuses on companion biomarkers for targeted cancer therapies. Specific biomarkers, known as companion diagnostics (CDx) are the focus of this review. CDx can be defined as a medical device (often *in vitro*) providing information for the safe and effective use of a corresponding intervention (1). CDx is the diagnostic test labelled to be used prior to the administration of a particular therapeutic product and thus, the treatment decision is made based on the biomarker testing result. That is, the use of a specific test is obligatorily proceeded by the provision of corresponding therapy (e.g. HER2 testing prior to trastuzumab). If test accuracy is not satisfactory, the treatment decision may detrimental to the patient outcomes when treated with the biomarker-guided therapy.

This study reviews current methodological approaches and challenges in EEs of cancer biomarkers. It highlights the complexity of evidence generation faced by test developers without clear guidance on evidentiary standards and data requirements. It aims to analyze the approaches currently adopted in EEs of biomarkers and to identify current practices and address policy implications. This review focuses on biomarkers co-licensed with therapeutic products, namely CDx. Also, the methodological issues commonly relevant to the classical therapeutic interventions are not of interest in this review. It only considers methodological challenges and issues faced in the evaluation of biomarker tests which do not arise with the evaluation of pharmaceutical drugs.

Methods

A systematic review of model-based health economic evaluations of companion diagnostics for targeted cancer therapies was undertaken. This review was conducted followed by recommendations of the Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA) guidelines (2, 3).

Literature search

A systematic literature search was conducted for EEs of cancer biomarkers co-licensed for the use of targeted therapies (hereafter, called “companion biomarkers”). Medline (Ovid), Embase (Ovid), EconLit, Cochrane library were used. Hand search was done by reviewing article citations and review articles. Four articles were then identified (4–7).

The electronic search was performed using Medical subject heading (MeSH) terms and keywords that were developed for disease (cancer), intervention (companion biomarkers for targeted therapies), and study design (economic evaluations). These were combined with free-word texts using relevant economic terms (e.g. “cost-effectiveness”) and the names of biomarker-guided therapeutic products both in brand and generic terms. The list of CDx approved by the US Food and Drug Administration (FDA) (8) was targeted in the literature search. Studies published in English were searched from 2014 to 2018. The 5-year search period was chosen given that this literature review aimed to explore current EE practice and to critically appraise them in depth. Five years was considered to be long enough to capture a sufficient number of recently published EEs and also to exclude any out-of-date approaches not applicable to current practice. Search terms are provided (Additional file 1).

Study selection

Studies were selected using pre-specified inclusion and exclusion criteria (Additional file 2) based on the PICOS (Population, Intervention, Comparator, Outcome, Study design) framework. Given the aims of this literature review, studies failing to report important information relevant to EEs of a companion biomarker (e.g. biomarker characteristics, biomarker-related modeling inputs) were excluded.

The study selection had three stages. First, identified articles from electronic databases were imported into EndNote® and duplicate citations removed. Second, the title and abstracts of the identified articles were screened to assess suitability by the first reviewer (MKS) and the studies clearly indicated as irrelevant were excluded but any studies with ambiguity were discussed with the second reviewer (JC). Third, remaining articles that met the inclusion criteria were read in full text by the first reviewer (MKS) and cross-checked by the second reviewer (JC). Any disagreements in all stages were resolved by discussion between two reviewers (MKS, JC) (Fig. 1).

Data analysis and synthesis

Ten methodological areas were selected to focus on in reviewing the current practices of methodological approaches of EEs for companion biomarkers. These key areas were formulated based on previous studies (9–12), the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist (13) and from our experience working in health technology assessments of cancer biomarkers for targeted therapies. The ten areas are as follows: (i) target population; (ii) viewpoint of analysis; (iii) the choice of alternative strategy arm(s); (iv) structure of comparative analysis (or structure of strategy comparisons); (v) measurement of clinical value of companion biomarkers; (vi) measurement and valuation of preference-based outcomes of companion biomarker tests; (vii) estimating resource use and costs; (viii) timing of the test use; (ix) uncertainty analysis; (x) data sources for biomarker-related data inputs. The narrative syntheses and analyses were performed for these ten methodological areas. To be more specific, a list of questions was developed based on these items (Table 1).

Table 1
A list of key methodological items in reviewing the EEs of biomarker-guided therapies

Question items	Yes	No
Q1. Did the EE target all patient groups regardless of biomarker status of test positive, negative, unknown?		
Q2. Did the EE justify the viewpoint of analysis? (I.e. Analysis perspective; third-party payer, society, hospital, etc.)		
Q3. Was the standard of care chosen as a comparator strategy?		
Q4. Was the test-treat strategy compared to the comparator strategy arm(s)?		
Q5. Was the clinical effectiveness of the companion biomarker test considered in the economic models? If not considered, justification/assumption provided?		
Q6. Were preference-based outcomes of companion biomarker tests were considered in the economic models? If not considered, has the assumption been provided with justifications?		
Q7-1. Were the details of the resource consequences of the use of companion biomarker testing considered and reported?		
Q7-2. Were the costs of companion biomarker test(s) considered and reported?		
Q8. Different timing of the test(s) was considered and reported? (i.e. at the time of diagnosis, at the time point of progression to metastasis, etc.)		
Q9. Was uncertainty with respect to the characteristics of the companion biomarker test(s) explored? (i.e. at least one component of the characteristics of biomarker test was tested; such as cost, cut-off threshold, sensitivity/specificity)		
Q10. Were the data sources for the model inputs clearly reported and justified? (i.e. meta-analysis, clinical trials, published papers, etc.)		
Q11. Was the name/type of biomarker test specified? (e.g. Cobas® BRAF V600 mutation test)		
Q12. Was the frequency/prevalence of biomarker status considered in the economic model? If not, has this been justified?		

Results

Overall, eleven papers assessed the cost-effectiveness of the corresponding drugs (14–25), while seven papers evaluated the cost-effectiveness of companion biomarkers per se (4, 5, 26–30). The most frequently used modeling type was a Markov model (eleven papers), followed by partitioned survival model (two papers) and semi-Markov model (two papers). All economic evaluations were performed from a third-party payer perspective except for one study which took a societal perspective. All studies were performed for high income countries except for four studies of China.

Study characteristics of included literature are detailed in Table 2. Figure 2 provides the synthesized overview of whether the key methodological areas were addressed or not in the evaluations. The most frequently ignored model inputs related to companion biomarkers were preference-based outcomes, clinical utility, resource use, and the timing of the test. The detailed analysis of key methodological areas per publication is provided in additional file 3.

