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REVIEW ARTICLE

How are Companion Diagnostics Considered in Economic Evaluations of Oncology Treatments? A Review of Health Technology Assessments

Melissa Gomez Montero[1] · Houcine El Alili[1] · Mahmoud Hashim[1,2] · Peter Wigfield[1] · Mariya Dimova[3] · Ralph Riley[4] · Katie Pascoe[5]

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Abstract

Background Companion diagnostic (CDx) testing is increasingly used to identify eligible patients for targeted treatments. Guidance on how CDx testing should be incorporated into cost-effectiveness models (CEM) is limited. This review evaluated how health technology assessment bodies and research organizations considered CDx in CEMs of targeted therapies in oncology and whether this ultimately impacted their decisions or time from regulatory approval to recommendations.

Methods An exhaustive list of approved CDx tests in oncology was compiled. For corresponding indications and treatments, NICE appraisals published between 2016 and 2019 were identified. Then, assessments for the same treatments issued from 11 other agencies were reviewed. Data extracted included background and CDx information, CDx's role in the CEM, and recommendations.

Results Twenty-seven NICE appraisals were identified; 15 considered CDx testing in the CEM, while 12 did not, mainly because testing had already been established for the comparators within the same class or in clinical practice from a prior treatment line. Both testing costs and mutation prevalence drove CDx testing costs per patient. The cross-comparison of assessments showed that CDx test characteristics were inconsistently reported. Time from regulatory approval to recommendations was not impacted by CDx cost inclusion in CEMs.

Conclusion CDx testing was included in cost-effectiveness models whenever mutation testing was required solely for patients receiving targeted treatment; cost per patient was based on test costs and mutation prevalence. It is unclear if expanded reliance on CDx testing will impact future assessments of targeted therapies. A future update is warranted to track trends over time.

Key Points for Decision Makers

Generally, CDx testing (and associated costs) were included in cost-effectiveness models whenever mutation testing was not embedded as standard practice in a health care system.

Cost per patient was driven by test costs and mutation prevalence.

Whether expanded reliance on CDx testing will impact future assessments of targeted therapies is still unclear.

Melissa Gomez Montero and Houcine El Alili contributed equally.

Mahmoud Hashim was an Ingress-Health employee during the initial development of the manuscript, and during the final review and submission, he was an employee of Janssen Global Services.

✉ Katie Pascoe
KPascoe1@its.jnj.com

1 Ingress-Health, Rotterdam, The Netherlands

2 Janssen Global Services Inc, 2340 Beerse, Belgium

3 Janssen Global Services Inc, 92787 Issy-les-Moulineaux, France

4 Janssen Global Services Inc, Raritan, NJ, USA

5 Janssen Oncology, Global Commercial Strategy Organization, 50-100 Holmers Farm Way, High Wycombe HP12 4EG, UK

1 Introduction

Advances in cancer care over the past decades can be attributed to the improved understanding of genomics and molecular biology, particularly with respect to the genetic and phenotypic abnormalities of cancer cells. The rapidly advancing knowledge of cancer biology has led to a shift toward a more precise or targeted approach to oncology treatments, in which the individual variability and complexity of the molecular profile of a patient's tumor are considered [1]. Precision medicine enables clinicians to tailor medical treatments to a patient's genetic profile and specific biomarkers targeting the specific genes and proteins involved in the growth and proliferation of cancerous cells, ultimately optimizing patient outcomes and improving safety profiles [2]. Examples of precision medicine include using targeted therapies to treat specific types of cancer cells, such as mutated epidermal growth factor receptor (EGFR) proteins in lung cancer or amplified human epidermal growth factor receptor 2 (HER2) proteins in breast cancer [1]. Still, precision medicine's day-to-day applications in cancer care continue growing.

The success of precision medicine inherently depends on the proper identification of patients that may benefit most from targeted therapy. This requires the use of companion diagnostics (CDx), medical tests that provide essential information for the safe and effective use of a corresponding drug or biological product [3]. Beyond the clinical benefits of prescribing targeted therapies, CDx testing could also help reduce healthcare costs by limiting the medication use to only the subgroup of patients who have a higher probability of responding favorably to the drug. The cost associated with these CDx tests can have an economic impact on the healthcare system and potentially impact treatment cost-effectiveness when CDx testing costs are identified to be drivers in the health economic model [4]. CDx costs are directly related to the disease and the evaluated technology, meaning that these costs are recognized as direct costs in a health economic model. Since these costs can vary from one healthcare system to another and are directly related to identifying an eligible patient population for a specific treatment, CDx costs should be included in evaluating technologies that require CDx testing. However, in cases where CDx testing is established as the standard of care or provided by the healthcare system to profile all patients, it becomes unclear when and how to incorporate these costs. This dilemma becomes more pertinent with more expensive CDx tests.

