



Health-Economic Analyses of Diagnostics: Guidance on Design and Reporting

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Abstract

Cost-effectiveness analyses (CEAs) can be used to assess the value of diagnostics in clinical practice. Due to the introduction of the European in vitro diagnostic and medical devices regulations, more clinical data on new diagnostics may become available, which may improve the interest and feasibility of performing CEAs. We present eight recommendations on the reporting and design of CEAs of diagnostics. The symptoms patients experience, the clinical setting, locations of test sampling and analysis, and diagnostic algorithms should be clearly reported. The used time horizon should reflect the time horizon used to model the treatment after the diagnostic pathway. Quality-adjusted life-years (QALYs) or disability-adjusted life-years (DALYs) should be used as the clinical outcomes but may be combined with other relevant outcomes, such as real options value. If the number of tests using the same equipment can vary, the economy of scale should be considered. An understandable graphical representation of the various diagnostic algorithms should be provided to understand the results, such as an efficiency frontier. Finally, the budget impact and affordability should be considered. These recommendations can be used in addition to other, more general, recommendations, such as the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) or the reference case for economic evaluation by the international decision support initiative.

1 Introduction

Over the past decades, policy makers in the healthcare sector have tried to control the rising costs of pharmaceuticals in different ways [1, 2]. As one approach, value-based pricing of new drugs aims to maximise the health-related and economic outcomes given a prespecified willingness to pay; in

many countries, this has become a widespread method to assess the pricing and reimbursement of new pharmaceuticals entering the market [3, 4]. In recent years, attention has also expanded towards companion diagnostics for innovative treatments: highly specialised diagnostic tests paired to a specific drug in the context of what is labelled personalised medicine [5, 6]. Personalised medicine entails that drugs are targeted more to specific patient subgroups, with the aim of reducing the uncertainty of whether the drug will be effective before administration and correspondingly improve cost effectiveness of the drug considered.

Diagnostic tests are used more widely in modern medicine than just as companion diagnostics, and often in less well-defined populations. Examples include C-reactive protein (CRP) tests to check whether a patient with a cough has a viral or bacterial infection, an international normalised ratio (INR) test to diagnose bleeding disorders, or an HbA1c test for diabetes. Many national pharmacoeconomic guidelines nowadays also consider the assessment of non-pharmaceuticals, such as diagnostics, although, in practice, these analyses are not as common [7]. There is limited evidence on the pricing and

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Key Points for Decision Makers

To assess the value of diagnostic interventions, cost-effectiveness analyses can be used; however, we previously identified some gaps in the design and reporting of these studies.

Compared with pharmaceutical interventions, assessing the cost effectiveness of diagnostic strategies can be more challenging, as various diseases or treatment options may be important to consider.

We provide eight recommendations related to the design and reporting of health-economic analyses of diagnostics, which can be used in addition to more general guidelines.

reimbursement policies of diagnostics [8, 9]. A recent report on pricing and reimbursement policies in various European countries concluded that health technology assessment is rarely used for diagnostics [8]. We believe the role of the cost effectiveness of diagnostic methods will increase in the coming years, but, with that, certain challenges will arise.

Compared with pharmaceuticals, for which the market entry regulations are well established for various jurisdictions [2], the evidence for diagnostics, and medical devices in general, is very limited [8]. In 2017, the new European Union (EU) regulation on in vitro diagnostic (IVD) medical devices was approved, which will come into full effect starting in 2022 [10]. An estimated 85% of IVDs will be under the oversight of a notified body, compared with 20% previously [11]. IVD companies will need to collect more data on the technical and clinical performance of new devices before market entry, and also increase postmarket surveillance [11]. Consistent and high-quality data will provide healthcare professionals and policy makers with more tools to assess the safety and effectiveness of new IVDs in clinical practice. We expect this will also lead to an increase in cost-effectiveness analyses (CEA) of these devices. Diagnostics are not limited to IVDs; software or devices used for the diagnosis of a disease fall under the EU regulation on medical devices (MDR) [12] and similar regulations related to oversight apply [11]. An example of this would be a smartphone application (app) used by clinicians to determine the most likely disease and optimal treatment, based on a patient's symptoms.

