Journal of Clinical Epidemiology 109 (2019) 1−11

Journal of Clinical Epidemiology

ORIGINAL ARTICLE

Model-based economic evaluations of diagnostic point of care tests were rarely fit for purpose

Katie Breheny[a,1], Andrew J. Sutton[a,2], Jonathan J. Deeks[b,c,*]

[a]Health Economics Unit, Institute of Applied Health Research, University of Birmingham, Birmingham B15 2TT, UK
[b]Test Evaluation Research Group, Institute of Applied Health Research, University of Birmingham, Birmingham, B15 2TT, UK
[c]NIHR Birmingham Biomedical Research Centre, University of Birmingham and University Hospitals Birmingham NHS Foundation Trust, UK

Accepted 5 November 2018; Published online 10 November 2018

Abstract

Objectives: Linked evidence models are recommended to predict health benefits and cost-effectiveness of diagnostic tests. We considered how published models accounted for changes in patient pathways that occur with point of care tests (POCTs) and their impact on patient health and costs.

Study Design and Setting: Model-based evaluations of diagnostic POCTs published from 2004 to 2017 were identified from searching six databases. For each model, we assessed the outcomes considered, and whether reduced time to diagnosis and increased access to testing affected patient health and costs.

Results: Seventy-four model-based evaluations were included: 95% incorporated evidence on test accuracy, but 34% only assessed intermediate outcomes such as rates of correct diagnosis. Of 54 models where POCTs reduced testing time, 39% addressed the economic and 37% addressed the health benefits of faster diagnosis. No model considered differences in access to tests.

Conclusion: Many models fail to capture the effects of POCTs in increasing access, advancing speed of diagnosis and treatment, and reducing anxiety and the associated costs. Many only consider the impact of testing from changes in accuracy. Ensuring models incorporate changes in patient pathways from faster and more accessible testing will lead to economic evaluations that better reflect the impact of POCTs.

Keywords: Diagnostic test; Point of care test; Decision model; Clinical pathway; Health economic model; Near patient test

1. Introduction

The decision to use a diagnostic test ideally should be based on evidence that it leads to better patient outcomes [1], and that improvements from testing are worth any additional costs involved. However, there are many logistical obstacles in directly evaluating the impact of tests on patient outcomes and their associated cost-effectiveness. There is a dearth of trials that randomly allocate participants between alternative testing strategies, evaluate resource use arising from testing and subsequent interventions, and compare final outcomes at the end of the health care episode [2]. Where they do exist, they are often underpowered to detect differences in outcomes, potentially biased, and there are challenges in using their results to inform practice because of lack of standardization and detail about the test-treatment strategies used [3,4].

Decision models provide an alternative approach to evaluate the likely effectiveness and cost-effectiveness of diagnostic tests. So-called linked evidence models combine evidence on the performance of each test with evidence of the effectiveness of interventions to predict outcomes for each test-treatment strategy. They can be used where there is no suitable evidence provided by randomized controlled trials and are recommended and routinely used by technology assessment organizations included the National Institute for Health and Care Excellence (NICE) in the UK [5] and the Agency for Healthcare Research and Quality (AHRQ) in the United States [6]. In their simplest

Conflict of interest statement: The authors have no conflicts of interest to declare.

[1] Current address: Research Associate, Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, BS8 1QU, UK, 0117 428 3144. katie.breheny@bristol.ac.uk.

[2] Current address: Institute of Health Economics, University of Alberta, #1200 10,405 Jasper Avenue, T5J 3N4 Edmonton, Alberta, Canada. asutton@ihe.ca

* Corresponding author. Tel.: +44-121-414-5328.
E-mail address: j.deeks@bham.ac.uk (J.J. Deeks).

https://doi.org/10.1016/j.jclinepi.2018.11.003
0895-4356/

What is new?

Key findings

- Point of care tests (POCTs) potentially benefit patients by speeding up decision-making, enabling patients to access appropriate treatment faster and reduce anxiety waiting for results.
- POCTs can also be undertaken in different settings allowing broader access to testing.
- Many published model-based economic models have not captured the relevant patient and economic benefits of POCTs, many focusing solely on the impact of differences in test accuracy.

What this adds to what was known?

- Conclusions from many models evaluating POCT may not be valid as they omit health and economic benefits associated with earlier testing or testing in different populations.

What is the implication and what should change now?