Several characteristics of CDx, beyond the cost of the test, can also influence its predictive and economic value. First, the prevalence of the biomarker of interest within a population group may influence whether testing with a CDx is necessary or justifiable. Second, the analytical validity of the CDx can inform how well the test can predict the presence or absence of the biomarker in patients. Third, the most appropriate positioning of the CDx test within the care pathway, whether before or after first-line therapy, needs to be considered together with the targeted therapy. Lastly, attention is needed when treatment pathways rely on the results of more than one CDx test performed either in parallel or in sequence [5]. When not properly addressed, these characteristics can lead to uncertainty in the economic model results of a targeted therapy [6].

Since healthcare payers evaluate the costs and benefits of new technologies, it is crucial to understand how CDx costs and characteristics are assessed in HTA submissions of targeted therapies. The most recent guidelines from the National Institute for Health and Care Excellence (NICE) in England advise on the inclusion of CDx characteristics when appropriate, the Canadian Agency for Drugs and Technologies in Health (CADTH) provides a detailed guidance specific for treatments with a CDx, and the Pharmaceutical Benefits Advisory Committee (PBAC) from Australia lists specific evidence requirements for the associated CDx test [7–9]. However, HTA bodies (HTABs) did not offer guidance on how to incorporate characteristics of CDx testing until very recently [10]. Therefore, we aimed to review and compare how different HTABs assess CDx testing in cost-effectiveness models of targeted oncology therapies up until 2019, and whether this ultimately impacted time from regulatory approval to reimbursement recommendations. This review explores how CDx testing is embedded in models for HTA appraisal during a period of time when targeted medicines were starting to be used more frequently in clinical practice. As CDx has become more commonplace in recent years, a subsequent review will explore appraisals from 2020 onwards to observe any changes in how these oncology medicines are evaluated.

2 Methods

2.1 Data Sources and Assessment Selection

A comparative review of publicly available appraisals from 12 HTABs and assessments from one research organization was conducted between May 2019 and December 2019. Initially, the identification of pharmacological treatments requiring CDx tests was based on an exhaustive list of approved CDx tests for targeted therapies in oncology, as published in May 2019 by the US Food and Drug Administration (FDA) [11]. Based on this list of targeted therapies, we conducted a targeted search of all technology appraisals

(TAs) from NICE, published between January 2016 and January 2019.

Considering that NICE is widely recognized by other HTABs, given its rigorous methodologies for appraisals of interventions [12], the identified NICE appraisals were used as a benchmark for comparison. They were cross-checked with assessments reported on the national or regional agency websites of 11 other selected HTABs and one research organization. The other selected HTABs included the Scottish Medicine Consortium (SMC); CADTH from Canada; PBAC from Australia; the Swedish Dental and Pharmaceutical Benefits Agency (Tandvårds- och läkemedelsförmånsverket (TLV)); the Haute Autorité de Santé (HAS) from France; the National Health Care Institute (Zorginstituut Nederland (ZIN)) from The Netherlands; Generalitat de Catalunya (GENCAT) from the Catalonia region in Spain; the Basque Office for Health Technology Assessment (OSTEBA) from the Basque Country in Spain; the Andalusian Health Technology Assessment Department (AETSA) from Andalusia, Spain; the Galician Agency for Health Technology Assessment (AVALIA-T) from Galicia, Spain; the Canary Islands Health Service Evaluation and Planning Service (SECS) from Spain; and the National Committee for Technology Incorporation (CONITEC) from Brazil. Additionally, the Institute for Clinical and Economic Review (ICER) from the USA was included in this study as a research organization conducting independent reviews rather than appraisals with a government mandate. Throughout this review, appraisals from HTABs and reviews from ICER are pooled and defined as assessments. These agencies were chosen as they provide a good representation of how technologies are appraised across different continents and have clear methodology and processes for handling evidence and utilizing economic evaluation as part of their HTA.