2 Aim and Approach

We recently systematically reviewed many CEAs of diagnostic strategies of infectious disease, focusing on the modeling techniques used [13, 14]. In the process, we identified several gaps in the reporting of diagnostic interventions, but also common structural problems related to the design of health-economic models. These gaps included incomplete descriptions of the assessed diagnostic and setting, short time horizons, and limited use of generalisable outcomes. Additionally, we consider our experience in consulting on the health-economic aspects of clinical trials of diagnostics. Our aim was to provide specific recommendations to aid in the design and reporting of CEAs of diagnostics.

Excellent recommendations are already available to aid in the design and reporting of economic evaluations. The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement is a collection of 24 recommendations aiding in the reporting of the methods and results of economic analyses for interventions in healthcare [15]. CHEERS is not tailored to any specific intervention and can be used for preventive measures, diagnostics and treatment [15]. The International Decision Support Initiative's reference case for economic evaluation provides 11 principles to guide the conduct and reporting of economic evaluations to improve their methodological quality and transferability [16]. The methodological specifications relate to the health outcomes used, and the estimation of costs and transparency, among others. However, due to their broad scope, these recommendations do not provide specific guidance for diagnostic strategies. We link this diagnostic-specific guidance to the related items of the more general CHEERS statement and the reference case [15, 16], to enable other researchers to use this guidance in addition to the already available recommendations.

3 Definition of Diagnostics

While many different tests are performed in the healthcare sector, not all of them can be considered diagnostic tests. We consider three types of strategies, depending on the aim of the test [17]:

- *Screening*: Finding diseases in a defined population, in people without, or unaware of, symptoms [18].
- *Diagnosing*: Identifying the most likely cause of, and, optionally, optimal treatment for, a previously undetected disease in a clinically suspect patient who is seeking care [13, 19]. A diagnostic specifically aimed at determining the optimal treatment option for a patient with a previ-

ously diagnosed disease is considered a companion diagnostic [5].

- *Monitoring*: Periodic or continuous tests to observe a biological condition or function, including the effectiveness of treatment [20].

Although similar or identical tests may be used for each of the strategies, the decision problem related to the various strategies is quite different, hence each strategy presents unique challenges when designing a CEA. In this paper, we specifically focus on diagnostic strategies.

4 Recommendations

An overview of our recommendations is displayed in Table 1, including related CHEERS recommendations [15] and specifications from the reference case for economic evaluations [16]. The recommendations are explained in more detail below.

4.1 Target Population

A common way to specify a certain population in the medical field is to identify patients having a specific disease, for example heart failure patients or patients with neuroendocrine tumours. Especially in clinical trials, these specifications are often extended to patient characteristics such as age and comorbidities or with ranges of disease-specific biomarkers. When diagnosing a patient, a specific disease is often not yet known, but the symptoms are. These specific symptoms will influence the clinician's decision to request additional diagnostic tests or use point-of-care (POC) diagnostics. Other determinants a clinician may use in deciding to use certain diagnostics include age, comorbidities and, if available, vaccination status.

Therefore, when specifying the target population of a diagnostic intervention, it is highly important to specify the symptoms patients have and other relevant determinants that may influence the clinician's decision to continue diagnosing a patient. Additionally, it should be clear whether the patient population is screened, diagnosed, or monitored. However, this may be more difficult in the case of genomic tests, with potential spillover effects to relatives, where the population of interest is broader than just the patient tested [21]; the diagnosis of one patient may lead to the screening of family members or may inform reproductive planning.