- We propose a checklist of considerations that should be made when developing models to evaluate the health economic impact of a POCT.
- Future studies that focus on the clinical and economic evaluation of POCTs should ensure that the specific characteristics of differences in timing and access to testing are incorporated in the analysis.

form, models are constructed by estimating the proportions of true positives, true negatives, false positives, and false negatives for each test strategy and assigning likely resource use and outcomes according to the disease state, and whether individuals receive appropriate effective treatment (dependent on whether the diagnosis is correct). A simplifying assumption is often made that the management of each patient is determined entirely by the test result obtained and both clinicians and patients follow through with the recommended treatment. Outcomes such as quality-adjusted life years (QALYs) are used to capture health benefits, as these allow comparisons of cost-effectiveness to be made for interventions across different settings [7]. They also incorporate the unintended harm [8] and adverse events from unnecessary treatments following a false positive result, or the impact of continuing to suffer from a disease following a false negative test result [9].

In recent years there has been substantial investment in the development and provision of point of care tests ([POCTs], also known as rapid tests or near patient tests) that can be conducted in close proximity (both in time and in setting) to a patient [10]. Examples include nucleic acid amplification tests to diagnose tuberculosis [11] and immunochromatographic tests for the diagnosis of influenza [12].

POCTs have the potential to revolutionize care pathways as they produce results more quickly than their laboratory counterparts, often allowing patient management to be determined in the same consultation when the test is deployed. This may shorten health care episodes through removing the time spent waiting for a diagnosis before any intervention can commence and has associated economic benefits in terms of a reduction in length of hospital stay, repeat hospital admissions and clinic visits, and reductions in the use of interventions for symptom control while test results are awaited [13,14]. Faster testing could also reduce the costs incurred by patients and carers that fall outside of the health care system [15] (societal costs), including productivity losses and transport costs. In some conditions, patient outcomes may also be improved by earlier testing, both by avoiding deterioration in health (and even death) while awaiting test results, or where earlier initiation of a treatment may enhance its effectiveness [10,13]. Patients may also experience a reduction in anxiety [16] caused by delays in waiting for test results and initiation of treatment. In the case of infectious diseases, faster testing may reduce disease transmission [17].

POCTs may also change the setting in which testing is undertaken as they are more portable than their laboratory equivalents, facilitating their deployment in community or primary health care settings rather than in secondary care. This may facilitate testing in settings where tests were not previously available. Thus, a further perceived benefit of the introduction of POCTs is to widen access with more individuals receiving testing, particularly in rural areas in low- and middle-income countries (LMICs).

The benefits of earlier diagnosis and wider access may mean introduction of a POCT may be cost-effective even if it is less accurate and more costly than current practice [18]. However, creating a decision model that fully captures the benefits of a faster and more accessible test requires incorporation of information about the likely difference in the timing of diagnosis on resource use, the effectiveness of earlier treatment on patient outcomes, and differences in the size and characteristics of the cohorts being tested.

In this review, we evaluated published model-based economic evaluations of POCTs to assess how evaluations have considered the impact of test timing and access to testing alongside differences in accuracy associated with the introduction of POCTs.

2. Methods

We identified recent model-based published economic evaluations of POCTs, assessed the structure of their models, the parameters that they include and their outcomes, to identify whether they have appropriately considered the impact and costs of using a POCT.

2.1. Search strategy

Published reports of model-based economic evaluations of point of care diagnostic tests were identified by searching electronic databases. Medline, Embase and PsycINFO, CINAHL, NHS Economic Evaluation Database (NHS EED), and Health Economic Evaluation Database (HEED) were searched in October 2017. Search strategies were developed based on validated algorithms for identifying health economic evaluations [19], and strings were used for the identification of POCTs in the published literature. Supplementary searches were conducted based on technical terms or proprietary names of tests found in the original searches and on the bibliographies of included studies. We restricted the search to English language articles published between 2004 and 2017 with the aim to understand methods currently used when conducting economic evaluations of POCT technologies. Search strategies are provided in the Appendix.

2.2. Inclusion criteria

Evaluations were included if they used a model-based approach, were reported in a published article, considered patients presenting with a specific complaint, signs, or symptoms, and where at least one strategy involved a POCT (defined as a test performed near the patient or treatment facility with a fast turnaround time and may lead to a change in patient management) [10]. We also included evaluations of accelerated laboratory tests that claimed similar changes to testing timeframes. The review was not restricted to any specific clinical specialities. We focused on diagnostic tests and thus excluded studies that considered monitoring and screening tests. We excluded models that focused entirely on estimating clinical impact and did not include any economic component.