2.2 Data Handling

Data extraction from the identified assessments was performed by two researchers (MGM and HEA). For assessments identified in English, French, Spanish, Portuguese, and Dutch languages, the review was conducted in its original language. For appraisals in Swedish, an online translation tool was used. Data extraction items included background information of the therapy (indication, treatment, pivotal study design), CDx and related genetic biomarker information if reported in the assessment, and the recommendations made by the respective agencies regarding the targeted treatment. However, no information regarding the economic evaluations' methodological elements (such as type of model, time horizon, discounting rate, or uncertainty analyses) was extracted in this review.

A qualitative analysis was performed to compare and contrast the inclusion of CDx information across assessments and their eventual impact on recommendations based on the extracted data. The data were synthesized to present the outcomes of interest for each therapy and each assessment body, grouped per treatment area (i.e., indication), and compared to the approach taken by NICE.

3 Results

3.1 Overview of Included Assessments

The initial search for NICE TAs of targeted treatments with a CDx resulted in 27 matching TAs. The search for corresponding assessments from other bodies resulted in 25 appraisals from SMC; 20 from CADTH; 20 from GENCAT; 17 from PBAC; 13 from HAS; 11 from TLV; 4 from ZIN; 2 from CONITEC; and 4 reviews from ICER. No assessments were identified from the public domains of the regional Spanish HTABs: OSTEBA, AETSA, AVALIA-T, and SESCS. Online Supplemental Material (OSM) Resource 1 presents the complete list of identified assessments.

3.2 Targeted Therapies

The identified assessments covered 15 pharmacological compounds across 27 different indications in oncology. Figure 1 shows the number of assessments identified per cancer group; most assessments involved treatments for non-small-cell lung cancer (NSCLC). Other assessments included targeted therapies in leukemia, urothelial cancer, breast cancer, melanoma, ovarian cancer, and colorectal cancer. Ceritinib and crizotinib were assessed in more than one indication in NSCLC and pertuzumab was assessed in two indications in breast cancer. Meanwhile, atezolizumab and pembrolizumab were assessed across cancer types in both NSCLC and urothelial cancer. Six of the identified therapies had an orphan designation at the time of their first NICE appraisal. OSM Resource 2 summarizes the characteristics of the therapies, patient populations, and characteristics of the associated CDx tests in the identified assessments.

3.3 Characteristics of Companion Diagnostic (CDx) Tests

Limited information regarding CDx tests' characteristics was reported in the identified assessments. Sensitivity and specificity of the CDx test and some testing-related costs such as the cost of tissue acquisition, consideration for repeat testing when needed, or the sequencing of multiple tests were often not reported. From the 27 identified NICE appraisals, we found that only 15 incorporated CDx testing in their economic evaluations. Similarly, CDx testing was included in 13 assessments from SMC; 11 from CADTH; nine from PBAC; five from HAS; three from TLV; two from ZIN; one from CONITEC; and three reviews from ICER (Table 1).