4.2 Setting and Location

Linked to the target population are the setting and location. Populations presenting in primary care are different from patients who are referred to hospital care, who are different

from patients admitted to the intensive care unit. In a health-care system where the general practitioner (GP) has a gate-keeping role, a decision, based on clinical experience, to refer a patient to a hospital without performing any tests should already be regarded as a diagnostic intervention. The probability of having a disease will be higher in the hospital setting, considering the GP does not refer everyone and does not refer at random. Not all health systems rely on the gate-keeping role of the GP [22], and factors for patients seeking care differ culturally [23]. These factors will have an influence on the prevalence and severity of diseases at different settings within the healthcare sector. Hence, this context is important to include when describing the setting in which diagnostic tests are performed.

Another consideration linked to the setting is the location where the test sample will be collected and where it will be analysed, and how this affects the overall costs. Historically, samples were analysed in the laboratory, but, increasingly, testing will be performed at the POC [24]. Clearly specifying the location of sample collection and analysis is important, especially when a CEA compares different tests at different locations. This may be especially relevant for low- and middle-income countries (LMICs), where logistics can be more challenging. Although POC tests may be relatively expensive compared with tests analysed in large-scale laboratories [24], having a test result available during a consult can more directly influence a clinician's decision on prescribing treatment and enables the clinician to use the information when communicating with the patient [25].

4.3 Comparators

The strategies being compared in the CEA should be clearly described [15]. While it may be convenient to think about comparing different individual tests in the context of CEAs of diagnostics, it may be more fitting to compare different diagnostic algorithms. A diagnostic cannot be regarded in isolation. If we consider a single diagnostic test, the diagnostic algorithm already contains three steps. First the clinician decides to perform the test, which is influenced by guidelines and the clinician's experience; then there is the diagnostic itself, which may present a binary result, i.e., positive or negative, but also a quantitative result, an image or a recommendation; the final step is the interpretation of this result by the clinician and/or the patient, which may result in a decision to make lifestyle changes, to start treatment or continue with other diagnostics. Different diagnostics can be added, either simultaneously or sequentially, based on the results of prior tests. There may also be differences in the implementation of the algorithm in clinical practice, e.g., the implementation in clinical decision support software. Eventually, a diagnostic algorithm should lead to determining the most likely cause of a patient's symptoms and aid

Table 1 Recommendations for CEAs of diagnostics, including direct quotations of relevant CHEERS recommendations [15] and reference-case specifications [16]

| Topic | Cheers recommendation [15] | Reference-case specification [16] | Diagnostic-specific recommendation | Relates to |
|--------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|
| Target population | Describe the characteristics of the base-case population and subgroups analysed, including why they were chosen | The decision problem must be fully and accurately described | Specify the target population of the test, including the symptoms patients experience and other relevant determinants that may influence the clinician when diagnosing patients. Clearly state whether the aim of the intervention is to screen, diagnose or monitor patients | Reporting |
| Setting and location | State relevant aspects of the system(s) in which the decision(s) need(s) to be made | The decision problem must be fully and accurately described | Specify the clinical setting in which the clinician operates, and where the diagnostic test is performed. Factors impacting the decision for patients to seek care and factors influencing the disease prevalence are important aspects that may influence the cost effectiveness of a diagnostic. The location where the diagnostic is performed may impact the costs and time to obtain a test result and subsequently its value within the diagnostic pathway | Reporting |
| Comparators | Describe the interventions or strategies being compared and state why they were chosen | Current practice in the context of the decision problem to serve as a comparator in the analysis Best supportive, non-interventional care in the context of the decision problem should be explored as a comparator as additional analysis | Specify the diagnostic algorithm, including clinicians' decision processes (decision to perform the test), the diagnostic tests (including brand, type and frequency), and the relevant treatment options (the outcome of the diagnostic algorithm) | Reporting |
| Time horizon | State the time horizon(s) over which costs and consequences are being evaluated and say why they are appropriate | Lifetime time horizon should be used in the first instance A shorter time horizon may be used when it is shown that all relevant costs and effects are captured | The assessed time horizon should be similar to the time horizon over which costs and consequences of treatment following the diagnostic process are typically evaluated | Design |
| Choice of health outcomes | Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed | Methodological choices include either DALYs averted or QALYs gained | Include either QALYs or DALYs when assessing the cost effectiveness of diagnostics. However, depending on the diagnostic technique and disease, other outcomes may be relevant to assess the value of the assessed diagnostic algorithm (e.g., adherence-improving factors, insurance value or real options value) | Design |
| Estimating resources and costs | Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs ^a | Estimates should reflect the resource use and unit costs/prices that may be expected if the intervention is rolled out to the population defined in the decision problem Analysis should include estimation of changes in cost estimates due to economies (or diseconomies) of scale | Consider the economy (or diseconomy) of scale related to collecting, transporting and performing more (or fewer) tests on the same equipment, as opposed to a fixed price per test. | Design |