2.3. Selection of articles

Titles and abstracts were screened for inclusion by one reviewer. Full-text copies were retrieved for articles meeting the inclusion criteria or those providing insufficient information in the abstract to determine their eligibility. A second reviewer independently assessed articles that still did not clearly satisfy the inclusion criteria. Excluded articles and reasons for their exclusion were documented.

2.4. Data extraction, analysis, and reporting

A data extraction form was developed and piloted on a selection of articles and modified accordingly. We extracted data to document the inclusion of test accuracy, impact of faster testing on patient outcomes, impact of faster testing on costs, the effectiveness measure, the perspective for the costs adopted, and difference in setting and participants included for each strategy. Data were extracted by one author and checked by a second. We report the proportions of economic evaluations that demonstrate each characteristic.

3. Results

Our search identified 10,302 unique articles, of which 343 were considered potentially eligible and reviewed in detail. In total, 74 model-based economic evaluations were identified as meeting our inclusion criteria (Fig. 1). Evaluations covered diverse clinical conditions and were undertaken in primary care, hospital care, and the community settings. There were multiple evaluations of tests for the diagnosis of tuberculosis, malaria, and influenza (Table 1).

Studies predominantly assessed the cost-effectiveness of implementing tests in Africa (31%), North America (24%), and Europe (22%). Twenty-four (32%) analyses were from the perspective of an LMIC country. Only one study evaluated a hypothetical test for tuberculosis [20]; all others evaluated commercially available tests.

3.1. Effectiveness outcomes

The majority of models used measures of patient health in the primary analysis (65%): 22 (30%) reported QALYs (1 LMIC country), 11 (15%) disability-adjusted life years

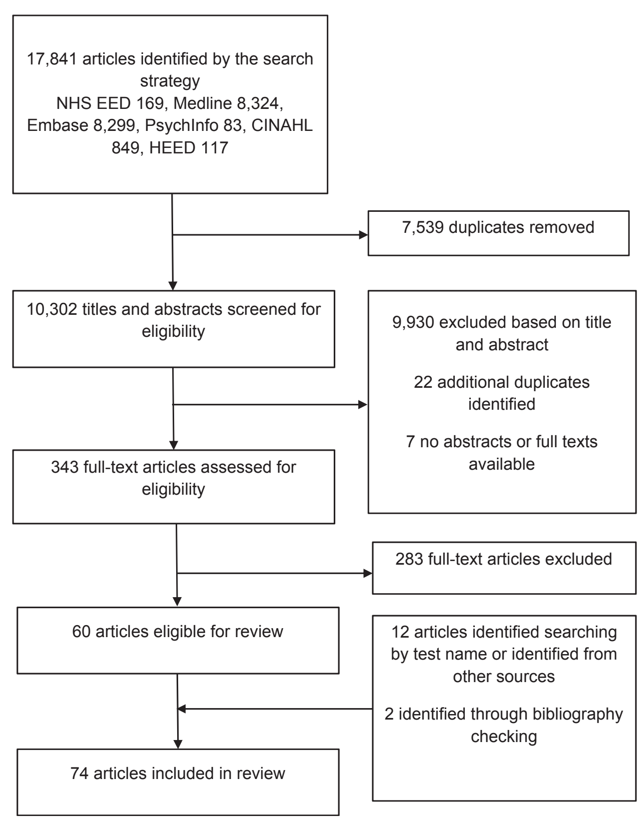

Fig. 1. Flow chart demonstrating selection of papers.