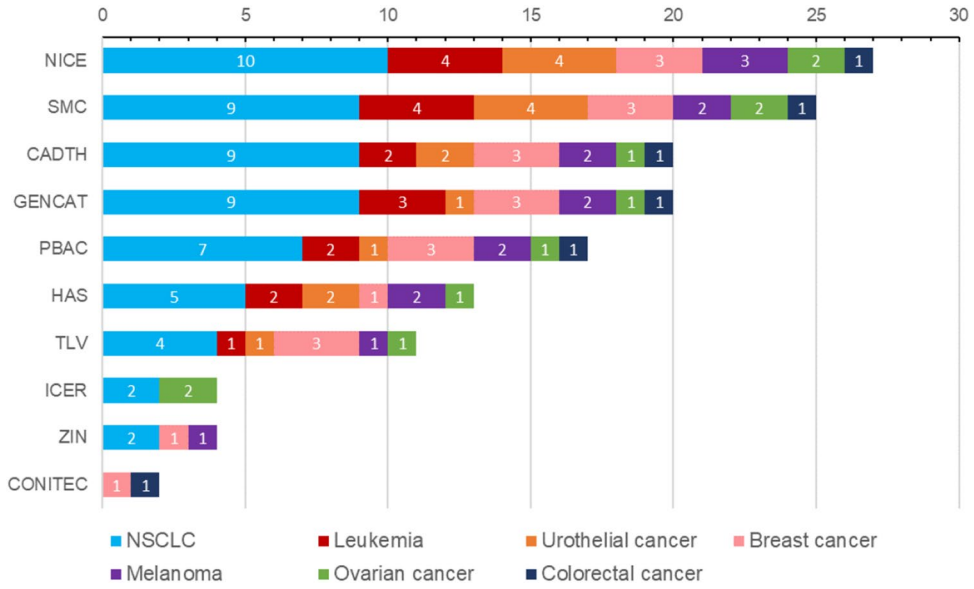

Fig. 1 Number of assessments identified per cancer group. *CADTH* Canadian Agency for Drugs and Technologies in Health, *CONITEC* Comissão Nacional de Incorporação de Tecnologias no SUS, *GENCAT* Generalitat de Catalunya, *HAS* Haute Autorité de Santé, *ICER* Institute for Clinical and Economic Review, *NICE* National Institute for Health and Care Excellence, *NSCLC* non-small-cell lung cancer, *PBAC* Pharmaceutical Benefits Advisory Committee, *SMC* Scottish Medicine Consortium, *TLV* Tandvårds- och läkemedelsförmånsverket, *ZIN* Zorginstituut Nederland

The remaining assessments did not report any CDx testing within their economic evaluations, as illustrated in Fig. 2. Note that for all appraisals by GENCAT, the importance of CDx testing prior to treatment prescription was acknowledged. Still, it was not reported whether the costs and other characteristics of CDx tests were included in the economic models of the targeted therapies. Information on the analytical validity (i.e., sensitivity and specificity) of the CDx test was often not reported in the reviewed assessments across all agencies. Other characteristics of importance regarding the CDx tests were poorly reported or disregarded altogether from the evaluated assessments.

3.3.1 Inclusion of CDx Testing and Calculation of CDx Costs

A cross-comparison of assessments allowed us to identify a pattern of CDx testing inclusion based on the comparator arm of the model. It was apparent that if mutation testing was not required for the comparator treatment, then CDx testing costs were incorporated in the active treatment arm of the model, as these would contribute to differences in costs between treatment arms, impacting the resulting incremental cost-effectiveness ratios.

Of the 15 submissions to NICE that incorporated CDx testing in their economic models, we could determine that the calculation of CDx testing costs per patient was driven by the cost of the test and the prevalence of the mutation. These costs were estimated by dividing the cost per test, which ranged between £40 and £600 in these appraisals, by the mutation-positive prevalence. This calculation yielded a cost per patient identified as having the mutation that ranged from £108 to £4500.

Considerations of the sensitivity and specificity of the test were rarely acknowledged in the calculation of CDx costs across TAs, and if reported, were often confidential. Only one appraisal on crizotinib for treating Proto-oncogene tyrosine-protein kinase ROS-positive (ROS1) advanced NSCLC in adult patients (TA529) presented information on how sensitivity and specificity were considered in the calculation of CDx cost [13]. In this appraisal patients were tested upfront for ROS1 mutation or after a negative test for EGFR and anaplastic lymphoma kinase (ALK) mutations. CDx testing was modeled in sequence, first with immunohistochemistry (IHC), then followed by confirmatory fluorescence in situ hybridization (FISH), which is considered to be the most pragmatic strategy by UK clinical experts. Specificity and sensitivity of IHC ROS1 testing were given as 83 and 100%, respectively. The false-positive rate and false-negative rate of IHC were calculated to be 17% (100–83%) and 0% (100–100%), respectively. The diagnostic accuracy of FISH for ROS1 testing was assumed to be perfect, as FISH was the reference test in the diagnostic accuracy study providing the specificity of IHC in ROS1 testing [13]. The cost per test for IHC was £50, and the cost for a FISH confirmatory test was equal to £120. However, FISH testing costs were based on the ROS1 incidence (i.e., 1.69%) and the proportion of true-positive and false-positive patients after IHC, meaning that FISH testing costs were equal to £22.44 (i.e., (1.69% + 17%) * 120). Total testing cost per patient were therefore estimated at £4287.92 (i.e., £50 + £22.44 = £72.44, and £72.44/1.69%).