Table 1 (continued)

| Topic | Cheers recommendation [15] | Reference-case specification [16] | Diagnostic-specific recommendation | Relates to |
|---------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|
| Incremental costs and outcomes | For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios | No specification | Use an efficiency frontier to visualise the incremental costs and outcomes of the different strategies, if several diagnostic algorithms are assessed simultaneously | Reporting |
| Affordability and reimbursement | No recommendation | Costs of all resource implications relevant to the decision problem, including donated inputs and out-of-pocket inputs from individuals Budget impact analysis should estimate the implications of implementing the intervention on various budgets Equity implications should be considered at all stages of the evaluation, including design, analysis, and reporting | Define the perspective of the economic evaluation and identify which payers are included in the budget impact analysis. Calculate the budget impact of implementing the assessed diagnostic algorithm within the overall clinical care pathway and consider setting-specific reimbursement regulations | Design |

CEAs cost-effectiveness analyses, CHEERS Consolidated Health Economic Evaluation Reporting Standards, DALYs disability-adjusted life-years, QALYs quality-adjusted life-years

^aFor model-based economic evaluations, Huseareu et al. [15] also provide a separate recommendation for single study-based economic evaluations

in identifying the most suitable treatment. These types of algorithms are already very common in economic analyses, where they translate into decision-tree models [13, 14, 26]. For diagnostic algorithms that include many different outcomes, i.e., a decision tree branching out to hundreds of outcomes, simplifications may be warranted or more flexible modelling approaches can be considered [27].

We highly recommend specifying these algorithms very clearly in any economic analysis of a diagnostic strategy. Even when comparing a switch from one diagnostic test to another, the algorithm in which the test operates may have a major impact. The decisions made and information gathered before performing the test influences the prior probabilities of obtaining a positive or negative test result. For diagnostic algorithms that are more expensive than the comparator, the eventual cost effectiveness is determined by to what extent the information gathered can improve patient outcomes, i.e., whether the information leads to more tailored treatment.

4.4 Time Horizon

Many economic evaluations of diagnostics primarily use the algorithm or decision tree to model the health-economic outcomes, as specified above. However, this may lead to challenges in assessing the long-term clinical outcomes for patients as these cannot be modelled explicitly. Generally, a lifetime horizon should be used [16], however there could be reasons to have a shorter time horizon but they should cover all relevant costs and outcomes. Economic analyses only assessing a time horizon as long as the diagnostic process, as seen rather frequently in literature [13], will in most cases not cover all relevant costs and outcomes. The time horizon should be similar to the time horizon over which costs and consequences of treatment following the diagnostic process are typically evaluated.

An additional factor to consider for economic evaluations of diagnostics, is the time to correct diagnosis. A faster diagnostic algorithm may result in time reductions for patients, clinicians or laboratory technicians, leading to a more efficient decision-making process [25]. In case of infectious disease, faster diagnosis may reduce the transmission of a disease, a factor generally considered to be an important aspect of value in health care (fear and risk of contagion) [28].