Table 1. Characteristics of model-based economic evaluations

	Total (N = 74)	LMIC	
		Yes (N = 24)	No (N = 50)
Indication	N (%)	N (%)	N (%)
Tuberculosis	24 (32)	10 (42)	14 (28)
Malaria	13 (18)	11 (46)	2 (4)
Influenza	11 (15)	0 (0)	11 (22)
Pharyngitis	4 (5)	0 (0)	4 (8)
Pulmonary embolism	3 (4)	0 (0)	3 (6)
Deep vein thrombosis	3 (4)	0 (0)	3 (6)
Dyspepsia	3 (4)	0 (0)	3 (6)
Sepsis	2 (3)	1 (4)	1 (2)
Acute coronary syndrome	2 (3)	1 (4)	1 (2)
Respiratory tract infection	1 (1)	0 (0)	1 (2)
Acute myocardial infarction	1 (1)	0 (0)	1 (2)
C-difficile	1 (1)	0 (0)	1 (2)
Chlamydia and gonorrhea	1 (1)	0 (0)	1 (2)
Conjunctivitis	1 (1)	0 (0)	1 (2)
Staphylococci infection	1 (1)	0 (0)	1 (2)
Staphylococcus aureus bacteremia	1 (1)	0 (0)	1 (2)
Visceral leishmaniasis	1 (1)	1 (0)	0 (0)
Meningococcal disease	1 (1)	0 (0)	1 (2)

(DALYs) (9 LMIC countries), and a further 9 (12%) used mortality measures (6 LMIC countries) (Table 2). Twenty-five analyses (34%) (8 LMIC countries) focused on intermediate outcomes related to test results, diagnoses, or treatment. Evaluations of tests for infectious diseases also considered markers of disease spread.

3.2. Cost perspective

The majority of the models that considered the impact of POCT on cost used a health care payer perspective (17/21) [21—38], and one model reported results using both a payer and societal perspective [39]. The remaining three models reported a societal perspective only [40—42].

3.3. Test accuracy and diagnostic errors

Seventy of the 74 (95%) models considered test accuracy and 51 studies considered how varying test accuracy in sensitivity analysis would impact on the conclusions drawn from the analyses. Incorrect and failed tests can have implications for patient health and costs and 57 models addressed these issues. Unnecessary harms, such as adverse events from inappropriate treatment were estimated in 17 studies [23,25,28,31,40,43—54], and the cost of treating a false positive or false negative patient in seven [33,42,55—59]. Three models adjusted for mortality rates [60—62] and five cost-utility analyses adjusted for utilities because of the untreated disease state [24,46,52,55,58]. The risk of transmission as a result of an incorrect diagnosis was incorporated in four infectious disease models [42,59,63,64], as was test failure [30,34,65,66]. The need for retesting after an incorrect result was considered in one study [67].

3.4. Effects of faster testing

The effects of timing of tests were judged of importance in 54 of the 74 models. The effects of diagnostic timing were not relevant in 20 studies (27%) [43,44,46—48, 52,54,64,68—79], where the POCT could not affect the

Table 2. Effectiveness outcomes in primary analysis of model-based economic evaluations

	Outcome used N = 74
Outcome	N (%)
QALYs/QALDs/DALYs/Quality-adjusted survival	35 (47)
Deaths averted/life years saved or lost/ death from target indication/cure without complications/symptom-free days or years	13 (18)
Infections prevented[a]	1 (1)
Correct diagnosis/correct treatment/ positive test/false positives/patients treated/work productivity gained[a]	25 (34)

Abbreviations: QALYs, quality-adjusted life years; QALDs, quality-adjusted life days; DALYs, disability-adjusted life years.

[a] Intermediate outcomes not demonstrating a direct health benefit.

speed of treatment compared to the alternative strategy, for example, when the only comparator was presumptive treatment or no test. These were predominantly economic evaluations of malaria or tuberculosis tests.

Only 29 studies [20,22−37,39−42,55,56,59,62,66, 80−82] incorporated the aspect of time to diagnosis in the model. Thus, some aspect of the benefits of quicker test results were incorporated in just over half (54%; 29/54) of the models where it was of relevance (see Web Table 4 in Appendix for description of how the 29 models incorporated time to diagnosis in terms of patient impact and/or costs).

Twenty models (37%) captured the impact of faster testing on patient outcomes: three by quicker resolution of disease (dyspepsia [40], pharyngitis [28,39]); four through reductions in disease progression or reduced mortality (chlamydia and gonorrhea progressing to pelvic inflammatory disease [35], mortality from sepsis [36], mortality from tuberculosis [24,37]); seven from increases in the numbers starting treatment through reductions in loss to follow-up (all tuberculosis [23,27,29,30,34,59,66]); three from reductions in harms through reduced use of presumptive treatment (chlamydia and gonorrhea [35], clostridium difficile infection [33], pharyngitis [25]), and one from reduced anxiety while waiting for results (chlamydia and gonorrhea [35]). Two reduced QALYs to reflect the disutility of time in intensive care [36,82].