The potential cost and clinical losses due to false positives or false negatives were not quantified nor qualitatively analyzed in the reviewed assessments. However, the inclusion of specificity and sensitivity of the test demonstrated an impact on the cost per diagnosed patient.

Table 1 Incorporation of companion diagnostic (CDx) testing in cost-effectiveness models and final recommendations

Drug (Indication)	NICE	SMC	CADTH	GENCAT	PBAC	HAS	TLV	ICER	ZIN	CONITEC
Alectinib (NSCLC) [32]	✓	×	×*	-		×				
Atezolizumab (NSCLC) [14]	×	×	✓*	-	×	×	×	✓	×	
Atezolizumab (Urothelial cancer) [33]	×	×		-			×			
Atezolizumab (Urothelial cancer, First-Line) [34]	×	×								
Ceritinib (NSCLC) [16]	×	✓	×*	-	×		×			
Ceritinib (NSCLC, First line) [15]	×			-						
Cetuximab and panitumumab (Colorectal Cancer) [35]	✓	✓	×	-	✓					✓
Cobimetinib in combination with vemurafenib (Melanoma) [17]	✓		×*	-	×	×				
Crizotinib (NSCLC) [36]	✓	✓	✓*	-	✓		✓			
Crizotinib (NSCLC, First-line) [37]	✓	✓	✓	-						
Crizotinib (NSCLC, ROS-1) [13]	✓	✓	✓*		✓					
Dabrafenib with trametinib (Melanoma) [18]	×	×	✓*		✓		×		✓	
Dasatinib, nilotinib and imatinib (Leukemia) [19]	✓	×		-						
Dasatinib, nilotinib and imatinib (Leukemia, First-line) [20]	✓	✓		-						
Midostaurin (Leukemia) [38]	✓	✓	×		×	✓				
Niraparib (Ovarian cancer) [39]	×	×				×		×		
Olaparib (Ovarian Cancer) [40]	✓	✓	✓*	-	✓		✓	✓		
Osimertinib (NSCLC) [41]	✓	✓	✓*	-	✓	✓	✓			
Pembrolizumab (NSCLC) [42]	✓	✓	✓*	-	✓	✓	×	✓	✓	
Pembrolizumab (NSCLC, First-Line) [43]	✓	✓	✓*	-	✓	✓	×			
Pembrolizumab (Urothelial cancer) [44]	✓	×	✓*		✓	✓	×			
Pembrolizumab (Urothelial cancer, First-Line) [45]	✓	✓	✓				×			
Pertuzumab with trastuzumab and docetaxel (Breast cancer) [46]	×	×	×*	-	×				×	×
Pertuzumab (Breast cancer) [47]	×	×	×	-	×		×			
Trametinib in combination with dabrafenib (Melanoma) [48]	×	×		-		×				
Trastuzumab emtansine (Breast cancer) [49]	×	×	×*	-	×	×				
Venetoclax (Leukemia) [50]	×	✓	×*	-	×	×	×			

Recommended
Not recommended
Decision was deferred at the time of review
Recommendation criteria in France are based on the added therapeutic value (SMR)

CADTH Canadian Agency for Drugs and Technologies in Health, *CDx* companion diagnostic, *CONITEC* Comissão Nacional de Incorporação de Tecnologias no SUS, *GENCAT* Generalitat de Catalunya, *HAS* Haute Autorité de Santé, *ICER* Institute for Clinical and Economic Review, *HTABs* health technology assessment bodies, *NICE* National Institute for Health and Care Excellence, *NSCLC* non-small-cell lung cancer, *PBAC* Pharmaceutical Benefits Advisory Committee, *SMC* Scottish Medicine Consortium, *TLV* Tandvårds- och läkemedelsförmånsverket, *ZIN* Zorginstituut Nederland