Table 2
Detailed characteristics of the included studies

Study	Focus	Objective	Biomarker test	Corresponding therapy compared	Strategies compared	Biomarker related model inputs considered	Country	Pe ve
Aguiar 2017	Rx	To assess cost-effectiveness of immune checkpoint inhibitor with and without the use of PD-L1 testing for patient selection.	PD-L1 expression.	Immunotherapy (Nivolumab, Pembrolizumab, Atezolizumab)	3 strategies compared: Treat-all with docetaxel. Treat-all with immunotherapy. Test-treat (if PD-L1 expressed with 1% or more, patients were treated with immunotherapy; if not, treated with docetaxel.)	PD-L1 testing cost. PD-L1 expression cut-off points (PD-L1 > 1% used in base-case analysis, while 5%, 10%and 50% tested in sensitivity analysis.)	USA	Th pa
Chouaid 2017	Rx	To assess the cost-effectiveness of afatinib versus gefitinib for EGFR mutation-positive NSCLCs.	EGFR mutation.	Afatinib, Gefitinib.	2 strategies compared on pre-specified patients: Treated with afatinib. Treated with gefitinib.	EGFR testing cost.	France	Th pa
Curl 2014	Rx	To compare three strategies (dacarbazine, vemurafenib, vemurafenib plus ipilimumab) for patients with BRAF positive metastatic melanoma.	BRAF mutation.	Dacarbazine, Vemurafenib, Vemurafenib plus Ipilimumab	3 strategies compared on pre-specified patients: Treated with dacarbazine. Treated with vemurafenib. Treated with vemurafenib plus ipilimumab.	BRAF testing cost (Cobas®)	USA	Th pa
Ewara 2014	Rx	To assess the cost-effectiveness of three strategies (bevacizumab plus FOLFIRI, cetuximab plus FOLFIRI, panitumumab plus FOLFIRI) for mCRC patients with KRAS WT.	KRAS mutation.	Bevacizumab, Cetuximab, Panitumumab.	3 strategies compared on pre-specified patients: Treated with bevacizumab plus FOLFIRI. Treated with cetuximab plus FOLFIRI. Treated with panitumumab plus FOLFIRI.	KRAS testing cost.	Canada	Th pa
Graham 2014	Rx	To assess the cost-effectiveness of panitumumab plus mFOLFOX6 compared with bevacizumab plus mFOLFOX6.	RAS mutation.	Panitumumab, Bevacizumab.	2 strategies compared on pre-specified patients: Treated with panitumumab plus mFOLFOX6. Treated with bevacizumab pus mFOLFOX6.	KRAS and RAS testing cost. RAS frequency.	USA	Th pa

Rx; Drugs, Dx; Companion biomark

Study	Focus	Objective	Biomarker test	Corresponding therapy compared	Strategies compared	Biomarker related model inputs considered	Country	Pe ve
Graham 2016	Rx	To assess the cost-effectiveness of subsequent-line treatment with cetuximab or panitumumab in patients with WT KRAS mCRC.	KRAS mutation.	Cetuximab, Panitumumab.	2 strategies compared on pre-specified patients: Treated with cetuximab. Treated with panitumumab.	KRAS testing cost.	USA	Th pa
Harty 2018	Rx	To investigate the clinical effectiveness and cost-effectiveness of panitumumab plus chemotherapy and cetuximab plus chemotherapy for rat scarcoma (RAS) wild-type (WT) patients for the first-line treatment of mCRC.	KRAS/RAS mutation.	Cetuximab.	2 strategies compared: Treated with FOLFIRI alone. Treated with cetuximab plus FOLFIRI.	EGFR testing cost. RAS testing cost.	UK	Th pa
Huxley 2017	Rx	To investigate the clinical effectiveness and cost-effectiveness of panitumumab plus chemotherapy and cetuximab plus chemotherapy for rat scarcoma (RAS) wild-type (WT) patients for the first-line treatment of mCRC.	RAS mutation.	Cetuximab, Panitumumab.	5 strategies compared on pre-specified patients: Treated with FOLFOX/FOLFIRI. Treated with cetuximab plus FOLFOX/FOLFIRI. Treated with panitumumab plus FOLFOX.	RAS testing cost. RAS prevalence (50% of patients assumed to be RAS wild-type).	UK	Th pa
Janmaat 2016	Rx	To determine the ICER of adding cetuximab to first-line chemotherapeutic treatment of patients with advanced esophageal squamous cell carcinoma (ESCC), based on RCT II trial.	EGFR expression.	Cetuximab.	2 strategies compared on pre-specified patients: Treated with cetuximab plus cisplatin-5-fluorouracil. Treated with cisplatin-5-fluorouracil.	EGFR testing cost. EGFR prevalence (60% patients assumed to be EGFR positive).	Netherlands	Th pa
Lim 2016	Dx	To evaluate the cost-effectiveness of treating patients guided by EGFR testing compared to no-testing (which is current practice in South Korea).	EGFR expression.	Erlotinib.	2 strategies compared: Test-treat (if EGFR positive, treated with erlotinib; if EGFR wild-type, treated with conventional chemotherapy; if unknown, re-biopsy required). No-testing (Treat all with conventional chemotherapy).	EGFR testing cost (Therascreen®, Cobas®). Testing accuracy (sensitivity/specificity).	South Korea.	Th pa

Rx; Drugs, Dx; Companion biomark

Study	Focus	Objective	Biomarker test	Corresponding therapy compared	Strategies compared	Biomarker related model inputs considered	Country	Pe ve
Lu 2018	Dx	To examine the economic outcome of three techniques for testing ALK gene rearrangement combining with crizotinib (first-line), compared with traditional regimen.	ALK gene rearrangement	Crizotinib.	3 ALK rearrangement testing techniques prior to crizotinib were compared (4 strategies compared): No gene screening - all treated with standard chemotherapy. Ventana IHC - if ALK rearrangement positive, treated with crizotinib; if ALK rearrangement negative, treated with standard chemotherapy. qRT-PCR - if ALK rearrangement positive, treated with crizotinib; if ALK rearrangement negative, treated with standard chemotherapy Conventional IHC - if IHC ALK rearrangement negative, treated with standard chemotherapy; if IHC ALK rearrangement positive, FISH testing (to confirm) to be performed and then, if FISH ALK rearrangement negative, treated with standard chemotherapy, if FISH ALK rearrangement positive, treated with crizotinib.	Cost of ALK rearrangement testing (Ventana IHC; IHC; qRT-PCR; FISH) Sensitivity and specificity respectively for Ventana IHC; IHC; qRT-PCR). ALK prevalence	China	Th pa
Morgan 2017	Rx	To assess the cost-effectiveness of crizotinib in untreated anaplastic lymphoma kinase-positive (ALK-positive) non-small-cell-lung cancer (NSCLC).	ALK expression.	Crizotinib	2 strategies compared on pre-specified patients: Treat all with crizotinib. Treat all with pemetrexed chemotherapy in combination with cisplatin or carboplatin.	ALK testing cost ImmunoHistoChemistry (IHC) testing cost Fluorescence in situ hybridisation (FISH) testing cost	UK	Th pa

Rx; Drugs, Dx; Companion biomark

Study	Focus	Objective	Biomarker test	Corresponding therapy compared	Strategies compared	Biomarker related model inputs considered	Country	Pe ve
Wen 2015	Dx	To explore the costs and effectiveness of RAS screening before monoclonal antibodies in mCRC based on FIRE-3 study.	RAS mutation.	Cetuximab, Bevacizumab.	Four strategies compared: KRAS tested - treated with cetuximab and FOLFIRI. RAS tested - treated with cetuximab and FOLFIRI. KRAS tested - treated with bevacizumab and FOLFIRI. RAS tested - treated with bevacizumab and FOLFIRI.	KRAS/RAS testing cost.	China	Th pa
Westwood 2014	Dx	To compare the performance and cost-effectiveness of KRAS mutation tests in differentiating adults with mCRC who may benefit from first-line treatment of cetuximab in combination with standard chemotherapy from those who should receive standard chemotherapy alone.	KRAS mutation.	Cetuximab.	10 different tests for KRAS mutation status. No comparator approach taken. Cobas KRAS Mutation Test Kit (Roche Molecular Systems). Therascreen KRAS RGQ PCR Kit (QIAGEN). Therascreen KRAS Pyro Kit (QIAGEN). KRAS LightMix Kit (TIB MOLBIOL). KRAS StripAssay (ViennaLab). HRM analysis. Pyrosequencing. MALDI-TOF mass spectrometry. Next-generation sequencing. Sanger sequencing.	KRAS testing cost. KRAS testing accuracy (sensitivity/specificity) KRAS prevalence (KRAS mutant, KRAS wild-type, KRAS unknown test result). Timing of the test – justifications given.	UK	Th pa
Wu 2017	Rx	To evaluate the economic outcome of adding cetuximab to the standard chemotherapy.	RAS mutation.	Cetuximab.	2 strategies compared: No testing – treat all with FLOFIRI. Test-treat (if RAS wild-type, treated with cetuximab plus FOLFIRI, if RAS mutant, treated with FOLFIRI).	RAS testing cost. RAS prevalence.	China	Th pa