Combining very short-term (time to correct diagnosis) and long-term modelling (a lifetime time horizon) may lead to rather complex models for economic assessments of diagnostics, such as a combination of a discrete-event simulation and a transmission model to model tuberculosis diagnostics in Tanzania [29]. Depending not only on clinical perspectives but also on data availability, it may be feasible to focus on only short- or long-term modelling. This decision process should be reported in a transparent manner.

4.5 Choice of Health Outcomes

Quality-adjusted life-years (QALYs) or disability-adjusted life-years (DALYs) are generally the preferred outcomes for economic analyses [16]. Possibly due to the relatively many studies in the field of diagnostics with a short time horizon, authors commonly focus on rather short-term outcomes other than QALYs and DALYs [13, 30, 31]. Examples are outcomes based on the technical performance of the test (e.g. proportion of correct diagnoses) or the treatment decision (e.g. antibiotics prescribed) [13]. As stated in the introduction, IVD companies will be required to gather more information on the clinically relevant outcomes of novel diagnostics [10], which presents an opportunity to also include utility-based outcomes. This is not to say that other outcome measures are not relevant—we believe they are.

Other elements of value of particular interest to diagnostics are reduction of uncertainty due to a new diagnostic, adherence-improving factors, fear of contagion (already described above), insurance value and real options value [28]. The reduction of uncertainty is relevant for both payers as it reduces the uncertainty of the effectiveness of reimbursed care, and for patients and providers, as it may lead to more informed treatment decisions. This may also lead to increased adherence to treatment. There are several elements of value for diagnostics that may benefit the individual patient and have broader societal advantages. The fear of contagion has already been described above, but closely related to this is the insurance value, which may relate to the risk of an individual becoming sick [28]. For hereditary diseases, the results of diagnosing one patient may affect family members [21], and, for infectious diseases, the data gathered by diagnosing one group of patients may inform empiric treatment for another group of patients [32]. Finally, real options value is relevant for infectious disease where resistance may occur. Prescribing treatment provides a risk that the treatment will be less effective in the future; simultaneously, it is uncertain that novel treatment options will be developed in the future. A diagnostic, which increases the adequacy of prescriptions, can decrease the probability of untreatable, resistant infections in the future [33]. Discussions on how to include these other, still novel, elements of value are ongoing and will depend on factors such as the disease area covered and the health system assessed [21, 28]. Continuing this discussion with all stakeholders, including policy makers, clinicians and patients, is important, as well as experimentation with novel methods in the field of CEAs. For some diseases with limited data on the effectiveness of treatment, such as genomic tests used for rare genetic disorders, it may be challenging to perform a CEA [21]. In these cases, multicriteria decision analysis may be a feasible alternative [34].

4.6 Estimating Resources and Costs

For CEAs in general, the included costs depend on the perspective used and the decision problem analysed. Depending on the perspective used, diagnostic and subsequent treatment costs may be included differently or even not be considered at all. For diagnostics, the costs are of particular interest as there may be more flexibility compared with most drugs. The whole chain from collecting the patient sample to the reporting of the result will impact the eventual cost of the diagnostic. While large volumes of tests performed in laboratories will be relatively inexpensive, a POC test performed by the GP may yield more diagnostic value, i.e., the test can immediately influence the clinical decision. The following costs will be relevant for a CEA assessing a novel diagnostic:

- diagnostic sample collection costs (including personnel, reagent and material costs);
- transport costs (if the test is not performed at the POC);
- costs of performing the test (including personnel, reagent, materials and depreciation costs);
- costs associated with reporting the test result to the clinician and/or the patient, and, if applicable, changing the clinical decision.

How precise test-related costs should be estimated depends on the perspective and decision problem—micro-costing will not always be useful or feasible [26]. However, using a fixed price per diagnostic test may underestimate the scale benefits associated with performing more tests using the same equipment [35]. Sensitivity analyses to assess the impact of various assumptions to the economies (and diseconomies) of scale related to performing more (or fewer) tests should be considered and should be consistent with the evaluated setting and populations, including any health system factors that may limit scale-up. For tests that can be used to diagnose various diseases (i.e., are part of several diagnostic algorithms, with patients experiencing different symptoms), these scale advantages should also be considered.