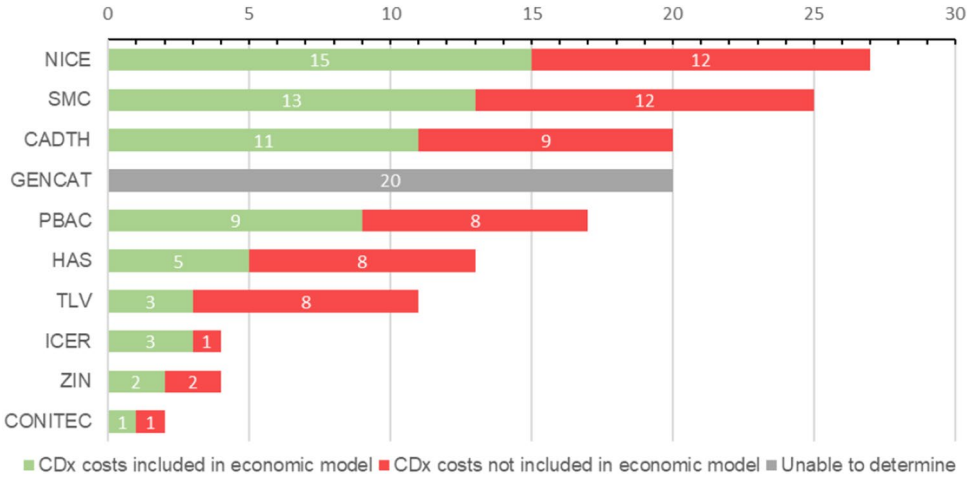

Fig. 2 Number of assessments including and excluding CDx costs in economic models. *CADTH* Canadian Agency for Drugs and Technologies in Health, *CDx* companion diagnostic, *CONITEC* Comissão Nacional de Incorporação de Tecnologias no SUS, *GENCAT* Generalitat de Catalunya, *HAS* Haute Autorité de Santé, *ICER* Institute for Clinical and Economic Review, *NICE* National Institute for Health and Care Excellence, *NSCLC* non-small-cell lung cancer, *PBAC* Pharmaceutical Benefits Advisory Committee, *SMC* Scottish Medicine Consortium, *TLV* Tandvårds- och läkemedelsförmånsverket, *ZIN* Zorginstituut Nederland

3.3.2 Exclusion of CDx Testing

The cross-comparison of assessments also allowed us to identify any rationale for excluding CDx testing from cost-effectiveness models. It was noted that when CDx testing was excluded from the model, it was principally because the CDx costs would not impact the model outcomes (i.e., the incremental cost-effectiveness ratio) as CDx was required for both treatment arms. This was the case in the atezolizumab appraisal, where testing costs were not included in the economic model since atezolizumab was compared to pembrolizumab, where PDL1 testing is routinely conducted [14]. Another finding from this review suggests that if gene mutations in patients were already identified through biomarker testing in a previous line of treatment, then the cost of CDx testing was consistently excluded from cost-effectiveness models in the assessments when used later in the disease course. In these cases, CDx testing was considered standard of care at earlier lines of treatment, and subsequent testing was no longer necessary for the targeted therapy because the target population for therapy would have already been identified. This was identified in two appraisals for ceritinib in untreated and treated advanced ALK-positive NSCLC [15, 16]. In both of these appraisals, ceritinib was compared to crizotinib, which also requires CDx testing in the untreated setting, and in the previously treated setting, patients would have been tested in an earlier line before receiving treatment with crizotinib.

3.4 Health Technology Assessement (HTA) Recommendations

Twenty-six of the 27 TAs included in this review received a positive recommendation from NICE. The only therapy not recommended by NICE was cobimetinib in combination with vemurafenib for adult patients with unresectable or metastatic melanoma [17]. This decision had no relation to the cost of CDx testing or the inclusion or exclusion of other CDx characteristics. The reason for this negative recommendation relates to the incremental cost-effectiveness ratios presented, which far exceeded the nationally accepted threshold.

Assessment recommendations made by other bodies were mostly consistent with the decisions made by NICE. Table 1 synthesizes the recommendations and indicates whether CDx testing costs were included in the cost-effectiveness models. Notedly, the inclusion or exclusion of CDx characteristics in economic models seemed to have had minimal impact on the final decisions from HTABs, as we did not identify any HTAB recommendation to be conditional on the use of a CDx product. Likewise, decisions that included non-recommendations or deferred recommendations were not related to CDx testing inclusion or exclusion criteria but were rather based on uncertainties in survival estimations (such as overall survival and progression-free survival estimates) from cost-effectiveness models; high incremental cost-effectiveness ratios that exceeded countries' thresholds; and the need for more evidence. Based on the identified

assessments, it remains unclear how HTABs will deal with more dependence on CDx testing and increased cost of identifying eligible patients in health economic models.