Rx; Drugs, Dx; Companion biomark

Study	Focus	Objective	Biomarker test	Corresponding therapy compared	Strategies compared	Biomarker related model inputs considered	Country	Pe ve
Zhou 2016	Dx	To evaluate the cost-effectiveness of predictive testing for extended RAS WT status in the context of targeting the use of cetuximab/bevacizumab.	RAS mutation.	Cetuximab, Bevacizumab.	4 strategies compared: KRAS WT tested-treated with cetuximab plus chemotherapy. KRAS WT tested-treated with bevacizumab plus chemotherapy. RAS WT tested-treated with cetuximab plus chemotherapy. RAS WT tested-treated with bevacizumab plus chemotherapy.	KRAS/RAS testing cost.	China	Sc pe
Saito 2017	Dx	To determine the cost-effectiveness of comprehensive molecular profiling before initiating anti-EGFR therapies in mCRC.	RAS mutation. Comprehensive profiling that includes PTEN + ERBB2, PTEN + SRC, and BRAF + RNF43 mutations (CancerPlex®).	Bevacizumab, Panitumumab.	3 strategies compared: No testing RAS screening Comprehensive screening	Biomarker testing cost. Proportion of molecular subgroups (proportion of patients per biomarker status).	Japan	Th pa
Butzke 2015	Dx	To evaluate the cost-effectiveness of UGT1A1 genotyping in patients with mCRC undergoing irinotecan-based chemotherapy compared to no-testing.	UGT1A1 genotyping	Irinotecan	3 strategies compared: No testing-treat all with standard dose of irinotecan. Test-treat (if tested wild-type, standard dose of irinotecan treated; if hetero-and homozygotes, treated with a dose reduction of irinotecan by 25%). Test-treat (all patients receive standard dose, and hetero-and homozygotes additionally received the growth factor 'pegfilgrastim').	Sensitivity/specificity.	Germany	Th pa

Rx; Drugs, Dx; Companion biomark

Target population

The patient population targeted in EEs of biomarker-guided therapies was varied but it can be broadly classified into two categories; one is a subgroup of patients with a specific biomarker status confirmed and the other is a group of patients with disease conditions regardless of biomarker status. Eight studies were performed on a pre-defined group of patients with a particular biomarker status (15–19, 21–23) however, they considered at least one characteristic of

companion biomarkers in their evaluations. Many EEs were conducted using a pre-specified patient group with a particular confirmed biomarker status, and authors used this to justify excluding some of the key characteristics of companion biomarkers from their evaluations. In addition, two studies were conducted on all patients regardless of biomarker status, while additional analyses were done for a subgroup of patients with a specific biomarker status (4, 20).

Analysis viewpoint

The analysis viewpoint defines the scope of costs and health benefits to be assessed in EEs; often referred to as study perspective. All included studies clearly reported the perspective of EEs conducted. A majority of studies showed that EEs were performed applying the third-party payer perspective. Only two studies stated that they employed a societal perspective (16, 30); one from China and the other from the US. However, the US study (16) was found to be more appropriately described as a third-party payer perspective (e.g. Medicare).

Given the nature of multiple purposes of biomarker testing application or use, and the indirect impact of companion biomarker diagnostics on patient health benefits, taking a perspective of third party payers might not be sufficient to capture all costs and benefits relevant to companion biomarkers in the clinical context of selecting patients suitable for the corresponding therapy. However, only one study considered indirect costs such as travel fees and absenteeism costs together with the cost of adverse events (30). However, this study did not consider any biomarker-related indirect costs either. For example, Schnell-Inderst and colleagues conducted a targeted review and highlighted measuring the potential effect modifiers such as the dependency of treatment effects on contextual factors and learning curve (31).

Choice of treatment alternatives (comparators)

It is widely accepted that the alternative strategy to be compared in EEs should be based on the current practice with respect to the target population (32, 33). Several different types of comparator strategies were employed in the EEs of companion biomarkers for targeted therapies. These different strategies can be categorized in five forms as below. Some papers used more than one comparator strategy arm (14, 17, 27).

First, all patients were tested prior to the administration of the corresponding biomarker-guided therapy and treated depending on the test result. For example, if the patients tested positive for a particular biomarker, they received the guided therapy; however, they were treated with the non-guided therapy if they tested negative. This '*test-treat strategy'* strategy was often employed as an intervention strategy rather than as a comparator in EEs of companion biomarker therapies. Five studies employed this strategy type as a comparator (4, 27–30) however, these studies focused on comparing the analysis among different biomarker types or testing kits rather than comparing biomarker-guided against non-guided strategy.

Second, patients were not tested but were treated with the biomarker-guided therapy; so-called *'no-testing-treat-all with the guided therapy'*. Only one study fell into this category (14). This study aimed to assess the cost-effectiveness of a new guided-therapy with and without the use of biomarker testing.

Third, no patients were tested but all patients were treated with the non-guided therapy; so-called *'no-testing treat-all with the non-guided therapy'*. Six studies used this strategy as their comparator (5, 14, 20, 24, 26, 27), and mostly a standard chemotherapy was chosen as the non-guided therapy.

Fourth, all patients modelled in EEs were already pre-specified like biomarker positive or negative, and all treated with the guided therapy; called *'biomarker-specified group treating all with the guided therapy'*. This type of comparator strategy is also commonly observed in EEs of biomarker-guided therapies in addition to the test-treat strategy. Two studies used this as their comparator strategy (15, 17). Both studies focused on assessing different guided therapies for the group of patients confirmed with a particular biomarker status. Only a handful of model parameters of companion biomarker tests were considered in their EEs and thus, they often failed to provide a full spectrum of decision-making information relevant to the use of companion biomarker medicines.

Fifth, all patients were biomarker positive or negative and treated with the non-guided therapy; called *'biomarker-specified group treating all with the non-guided therapy'*. Seven studies employed this as their comparator strategy (16–19, 21–23). This strategy is the most frequently employed comparator arm in EEs of companion biomarker medicines in cancer.

Structure of strategy comparisons

We found a wide range of inconsistencies in structuring the strategies to be compared in EEs of companion biomarker therapies. Structuring the comparative strategy arms can be determined by various factors such as eligible patient populations, decision-making bodies' EE guidelines, and local clinical settings. For example, an EE study aiming to compare a guided therapy against a standard of care applied the structure of comparing the test-treat therapy against treat-all with the guided therapy or with the non-guided therapy. Or, a similar study aiming to assess the cost-effectiveness of a new therapy with or without biomarker testing could employ the comparative structure of a testing strategy against a no-testing strategy on a particular group of patients with known biomarker status. The structure of comparing strategies in comparative analysis can be classified into five types as described in Fig. 3.

The comparative structure of applying strategy arms in EEs of companion biomarkers was so varied, it would likely lead to a different or even conflicting conclusion in terms of cost-effectiveness of companion biomarker therapies depending on the comparator strategy chosen.