Twenty-one models (39%) incorporated the impact of implementing a POCT on costs. Cost advantages for POCT arose from fewer visits to health care providers to receive results, less clinician time to conduct the test, and shorter length of stay because of faster decision-making and treatment initiation [22−26,28−36,39,41,42,80−82]. Reduced treatment or testing costs were observed as a result of avoiding presumptive treatment, additional tests, and the need to treat disease that had progressed [24−27,31, 33,35,37,40,41,82]. Three models incorporated the time taken for testing, but it was unclear from the model descriptions how this would impact on costs or patient outcomes [20,56,62].

Figure 2 summarizes how frequently the economic models considered faster testing in the analysis. ‘‘Included in model’’ refers to any economic or patient impact parameterized in the model. Patient impact includes more effective earlier treatment, earlier treatment initiation, and duration of illness reduced. Harms from unnecessary or inappropriate treatment are also incorporated, as are anxiety during the diagnostic delay and reduced disease progression. Impact on operational costs refers to costs incurred when delivering treatment or testing procedures, such as clinical consultations or residing in hospital.

3.5. *Costs of the test-treatment pathway*

Twenty-five studies included societal costs in the economic evaluation. In the case of influenza, antiviral treatment guided by rapid testing reduced symptom duration and productivity losses for patients or their carers were considered [43−46,48,64,70], while in one tuberculosis study income loss was reduced as a result of fewer days of hospitalization waiting for smear/culture results [42]. Other costs borne by patients and captured in the analyses included loss of income related to the duration of their clinic visit [40,83] and travel costs [42,50,69,83−85]. The costing of productivity loss could enhance the cost-effectiveness of the POCTs, although in 85% of studies this was omitted. The majority of models included the cost of one course of treatment, such as antimalarials or antibiotics.

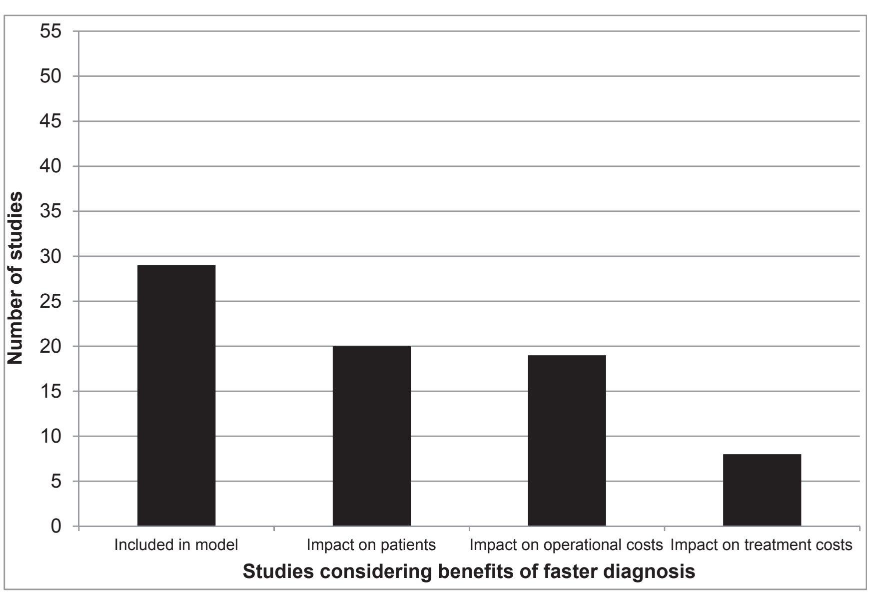

Fig. 2. Frequency of the consideration of the effects of faster testing in the 54 model-based economic evaluations where timing of tests differed between strategies compared (Included in model indicates that any difference in outcome or cost was considered).

Table 3. Impact of POCT on access to testing

	Total (*N* = 74)	LMIC	
		Yes (*N* = 24)	No (*N* = 50)
Change in location or population tested	***N* (%)**	***N* (%)**	***N* (%)**
Change in geographical location (eg, primary to secondary care)	8 (11)	3 (13)	5 (10)
Access to testing			
Yes (slower test and no test/presumptive treatment)	15 (20)	6 (25)	9 (18)
Yes (no test alternative)	9 (12)	5 (21)	4 (8)
Tested a different population	0 (0)	0	0 (0)

Costs of treating complications from unresolved illnesses or adverse events were frequently included. A minority (5%) did not include any costs beyond the testing procedure [65,86−88].