3.5 Time to Decision

Considering that the simultaneous assessment of a targeted therapy and its associated CDx may potentially delay the approval and access for a therapy, we aimed to understand whether the inclusion of CDx criteria had a direct influence on the time to recommendation. When looking at the time of regulatory approval from the European Medicines Agency to the time of NICE recommendation, we observed time frames of less than 3 months for dabrafenib and trametinib in the adjuvant treatment of melanoma [18] to up to 10 years for dasatinib, nilotinib, and high-dose imatinib in the treatment of chronic myeloid leukemia [19, 20]. Similar time frames were observed on SMC recommendations for the same targeted therapies, possibly explained by the similarities in their healthcare systems. The time to decision from other HTABs ranged from less than 2 months for CADTH's positive recommendation of pembrolizumab in the first-line treatment of metastatic NSCLC [21] to up to just over 6 years for GENCAT's positive recommendation of crizotinib in the treatment of anaplastic lymphoma kinase-positive advanced NSCLC [22]. However, the variation in these time frames was not influenced by the inclusion or exclusion of CDx testing. There were no patterns or criticisms identified on the role of CDx testing and the time between regulatory approval and date of publication.

4 Discussion

As precision medicine evolves in oncology, CDx tests are increasingly being adopted to guide treatment decisions. They are used to identify subgroups of patients most likely to benefit from targeted therapy, potentially increasing success rates and limiting resource expenditure for patients that would respond favorably to the treatment. However, this can come with an added upfront cost for testing the patient population for the genetic mutation(s), which may be an important aspect to be considered in cost-effectiveness models that aim to assess the value of targeted therapies. This review evaluated assessment reports from several HTABs and one research organization to understand how CDx testing was incorporated in cost-effectiveness models of targeted therapies in oncology, and whether this ultimately impacted the decision to recommend the therapy.

Similar studies have examined the economic evidence from the literature or have inspected the HTAs from a single country or region [23–26]. Our study reviews HTA reports produced by HTABs or organizations involved in the assessments of novel therapies and goes beyond a regional interpretation to qualitatively compare assessments across 12 HTA-focused healthcare systems. We reviewed publicly available assessment reports of 15 medicines in 27 indications from 12 different HTABs and one research organization. Except for NICE TAs, most of the reviewed assessments from other bodies failed to present sufficiently detailed reports on how CDx testing was incorporated into the economic models for targeted therapies. Our review showed that if patients from both arms in the model required mutation testing for treatment or if patients were already identified through biomarker testing in a previous line of treatment, then the cost of CDx testing was systematically excluded from cost-effectiveness models. This is considered methodologically accepted, as including the same cost in the intervention and comparator arms would not contribute to differences in costs between treatment arms, and would ultimately have no impact on the incremental cost-effectiveness ratios. On the other hand, the inclusion of CDx testing occurred whenever mutation testing was required solely for patients receiving the novel treatment. In this case, the cost of the test and the mutation prevalence were the main drivers of CDx costs per patient. Meanwhile, limited information was reported regarding CDx diagnostic accuracy and other characteristics' contribution to the CDx testing costs calculation.

Based on the identified assessments, it was recognized that neither the decision to recommend a treatment nor the time from regulatory approval to decision date were impacted by specific CDx characteristics in cost-effectiveness models of targeted therapies. Contrary to our findings, reports of Australian submissions have suggested that cancer medicines with a CDx take longer to receive a recommendation from the HTAB [27, 28]. However, this may be largely impacted by the by the required procedures in this healthcare system to evaluate the drug and the CDx test separately, as opposed to the inclusion or exclusion of the CDx testing characteristics in the cost-effectiveness model of the drug. Having a wide range of alternative CDx tests used in routine clinical practice may be yet another source of delay for the recommendation of the therapy when these alternatives need to be considered in the HTA process [4]. Similarly, the decision to recommend the therapy was the result of the clinical and economic characteristics of the therapy, or the impact of the comparative evidence submitted, and had no direct relation to the CDx considerations. In particular, we did not identify any HTAB recommendation to be conditional on the use of a CDx product, possibly explained by the marketing authorization for the targeted therapy, which could already be restricted to patients exhibiting the mutation. Recommendations were therefore conditional on the identification of an eligible patient population, and aligned with the regulatory indication, rather than the use of a specific CDx test.