Measuring the clinical value of companion biomarkers

No consensus currently exists on data requirements when incorporating the clinical value of biomarkers into the modeling of EEs of biomarker-guided therapies. For example, the Diagnostic Assessment Program requires testing accuracy in appraisal of diagnostic tests (34), although it is not always feasible in practice especially when assessors are faced with no data on test accuracy at all. On the other hand, NICE methods guide of technology appraisal does not necessarily require the testing accuracy but requires the incorporation of the associated costs of biomarker testing (32). Furthermore, none of the EEs reviewed

examined the accuracy of a companion biomarker diagnostic test separately, for example by testing different cut-off thresholds including false positive and false negative results as part of uncertainty analysis. The cut-off threshold is the cut-off point defining the presence of the biomarker, determining biomarker-positive and biomarker-negative patients for the administration of corresponding co-dependent therapeutic agents (35–37). Varying levels of accuracy may lead to different patient subgroups being eligible for the corresponding drugs. According to previous studies (9, 11), the clinical value of biomarker tests could be assessed in three ways; analytic validity, clinical validity, and clinical utility. Analytic validity is about how well a test detects the presence or absence of a particular marker (33). Clinical validity refers to the performance of a test (diagnostic accuracy) in detecting the presence of a specific disorder; so-called sensitivity and specificity (11). Clinical utility is defined in the ACCE (analytical validity, clinical validity, clinical utility, and ethical/legal/social implications) model project as "how likely the test is to significantly improve patient outcomes", which goes beyond sensitivity and specificity and then which may change treatment options for the patient (38). In other words, clinical utility (effectiveness) of companion testing technology is based on the ability to improve patient health outcomes by altering treatment decisions (39, 40).

Relatively few EEs considered the diagnostic accuracy of biomarker testing using data on sensitivity and specificity (26, 27, 29). Many EEs did not consider the performance of biomarker testing or often did not mention this at all (4, 5, 14–19, 22, 30). Otherwise, some studies provided some assumptions or justifications why they did not consider the clinical value of a companion diagnostic test (20, 21, 23, 24, 28). It is often assumed that the technical accuracy of patient stratification by biomarker testing is perfect and thus, the sensitivity and specificity were either not considered or assumed to be 100%. However, no studies explicitly considered or assumed the clinical utility of companion biomarkers in their EEs. For example, no studies stated that the clinical value of companion biomarker testing was supposedly incorporated into the clinical effectiveness of the corresponding drug based on the clinical trial of the sub-population delineated by the diagnostic.

Meanwhile, a handful of studies considered the frequency or prevalence of a particular biomarker status among their target patient populations (4, 18, 22, 26, 27, 29). Among them, only one study considered the probability of unknown test result in the analysis (29).

Measurement and valuation of preference-based outcomes

The quality-adjusted life-year (QALY) is a preference-based health outcomes widely used in EEs of therapeutic products(41, 42). It is widely accepted because it allows comparisons of health benefits and costs across different disease areas and therapeutic interventions. However, challenges emerge with the economic assessment of companion biomarkers given the nature of targeted therapies guided by companion biomarker testing and indirect impact of companion biomarker testing on patient outcomes. The current metrics for measuring preference-based outcomes using population-based preferences cannot fully capture patient preferences for biomarker tests (43). There seems to be more aspects of individual patient preference when valuing biomarker tests compared to the valuation of conventional drugs. For example, patients could be informed in advance of the likelihood of therapeutic response or unresponsiveness prior to the provision of treatment.

Or, patients can have an improved sense of controlling their own choices of therapeutic options informed by their biomarker status. Shared decision making (SDM) and communication between patients and clinicians will put patients at the centre of treatment decisions guided by companion biomarker test results. Patients may feel empowered to make informed decisions about their own treatment and care (44–46). Although the provision of biomarker-guided therapy is dictated by the patient's biomarker status, being informed of the biomarker status can support the SDM of both clinicians and patients to explore more fully the potential benefits and risks. It can then potentially improve patient satisfaction with health services.

Or, companion diagnostics for cancer patients usually require collecting a bio-sample for analysis, and this gives rise to the existence of process utility (including reassurance or information) (47–49). Brennan and Dixon's study (50) supported the existence of process utility and found that different approaches were being used to detect and measure process utility such as gamble techniques, time trade-off, conjoint analysis. Some biomarker tests involve relatively invasive methods to collect the bio-sample, such as tissue biopsy, needle biopsy, skin biopsy in diagnosing cancer (51, 52), that can be measured and incorporated into QALY estimates. Yet, how to measure and incorporate process utility into cost-utility analyses needs to be further researched with more empirical studies in HTA. Or, if companion biomarker tests were already integrated into the clinical study of measuring patient reported outcomes (PROs) for co-dependent therapeutic agents, it can be assumed that the disutility or utility value of companion biomarker testing is already embedded or indirectly expressed in PROs of the corresponding therapy. Yet, this aspect should be transparently reported in health economic models of companion biomarkers or biomarker-guided therapies. Nevertheless, none of the EEs included in this systematic review discussed these aspects of companion biomarker testing or indicated how preference-based outcomes of companion biomarker devices were measured and valued. For example, no studies explicitly included utility or disutility values for biomarker testing. Where biomarker testing uses tissues collected in a previous biopsy, it can be argued that patient preferences do not need to be considered in the economic modeling. However, none of the EEs mentioned this aspect or attempted to justify the omission of preference-based outcomes of biomarker testing. As an example, patients might need to undergo another biopsy for the purpose of biomarker testing after the cancer has progressed to metastasis. Or, a second biopsy might be needed to confirm the biomarker status when the testing accuracy was unsatisfactory. Or, turnaround time of biomarker testing may lead to additional waiting time for patients to access the treatment. Or, patients might experience anxiety or hopelessness when they are informed that the test predicts non-response to the targeted therapy and no alternative therapy options are available.

Estimating resource use and costs

All included EE studies considered the costs of biomarker testing however, some details were ignored. Some papers did not report the cost of biomarker testing devices (14) and often a total lump sum cost was modelled without providing details on how the total cost calculated (15–17, 22, 28, 30). Several studies reported at least some details regarding data source or the names/types of biomarker testing kits (4, 5, 18–21, 23, 24, 26, 27), but many EEs did not consider or report the resource use parameters relevant to the testing of companion biomarkers. None of the studies considered the capital cost related to the initial purchase of a biomarker test kit or diagnostic equipment as well as other costs such as training staff, relevant consumables, or lab reporting tools. Even in the situation where laboratories can re-purpose existing testing platforms to deliver the new test, relevant costs of consumables and staff with appropriate skills

need to be considered. As an example, the NICE committee was aware that ALK testing would be not carried out in this specific clinical setting if crizotinib was not available (53), and therefore it is highly likely that the hospitals will need to purchase the testing equipment (i.e. capital costing items) however, it was not considered in their EE.

Timing of the test use

Details of where in the clinical pathway testing was undertaken were often not reported. Only two studies (4, 29) provided some explanation on this aspect, however, it was not clear how the timing of the test use was considered in the analysis of the Westwood study (54). Whereas, Saito and colleagues (4) provided and justified their assumptions. Given the nature of companion biomarkers, the health benefit to the patient arises from the corresponding therapy guided by the testing result, which is best understood as it being part of the clinical pathway in relation to its indirect impact on patient outcomes. Therefore, the value of companion biomarkers is best assessed while considering the timing of the test use; for example, whether the testing was done at diagnosis or following progression to metastasis. Westwood and colleagues (29) noted that the timing of KRAS testing may vary; some clinicians might undertake routine testing for all patients at diagnosis or some might wait until metastases have been detected. Yet, they did not specify how their evaluation was done in this respect.