4.7 Incremental Costs and Outcomes

It is common to compare various diagnostic algorithms simultaneously within a CEA [13], as explained above. The different algorithms may not only contain different diagnostic techniques but may also be performed in different sequences or at different locations (e.g., at the POC or in a laboratory). Clearly presenting the differences in incremental costs and outcomes is important. A common graphical method to present the incremental costs and outcomes of various algorithms is an efficiency or cost-effectiveness frontier [29, 36, 37]. This may be more easily interpretable than only providing a table of the results. An added benefit is that

the efficiency frontier can be used to draw conclusions about the cost effectiveness in the absence of a willingness-to-pay threshold, as described elsewhere [38].

4.8 Affordability and Reimbursement

Factors outside of the direct scope of a CEA, but very relevant for its context, are the affordability and reimbursement of diagnostic interventions. The budget impact was seldom included in CEAs of diagnostics [13]; however, we believe this may provide important information regarding the affordability [39]. Especially if the current standard-of-care is based on clinical expertise, a new diagnostic test may greatly increase the total costs and may have a major budget impact. This is particularly relevant for LMICs, where resource constraints are more prevalent than in high-income countries. An additional constraint in LMICs may be the availability of skilled personnel to perform and operate new diagnostic tests [16].

In general, the perspective of the budget impact analysis is important, and also in relation to reimbursement of the various diagnostics considered and the payers involved: can healthcare providers claim the diagnostic costs, should they pay for it themselves, or should a patient pay a fee? Additionally, it is relevant whether the diagnostic test is funded out of the same budget as subsequent treatment. This does not directly influence the cost effectiveness, but it will probably affect the implementation and uptake of a novel diagnostic test, e.g., a very cost-effective test for which the patient has to pay may have a lower uptake than a test that is provided free of charge (i.e., paid for by the health system). These factors can be explored in the discussion of an economic analysis of a novel diagnostic.

5 Summary and Conclusions

In this paper, we formulated eight recommendations for CEAs of diagnostics. The symptoms patients experience, the clinical setting, locations of test sampling and analysis, and diagnostic algorithms should be clearly reported. The used time horizon should reflect the time horizon used to model the treatment after the diagnostic pathway. QALYs or DALYs should be used as the clinical outcomes but may be combined with other relevant outcomes, such as real options value. If the number of tests using the same equipment can vary, the economy of scale should be considered. An understandable graphical representation of the various diagnostic algorithms should be provided to understand the results, such as an efficiency frontier. Finally, the budget impact and affordability should be considered.

These are not meant to supplant the CHEERS recommendations or reference case for economic evaluations but

may provide useful additions when designing and reporting CEAs of diagnostics. Although we based the recommendations in this paper on extensive reviews of the literature [13, 14] and the views of the authors, they were not developed or validated through a formal process, such as a Delphi process. Although we expect the issues raised in the paper to be generalisable to diagnostics or all disease areas, some issues relevant for specific disease areas may not have been included. However, this research could be used as a starting point for a follow-up project to further develop diagnostic-specific guidelines or a reference case for diagnostic CEAs.

Compared with pharmaceutical interventions, assessing the cost effectiveness of diagnostic strategies can be more challenging as various diseases or treatment options may be important to consider. At the same time, the EU IVDR and MDR [10, 12] may drive manufacturers to collect more clinical evidence, which aids in the assessment of the value of diagnostics, providing opportunities for investments in better diagnosis and improved clinical care. The recommendations provided in this paper can be used to improve the design and reporting CEAs in the field of diagnostics, resulting in well-informed reimbursement decisions by policy makers.

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Author Contributions All authors contributed to the study conception and design. The first draft of the manuscript was written by SvdP and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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