In the same way, whether the biomarker status had been predetermined in the modelled population, or whether the modelled comparator also required prior testing, determined the incorporation of the CDx in the model. To date, specific CDx costs or characteristics did not have a direct impact on the final decisions, however, it remains unclear how the extended reliance on CDx testing and increased costs of identifying eligible patients will be assessed by HTABs. Given only 15 appraisals had incorporated CDx costs in this time period, sub-group analysis to explore the influence of higher cost/patient versus lower cost/patient appraisals could not be explored at this stage. As more appraisals become available, future analyses should explore whether CDx factors do start to influence HTA decision outcomes.

The assessments identified in this review covered a wide range of oncology indications. Importantly, because CDx testing is not specific to a particular indication but rather used across a wide range of indications, it represents an important aspect of novel therapies in oncology. However, in undertaking this study, and consistent with previous findings [23, 29, 30], we observed considerable variability in the amount of information reported on CDx testing for the targeted therapies in oncology, posing a significant limitation to our study. A recent systematic literature review of 22 economic evaluations of CDx for targeted therapies also found that there is no consistent approach in modeling CDx characteristics, specifically in terms of transparency and the level of detail regarding the calculation of costs for the CDx [23]. Other reviews of HTA reports identified an increased number of submissions for drugs associated with a CDx over the past years, with limited transparency with respect to the CDx components and payers taking varying approaches to assess CDx [24–26]. Another limitation to this study is that our findings are based merely on publicly available reports; therefore, our conclusions regarding assessment bodies with limited published information might have been biased in an unquantifiable way. CDx testing plays an important role for patient access to the treatment, and any HTA deliberations on CDx testing requirements, separate from the cost-effectiveness model, remain outside the scope of our research. Lastly, the impact of including CDx testing cost assessments was based on a relatively low range of testing costs. Assessment bodies' recommendations might be affected in the future in instances of higher testing costs, and/or lower mutation prevalence.

Given the current limitation with publicly available information, and the ongoing shift towards precision medicine in oncology, understanding of CDx and its' impact on health economic models is becoming more relevant over time. Therefore, transparency and clear guidance from the agencies responsible for assessing economic models of new treatments are needed [10, 29, 31]. Further research, including a future update of this review, is also warranted. Such an update would include an evaluation of adherence to recommendations from existing literature, such as greater transparency, better communication, and the set-up of clear national guidance by the agencies [10]. Consequently, these reviews would expand our understanding of potential links between the role of CDx in appraised assessments and funding decisions by HTABs.

5 Conclusions

CDx testing was included in cost-effectiveness models whenever mutation testing was required solely for patients receiving the targeted treatment and when testing was not performed in a previous line of treatment. CDx testing costs per patient represented necessary costs to find one patient eligible for treatment and, therefore, were driven by both testing costs and mutation prevalence. The cross-comparison of assessments showed that CDx testing was handled differently regarding the inclusion of costs and the reporting transparency across included HTABs. Based on the identified assessments to date, the time from regulatory approval to the recommendation was not impacted by the inclusion of CDx testing in assessed models. Nevertheless, it is still unclear if the expanded reliance on CDx testing will impact the future assessments and recommendations of targeted therapies. Clear guidance from the agencies responsible for assessing economic models of new treatments is needed as the volume of medicines accompanied by a CDx is rapidly increasing. As a concequence, manufacturers are expected to critically consider and justify the inclusion or exclusion of CDx cost in submitted economic models. A future update of this review is warranted to track trends in CDx testing in oncology appraisals over time.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s41669-022-00350-6.

Declarations

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Author contributions KP, MD, and MH participated in the study's design; HEA and MGM performed all the research activities and data synthesis for the study; MGM developed the first draft of the manuscript; MGM and HEA worked on the revisions for the manuscript; and all authors participated in the review and approval of the final manuscript.

Conflict of interest KP, MD, MH, and RR are employees of Janssen. MGM, HEA, and PW are employees of Ingress-Health (a Cytel company) and provide consultancy services to pharmaceutical companies.

Availability of data and material (data transparency) Not applicable.

Code availability (software application or custom code) Not applicable.

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

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