Uncertainty analysis

Six studies (14, 20–22, 26, 27) explored the impact of cost-effectiveness of varying at least one component of the characteristics of companion biomarker tests being evaluated such as unit cost, total testing cost, test accuracy, cut-off thresholds, and biomarker prevalence. However, many studies did not examine the characteristics of a test separately from that of the corresponding therapy. According to HTA guideline, “if a diagnostic test to establish the presence or absence of the biomarker is carried out solely to support the treatment decision… a sensitivity analysis should be provided without the cost of the diagnostic test” (32). However, out of three UK studies, two studies performed a sensitivity analysis on biomarker testing cost (20, 21).

Data sources for biomarker-related data inputs

All papers except for three studies (14, 17, 22) provided data sources used for the characteristics of biomarker tests. However, several studies did not provide a specific name of companion biomarker testing kits, although some of them reported a general biomarker testing type (e.g. RAS testing) and therefore, several studies were not transparent and reproducible. The most frequently used data sources were previous published literature. However, testing cost inputs were mostly sourced from reimbursement schedules (16, 19, 20, 22, 24), manufactures or laboratories (18, 29, 30), and if such information was unavailable, expert opinions were sought (21).

Discussion

Altogether, eighteen papers were included in this review. One existing systematic review found to be similar to this study in terms of study scope and objective (10). However, it mainly focused on reviewing the sensitivity and specificity of companion diagnostics and the cost of testing. It did not provide a comprehensive review of methodological approaches to EEs for assessing the value for money of companion biomarkers in the context of precision medicine. To the best of our knowledge, this is the first review providing a comprehensive report on current practices and possible solutions in terms of methodological approaches and evidence requirements in assessing the value for money of companion biomarkers. Table 3 summaries possible solutions and suggestions to address the methodological issues identified in this review.

Table 3
Summary of current practices and solutions in economic evaluations of companion biomarkers

Methodological areas	Issues identified in the current practice of economic evaluations	Possible solutions/suggestions	
		Methodological approaches	Data requirements
Target population	Pre-selected population group with known biomarker status was targeted in EEs.	Target the entire patient group including biomarker positive, negative, and unknown.	Clinical data on all patients including false positive, false negative, unknown biomarker status.
Perspective	Payer perspective was mostly used following the HTA guidelines by the reimbursement authority.	Holistic viewpoint desired (e.g. societal perspective). However, if infeasible, biomarker testing related cost items should be included in evaluations.	Cost data collected from administrative database or real-world setting.
Comparator	With versus without the use of biomarker testing compared in evaluations yet in the context of the same targeted therapy.	SOC in current routine clinical practice should be employed as a comparator in the context of treating the disease condition of interest and the target patient population.	Evidence on standard of care being routinely practiced for the target patient population with the disease condition in a country-specific setting.
Comparison structure	No consistency in structuring strategies to be compared in comparative analysis of companion biomarkers for targeted therapies.	Test-treat versus treat-all with SOC is suggested as a base-case comparison structure.	Clinical data on patients treated all with SOC without biomarker tested. Clinical data on patients tested negative.
Clinical effectiveness	Clinical value of companion biomarkers was limited to sensitivity/specificity. Often, biomarker prevalence data was ignored. Sensitivity /specificity was often assumed to be 100% or excluded completely from the economic model inputs.	Clinical value of companion biomarkers beyond sensitivity /specificity should be incorporated in economic evaluations of biomarker-guided therapies.	Clinical evidence generated from clinical trials on both the drug and the diagnostic. If possible, separate RCTs in test positive and test negative patients respectively treated with guided therapy and non-guided therapy. In addition, the clinical utility values including the change of clinician's behavior in choosing this treatment option over SOC should be captured.
Preference-based outcome	Utility and/or disutility values related to biomarker testing were not considered.	Biomarker related patient preferences should be incorporated in economic evaluations of biomarker-guided therapies.	Individual patient utility (or disutility) values on the use of a companion biomarker test prior to the administration of targeted therapy. Patient preference data can be acquired along the clinical trials, reflecting all biomarker relevant preference items.
Timing of the test use	The timing of the use of companion biomarker testing is often not incorporated and not reported in economic evaluations.	The value of companion biomarkers should be understood throughout the clinical pathways applicable to the decision-making of clinicians.	The timing of the test use in clinical routine settings is preferred over the RCT setting.
Uncertainty analysis	Many economic evaluations did not examine the characteristics of a test separately from that of the corresponding therapy.	The characteristic components relevant to a companion biomarker diagnostic should be tested separately as part of uncertainty analysis of biomarker-guided therapy.	Value of information analysis can be useful to inform the uncertainty around current information/data against perfect or partial perfect information.
Information and model inputs to be incorporated in economic evaluations of companion biomarkers	Limited number of model parameters pertinent to biomarker testing was incorporated into the economic assessment of companion biomarkers.	Model inputs relevant to companion biomarker testing should all be captured and incorporated in economic evaluations of biomarker-guided therapies.	Name/type of biomarker testing diagnostic/kit. Resource use of testing. Unit cost of testing. Capital cost if the testing device is not currently available in current clinical settings. Prevalence of biomarker status in patient population. Sensitivity/specificity. Utility and/or disutility values of performing the test in relation to preference-based outcomes. Clinical pathways including the test (for example, when the test is performed in routine clinical settings).

Many of the EEs of biomarker-guided therapies target a pre-selected patient group with a specific biomarker status instead of including all patients with a disease regardless of their biomarker status. This is then often used as a justification for excluding companion biomarker testing from EE, leading to a lack of robust economic evidence for the entire patient group with the disease. It is important to consider all patients regardless of biomarker status and then, to perform the economic assessment of companion biomarker therapies for all populations of interest with the condition or disease.

Also, EEs need to be consistent with the decision problem being addressed for targeted patient populations using a payer perspective. EEs usually adopt a perspective proposed in country-specific health technology assessment guidelines and then, the third-party payer perspective is the most frequently employed viewpoint of analysis. However, considering the multiple purposes of biomarker tests and the indirect health impact of companion biomarkers on patient outcomes of corresponding therapies, it might be better to adopt a holistic viewpoint and capture the full spectrum of health economic consequences of biomarkers. This would then permit the inclusion of non-health related costs and benefits such as early information or reassurance on treatment option.

Applying comparator strategy of relevance in specific clinical settings is crucial and may change the cost-effectiveness outcomes of the intervention being assessed. Economic evaluation of biomarker-guided therapies often requires more than one comparator arm such as biomarker-guided therapy without biomarker testing and standard of care without biomarker testing (55). A previous study (12) sometimes found conflicting cost-effectiveness results depending on the comparator strategy chosen such as test-treat versus treat-all with standard of care (SOC) and test-treat versus treat-all with new therapy. We found no consistency in the choice of comparator strategies and in structuring the strategies to be compared. Biomarker-guided therapies are often evaluated by comparing biomarker testing and no-testing strategies in administering the new intervention being evaluated. Such comparative analyses often ignore the standard of care being provided in current clinical practice.

There are challenges in determining the clinical value of companion biomarkers. If the companion biomarkers were integrated as an integral part of the clinical trials of their corresponding therapies, determining the clinical utility of companion biomarkers can be assumed or justified that it is already reflected in the clinical effectiveness of corresponding therapies (56). Otherwise, it is difficult to show the clinical utility of companion biomarkers in clinical practice. Often, biomarker tests are developed independently from the drug and the common practice of biomarker test developers in terms of evidence generation is only limited to provide clinical validity (i.e. sensitivity and specificity). Reflecting this common practice in the generation of clinical evidence for biomarkers, we found that the assessment of the clinical value of companion biomarkers in EEs is limited to a consideration of the sensitivity and specificity of the test.