3.6. Access to testing

The introduction of a POCT changed the location of testing in eight models [26,28,41,51,69,80,84,85] (Table 3). This was predominantly a move from secondary to primary care settings, with one model examined the provision of testing in a pharmacy setting [28].

Twenty-four analyses included a comparator arm of either presumptive treatment or no test. Of these, nine [44,47,48,50,73,75,76,78,79] did not include any slower testing method and therefore modeled a situation where testing was previously unavailable. In total, 11 (45.8%) economic evaluations conducted from the perspective of LMICs analyzed the impact of introducing a test where current practice could result in a patient receiving no diagnostic test [47,49−51,68,76,78,79,83,84,89].

All models assumed that the same patient group would follow through each of the strategies considered; there was no allowance made in the POCT arms for inclusion of additional patients who access standard laboratory testing.

4. Discussion

Introduction of a POCT into a diagnostic pathway can substantially change diagnostic and treatment pathways, altering who is tested, when and where testing is done, when treatment can commence, and the health care resources, staff, and equipment required. These changes impact on patient pathways, potentially changing patient outcomes.

In this review of recently published economic evaluations, we found that many economic models evaluating POCT strategies failed to capture the key routes by which POCTs may create patient benefit and change resource use. In the models where there was a difference in timing of diagnosis between strategies, only 37% considered possible health benefits and 39% considered differences in resource use arising from reducing the time to diagnosis through switching to a faster test. There were no evaluations that considered how POCT availability and access may increase numbers undergoing testing.

In contrast, 95% of the reviewed models considered the impact of differences in accuracy (higher than the 63% of cost-utility analyses of laboratory tests reviewed by Fang et al. [8]). As POCTs may have inferior accuracy compared to their laboratory-based equivalents, it is important that any increase in false positive and false negative diagnoses through reduced accuracy is included in a decision model. Incorrect test results can have implications on costs, patient outcomes, affect disease transmission, and delay the diagnosis of other serious conditions, thus justifying their importance in analyses [90]. However, where differences in accuracy are small, the greatest impact on outcomes and resource use is likely to occur from differences in the diagnostic and treatment pathways.

Around half the models reported utility-based outcomes, such as the QALY, DALY, and QALD. NICE [91] and The World Health Organisation Choosing Interventions that are Cost Effective (WHO-CHOICE) [92] project recommend the QALY and the DALY as effectiveness outcomes as they allow incorporation of patient benefits and harms into a single metric. It is encouraging that these standardized measures are being used as the value of these tests can be assessed in comparable terms to treatments and other health technologies. However, the appropriateness of an outcome predominantly comprised length of life for capturing benefits and harms in a testing situation is debatable. For example, how comparable are 10,000 patients waiting less time for a test result and increasing life expectancy of four patients by 6 months? Only one study addressed the psychological impact of waiting for test outcomes. When comparing a rapid test to a slower comparator, omitting a utility decrement or other methodology that captures anxiety experienced because of delay might not truly reflect the incremental benefit of a rapid test.

Intermediate outcomes related to tests or interventions were reported as the primary outcome in 32% of studies.

In some circumstances, these endpoints may be appropriate as surrogates for patient benefits, but they fail to consolidate the multiple ways in which tests impact on patients into a single measure. A minority of studies only considered the cost of the test and not the test-treatment pathway. As the intention of testing is to inform patient management and improve their health, these models fail to capture the true economic and health implications of the testing pathway.

Two-thirds of models excluded costs incurred by patients, their carers, and any impacts on productivity. The omission of these costs may be a consequence of adopting the perspective recommended by the target decision maker. In the UK, NICE [91] recommend that only costs borne by the NHS and personal social services are included. In contrast, The Netherlands prescribe a societal perspective, to include costs of patient's time (leisure time and paid/unpaid work) and travel. Adhering to these guidelines limits the transferability of the results, yet may be an unavoidable consequence. Excluding societal costs may particularly undervalue POCT technologies as they typically provide savings to patients through reductions in time spend in contact with health services.