Most studies considered and included the cost of companion biomarker testing in their EEs. However, they often did not provide sufficient details on how they calculated the cost of testing and what data sources were used. This posed challenges in terms of transparency and reproducibility of EEs of companion biomarkers. This may be because testing cost is not standardized (e.g. no coding systems exist for biomarker testing in medical records) or not publicly available (e.g. secret pricing or individually negotiated price at a hospital/laboratory level) in many countries. Given that no standardized cost information such as unit costs is publicly available, most economic evaluations might need to rely on laboratory charges.

It is said in the field of precision medicine that we need to introduce more flexible reimbursement systems in order to reward innovation, reflecting the added value of diagnostics or biomarker tests (57). Otherwise, the value of biomarkers will not be fully captured and reflected in EEs. This also leads to an issue of understanding the entire clinical pathways in relation to the biomarker test and capture the right place of the added value of biomarkers in the continuum course of disease management and cure. Our study showed that many evaluations failed to reflect this aspect by not even reporting the timing of the test use. Furthermore, the patient preference utility of companion biomarkers in terms of HRQoL or adverse events was widely ignored.

Conclusion

It is in the public interest to ensure timely integration of new technologies into clinical use through adequate levels of reimbursement and coverage. However, it requires that test developers demonstrate robust evidence of the health economic impact of biomarker tests. Companion biomarker characteristics captured in EEs are often limited to the cost or the accuracy of the test. Often, only the costs of biomarker testing are modelled. Clinical outcomes or utilities are often difficult to include due to the limited data generated by clinical trials.

We found that there was no consistent approach applied in assessing the value of biomarkers and including the characteristics of biomarkers in an economic evaluation of targeted oncology therapies. Currently, many EEs fail to capture the full value of companion biomarkers beyond sensitivity/specificity and cost related to biomarker testing.

List Of Abbreviations

CDx Companion Diagnostics

EE Economic Evaluation

FDA Food and Drug Administration

PICOS Population, Intervention, Comparator, Outcome, Study design

PRISMA Preferred Reporting Items of Systematic Reviews and Meta-Analyses

CHEERS Consolidated Health Economic Evaluation Reporting Standards

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analysed during this study are included in this published article and its additional files.

Competing interests

The authors declare that they have no competing interests

Funding

Mikyung Kelly Seo receives a PhD studentship from the Centre for Cancer Biomarkers (CCBIO), Centre of Excellence at the Faculty of Medicine and Dentistry, University of Bergen. No sources of funding were used to conduct this study or prepare this manuscript.

Authors' contributions

Conceptualization: MKS, JC.

Data curation: MKS.

Formal analysis: MKS.

Investigation: MKS.

Project administration: MKS.

Supervision: JC.

Validation: JC.

Writing – original draft: MKS.

Writing – review & editing: JC.

Acknowledgements

Mikyung Kelly Seo is grateful to the Centre for Cancer Biomarkers (CCBIO) for PhD scholarship.

References

1. US Food and Drug Administration. Companion Diagnostic. https://www.fda.gov/medical-devices/vitro-diagnostics/companion-diagnostics Accessed 12 May 2019.
2. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Journal of clinical epidemiology. 2009;62(10):e1-e34.
3. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg. 2010;8(5):336–41.
4. Saito S, Kameyama H, Muneoka Y, Okuda S, Wakai T, Akazawa K. Cost-effectiveness analysis of the use of comprehensive molecular profiling before initiating monoclonal antibody therapy against metastatic colorectal cancer in Japan. Journal of cancer policy. 2017;12:61–6.
5. Butzke B, Oduncu FS, Severin F, Pfeufer A, Heinemann V, Giessen-Jung C, et al. The cost-effectiveness of UGT1A1 genotyping before colorectal cancer treatment with irinotecan from the perspective of the German statutory health insurance. Acta Oncologica. 2016;55(3):318–28.
6. Lu S, Zhang J, Ye M, Wang B, Wu B. Economic analysis of ALK testing and crizotinib therapy for advanced non-small-cell lung cancer. Pharmacogenomics. 2016;17(9):985–94.
7. Squires H, Stevenson M, Simpson E, Harvey R, Stevens J. Trastuzumab Emtansine for Treating HER2-Positive, Unresectable, Locally Advanced or Metastatic Breast Cancer After Treatment with Trastuzumab and a Taxane: An Evidence Review Group Perspective of a NICE Single Technology Appraisal. PharmacoEconomics. 2016;34(7):673–80.
8. US Food and Drug Administration. List of cleared or approved companion diagnostic devices (In vitro and imaging tools). Available from: https://www.fda.gov/medical-devices/vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-vitro-and-imaging-tools [Last accessed 27 November 2018].
9. Seo MK. Economic evaluations of cancer biomarkers for targeted therapies: practices, challenges, and policy implications. In: Blanchard, A. and Strand, R., editors. Cancer biomarkers: ethics, economics and society. Megaloceros Press, 2017. p. 25–38.
10. Doble B, Tan M, Harris A, Lorgelly P. Modeling companion diagnostics in economic evaluations of targeted oncology therapies: systematic review and methodological checklist. Expert review of molecular diagnostics. 2015;15(2):235–54.
11. Annemans L, Redekop K, Payne K. Current methodological issues in the economic assessment of personalized medicine. Value Health. 2013;16(6 Suppl):S20-6. doi: 10.1016/j.jval.2013.06.008.

12. Seo MK, Cairns J. Do cancer biomarkers make targeted therapies cost-effective? A systematic review in metastatic colorectal cancer. PloS one. 2018;13:e0204496.
13. Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, et al. Consolidated health economic evaluation reporting standards (CHEERS)—explanation and elaboration: a report of the ISPOR health economic evaluation publication guidelines good reporting practices task force. Value in Health. 2013;16(2):231–50.
14. Aguiar PN, Perry LA, Penny-Dimri J, Babiker H, Tadokoro H, de Mello RA, et al. The effect of PD-L1 testing on the cost-effectiveness and economic impact of immune checkpoint inhibitors for the second-line treatment of NSCLC. Annals of Oncology. 2017;28(9):2256–63.
15. Chouaid C, Luciani L, LeLay K, Do P, Bennouna J, Perol M, et al. Cost-Effectiveness Analysis of Afatinib versus Gefitinib for First-Line Treatment of Advanced EGFR-Mutated Advanced Non-Small Cell Lung Cancers. Journal of thoracic oncology. 2017;12(10):1496–502.
16. Curl P, Vujic I, Van 't Veer LJ, Ortiz-Urda S, Kahn JG. Cost-effectiveness of treatment strategies for BRAF-mutated metastatic melanoma. PloS one. 2014;9 (9) (no pagination)(e107255).
17. Ewara EM, Zaric GS, Welch S, Sarma S. Cost-effectiveness of first-line treatments for patients with KRAS wild-type metastatic colorectal cancer. Current Oncology. 2014;21(4):e541-e50.
18. Graham CN, Hechmati G, Hjelmgren J, De Liege F, Lanier J, Knox H, et al. Cost-effectiveness analysis of panitumumab plus mFOLFOX6 compared with bevacizumab plus mFOLFOX6 for first-line treatment of patients with wild-type RAS metastatic colorectal cancer. European Journal of Cancer. 2014;50(16):2791–801.
19. Graham CN, Maglinte GA, Schwartzberg LS, Price TJ, Knox HN, Hechmati G, et al. Economic Analysis of Panitumumab Compared With Cetuximab in Patients With Wild-type KRAS Metastatic Colorectal Cancer That Progressed After Standard Chemotherapy. Clinical therapeutics. 2016;38(6):1376–91.
20. Harty G, Jarrett J, Jofre-Bonet M. Consequences of Biomarker Analysis on the Cost-Effectiveness of Cetuximab in Combination with FOLFIRI as a First-Line Treatment of Metastatic Colorectal Cancer: personalised Medicine at Work. Applied health economics and health policy. 2018:1–11.
21. Huxley N, Crathorne L, Varley-Campbell J, Tikhonova I, Snowsill T, Briscoe S, et al. The clinical effectiveness and cost-effectiveness of cetuximab (review of technology appraisal no. 176) and panitumumab (partial review of technology appraisal no. 240) for previously untreated metastatic colorectal cancer: A systematic review and economic evaluation. Health Technology Assessment. 2017;21(38):V-241.
22. Janmaat VT, Bruno MJ, Polinder S, Lorenzen S, Lordick F, Peppelenbosch MP, et al. Cost-effectiveness of cetuximab for advanced esophageal squamous cell carcinoma. PloS one. 2016;11 (4) (no pagination)(e0153943).
23. Morgan P, Woolacott N, Biswas M, Mebrahtu T, Harden M, Hodgson R. Crizotinib for Untreated Anaplastic Lymphoma Kinase-Positive Non-Small-Cell Lung Cancer: an Evidence Review Group Perspective of a NICE Single Technology Appraisal. PharmacoEconomics. 2017:1–11.
24. Wu B, Yao Y, Zhang K, Ma X. RAS testing and cetuximab treatment for metastatic colorectal cancer: a cost-effectiveness analysis in a setting with limited health resources. Oncotarget. 2017;8(41):71164–72.
25. Tikhonova IA, Huxley N, Snowsill T, Crathorne L, Varley-Campbell J, Napier M, et al. Economic Analysis of First-Line Treatment with Cetuximab or Panitumumab for RAS Wild-Type Metastatic Colorectal Cancer in England. Pharmacoeconomics. 2018;36(7):837–51. doi: 10.1007/s40273-018-0630-9.
26. Lim EA, Lee H, Bae E, Lim J, Shin YK, Choi SE. Economic evaluation of companion diagnostic testing for EGFR mutations and first-line targeted therapy in advanced non-small cell lung cancer patients in South Korea. PloS one. 2016;11 (8) (no pagination)(e0160155).
27. Lu S, Yu Y, Fu S, Ren H. Cost-effectiveness of ALK testing and first-line crizotinib therapy for non-small-cell lung cancer in China. PloS one. 2018;13 (10) (no pagination)(e0205827).
28. Wen F, Yang Y, Zhang P, Zhang J, Zhou J, Tang R, et al. Cost-effectiveness of RAS screening before monoclonal antibodies therapy in metastatic colorectal cancer based on FIRE3 Study. Cancer Biology and Therapy. 2015;16(11):1577–84.
29. Westwood M, van Asselt T, Ramaekers B, Whiting P, Joore M, Armstrong N, et al. KRAS mutation testing of tumours in adults with metastatic colorectal cancer: A systematic review and cost-effectiveness analysis. Health Technology Assessment. 2014;18(62):i-xxii + 1-131.
30. Zhou J, Zhao R, Wen F, Zhang P, Tang R, Chen H, et al. Economic evaluation study (CHEER-compliant): Cost-effectiveness analysis of RAS screening for treatment of metastatic colorectal cancer based on the CALGB 80405 trial. Medicine (United States). 2016;95 (27) (no pagination)(e3762).
31. Schnell-Inderst P, Hunger T, Conrads-Frank A, Arvandi M, Siebert U. Ten recommendations for assessing the comparative effectiveness of therapeutic medical devices: a targeted review and adaptation. J Clin Epidemiol. 2018;94:97–113.(doi):10.1016/j.jclinepi.2017.09.022. Epub Oct 28.
32. National Institute of Health and Care Excellence. Guide to the methods of technology appraisal. 2013. Available: https://www.ncbi.nlm.nih.gov/books/NBK395867/pdf/Bookshelf_NBK395867.pdf [Last accessed: 10 May 2019].
33. Canadian Agency for Drugs and Technologies in Health. Guidelines for the economic evaluation of health technologies: Canada [3rd edition]. Ottawa: Canadian Agency for Drugs and Technologies in Health. Available http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Guidelines_for_the_Economic_Evaluation_of_Health_Technologies.pdf. 2006
34. National Institute for Clinical Excellence (NICE). Diagnostic Assessment Programme Manual. 2011.: Available: https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-diagnostics-guidance/Diagnostics-assessment-programme-manual.pdf [Last accessed: 23 April 2020]
35. Fridlyand J, Simon RM, Walrath JC, Roach N, Buller R, Schenkein DP, et al. Considerations for the successful co-development of targeted cancer therapies and companion diagnostics. Nature Reviews Drug Discovery. 2013;12(10):743–55.
36. US Food and Drug Administration. Developing and labeling in vitro companion diagnostic devices for a specific group of oncology therapeutic products: Guidance for industry. Available at https://www.fda.gov/media/120340/download. 2020.

37. Subtil F, Rabilloud M. Estimating the optimal threshold for a diagnostic biomarker in case of complex biomarker distributions. BMC medical informatics and decision making. 2014;14(1):53.
38. National Academies of Sciences E, Medicine. Biomarker tests for molecularly targeted therapies: key to unlocking precision medicine: National Academies Press; 2016.
39. Lesko L, Zineh I, Huang SM. What is clinical utility and why should we care? Clinical Pharmacology & Therapeutics. 2010;88(6):729–33.
40. Sorich MJ, Coory M. Interpreting the clinical utility of a pharmacogenomic marker based on observational association studies. The pharmacogenomics journal. 2014;14(1):1–5.
41. Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. Methods for the economic evaluation of health care programmes: Oxford university press; 2015.
42. National Institute for Clinical Excellence (NICE). Guide to the methods of technology appraisal. https://wwwniceorguk/process/pmg9/chapter/the-reference-case#exploring-uncertainty. 2013.
43. Oosterhoff M, van der Maas ME, Steuten LM. A systematic review of health economic evaluations of diagnostic biomarkers. Applied health economics and health policy. 2016;14(1):51–65.
44. Coulter A, Collins A. Making shared decision-making a reality. London: King's Fund. 2011.
45. Charles C, Gafni A, Whelan T. Shared decision-making in the medical encounter: what does it mean?(or it takes at least two to tango). Social science & medicine. 1997;44(5):681–92.
46. Weston WW. Informed and shared decision-making: the crux of patient-centred care. Cmaj. 2001;165(4):438–9.
47. Donaldson C, Shackley P. Does “process utility” exist? A case study of willingness to pay for laparoscopic cholecystectomy. Social science & medicine. 1997;44(5):699–707.
48. Mooney G. Key issues in health economics: Harvester Wheatsheaf; 1994.
49. Gerard K, Mooney G. QALY league tables: handle with care. Health economics. 1993;2(1):59–64.
50. Brennan VK, Dixon S. Incorporating process utility into quality adjusted life years: a systematic review of empirical studies. PharmacoEconomics. 2013;31(8):677–91.
51. Mayo Clinic. Biopsy: Types of biopsy procedures used to diagnose cancer. https://www.mayoclinic.org/diseases-conditions/cancer/in-depth/biopsy/art-20043922 Accessed 7 June 2020 2020 [
52. J Sorich M, A McKinnon R. Personalized medicine: potential, barriers and contemporary issues. Current drug metabolism. 2012;13(7):1000–6.
53. Centers for Disease Control Prevention. Genomic Testing: ACCE model process for evaluating genetic tests. CDCP, Atlanta (available online at: www. cdc. gov/genomics/gtesting/ACCE); 2010.
54. Westwood M, Asselt A, Ramaekers B, Whiting P, Joore M, Armstrong N, et al. KRAS mutation testing of tumours in adults with metastatic colorectal cancer: a systematic review and cost-effectiveness analysis. 2014.
55. Faulkner E, Annemans L, Garrison L, Helfand M, Holtorf A-P, Hornberger J, et al. Challenges in the development and reimbursement of personalized medicine—payer and manufacturer perspectives and implications for health economics and outcomes research: a report of the ISPOR Personalized Medicine Special Interest Group. Value in Health. 2012;15(8):1162–71.
56. National Institute of Health and Care Excellence. Crizotinib for previously treated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer. Technology Appraisal Guidance TA422. 21 December 2016. Available: https://www.nice.org.uk/guidance/ta422.
57. Cohen JP, Felix AE. Personalized Medicine's Bottleneck: Diagnostic Test Evidence and Reimbursement. Journal of personalized medicine. 2014;4(2):163–75.

Figures

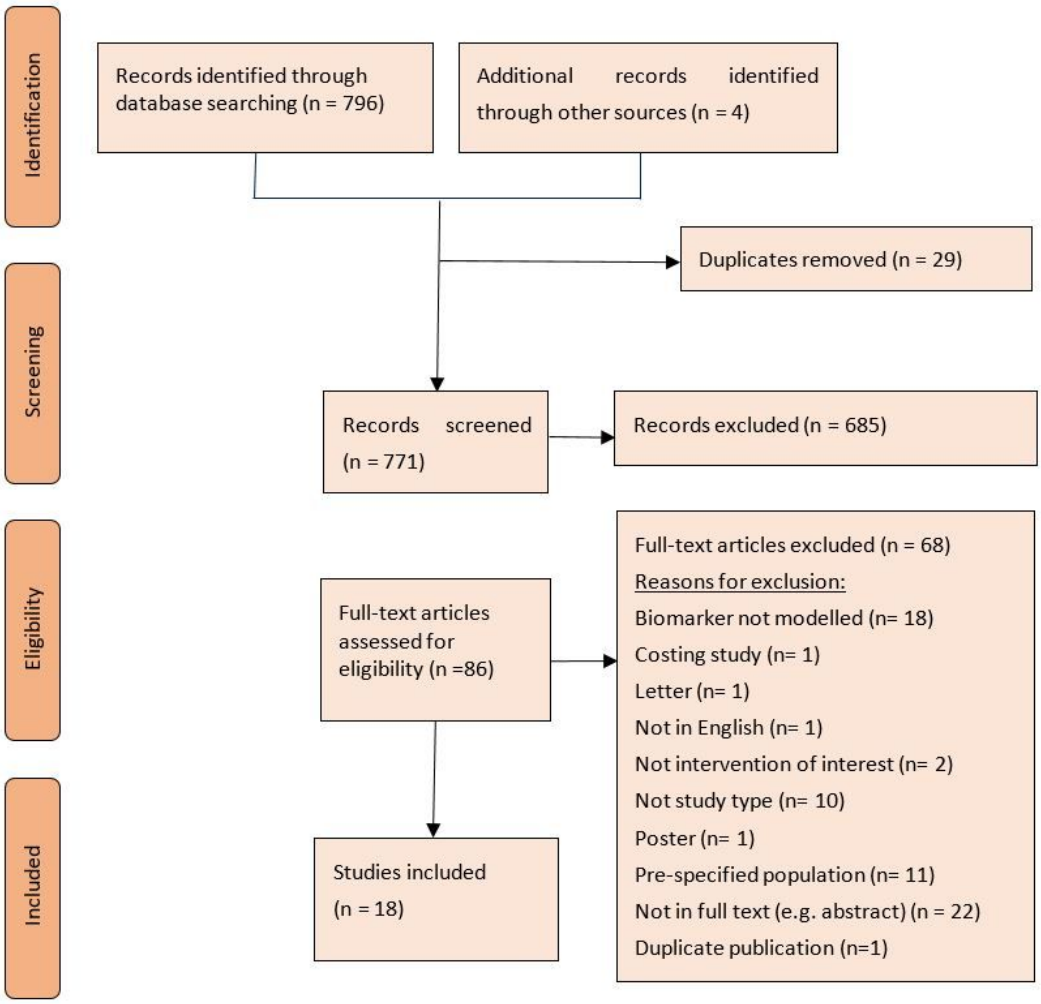

Figure 1

PRISMA Flow Diagram of Study Selection

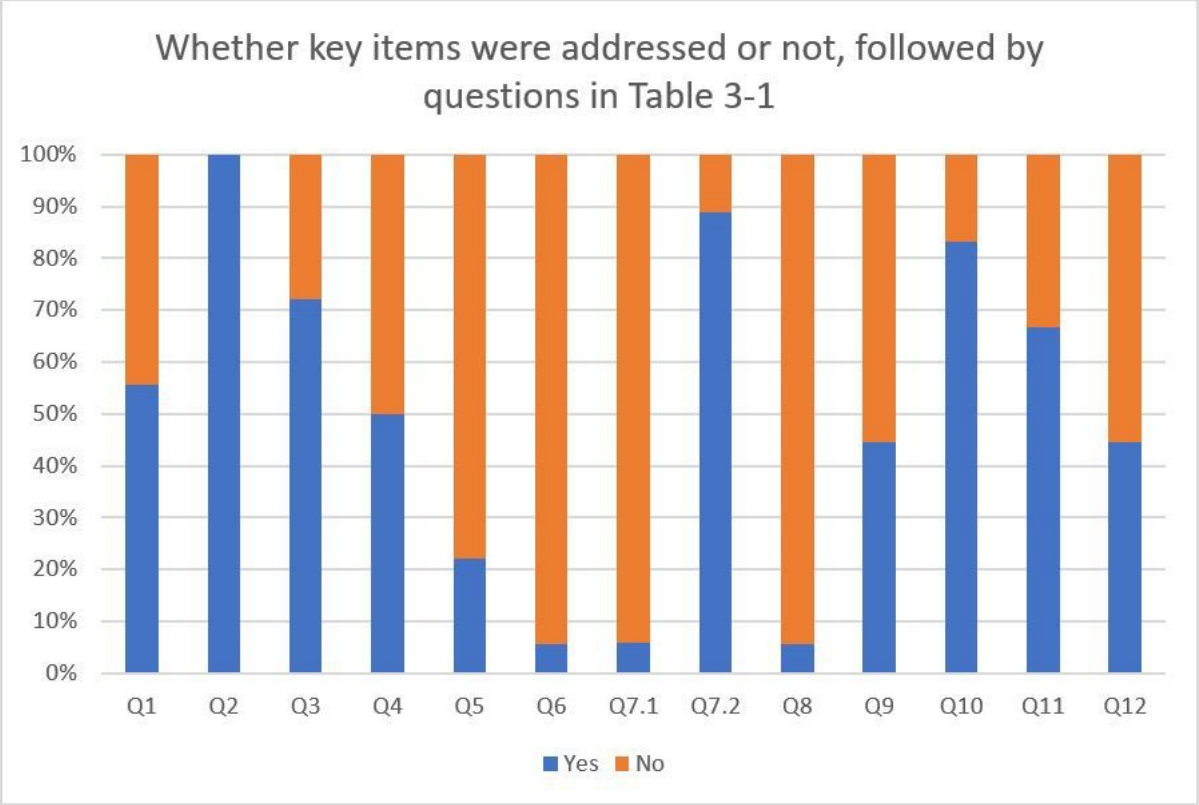

Figure 2

Graph of including the characteristics of companion biomarkers in economic evaluations