A previous evaluation considered models for evaluating POCT tests for tuberculosis [93]. Challenges identified included uncertainties regarding transmission relative to time of diagnosis, treatment initiation, and loss to follow-up. The ability of the health system to inform patients of test results and the timely initiation of treatment were described in some transmission and health system models, although not those evaluating cost-effectiveness [93]. Similar to our findings, the cost-effectiveness models failed to model the full test-treatment pathway and omitted patient incurred costs. As tuberculosis is a disease associated with poverty, patient costs could prove a barrier to testing. Drain et al. proposed a specification [94] for an ideal evaluation of POCTs for use in resource-limited settings, suggesting a shift in emphasis from test accuracy to outcomes such as time to treatment initiation or patient notification rate. In resource-limited settings, clinical

Extra Considerations When Modeling the Cost-Effectiveness of POCTS

Patient and process related outcomes

Does a difference in test setting or time to diagnosis and treatment impact on:

1. Who will be tested
2. Survival to the start of treatment
3. The health state at the start of treatment / disease progression
4. Effectiveness of treatment (e.g. survival following the initiation of treatment / time to symptom resolution)
5. Psychological harms (e.g. anxiety waiting for results)
6. Time in poor health before treatment
7. Harms of inappropriate treatment
8. Patients lost to follow-up / not commencing treatment
9. Disease spread (infectious diseases only)

Resource use (costs) and changes to the diagnostic pathway

Does using a POCT change:

1. Numbers being tested (e.g. access in resource limited settings)
2. Use of empiric/presumptive therapy
3. Clinician time to administer tests
4. Individuals able to administer tests
5. Number of healthcare consultations (e.g. receipt of results)
6. Logistic requirements for testing, delivery and storage (e.g. refrigeration)
7. Training requirements
8. Costs incurred by patients (e.g. work productivity, transport)

Test characteristics

1. Differences in the number of true positives/false negatives (sensitivity: the percentage with target condition who receive the right diagnosis)
2. Differences in the number of true negatives/false positives (specificity: percentage without target condition who get right diagnosis)

Fig. 3. Proposed considerations during model development.

benefit from expediting decision-making may be of greater value than test accuracy.

Evaluating the impact of a test strategy that substantially changes diagnostic and treatment pathways, potentially leading to increased access to testing and subsequent health care is challenging. A primary assumption made in the all the decision models considered is that the hypothetical cohort of patients in the model can all follow each of the strategies being compared. In reality, this is unlikely to be the case when a POCT is introduced, particularly when the POCT allows testing in a different health care setting. For example, the models considering testing for malaria typically compare strategies of treatment based on results of POCT with a strategy of treatment based on microscopy (laboratory) testing. They do not include patients who in reality would receive a POCT if available but could never have access to microscopy—who potentially would receive either empirical treatment or no treatment at all. Future models could consider incorporation of comparative strategies, which include a realistic mixture of alternative pathways.

We believe that there are two main reasons why the omissions in economic evaluations for POCTs described in our review occur. First, there is lack of awareness of the routes by which tests impact on patients beyond test accuracy. Many courses, guides, and textbooks on test evaluation solely focus on sensitivity, specificity, and other measures of test accuracy. Recently a framework of mechanisms by which tests impact on patients was published based on a review of over 100 clinical testing scenarios evaluated in randomized controlled trials [95]. The framework identified issues related to testing timeframes as key mechanisms for creating patient benefit, alongside accurate and confident decision-making, and reducing the direct harms of testing. We would recommend using the checklist that accompanies this framework when scoping models for test scenarios. Second are the challenges in obtaining estimates of the parameters required to create a decision model that factors in the impact of changing time frames and setting on patient outcomes and costs. There may often be a lack of empirical evidence on which to base parameter estimates, although expert judgment and sensitivity analyses may also be required. As a minimum, authors should acknowledge the limitations of their models and simplifications that have been made where they do not fully represent the reality of how POCTs impact on patients and costs. We have developed a set of considerations that could be consulted during the development of economic models of POCTs (Fig. 3). These address key issues we have identified that will enable the development of models that adequately capture both patient-related outcomes and cost implications of these technologies. Although not all items will be relevant to every test, we hope these will address the inadequacies this review has highlighted.

There are a number of limitations to the present study. We restricted searches to the last 13 years, and our searches will inevitably have missed some eligible economic evaluations, both those in non-English language journals and those which use different terminology than that included in our electronic search. A database of test names or additional terminology not used in original searches was developed during abstract screening and supplementary searches were subsequently conducted. However, we would not expect the models we have missed to be qualitatively different than those we have evaluated. It is possible that study reports failed to fully report their models as a consequence of space limitations and omitted information about pertinent costs or outcomes. We noted relevant information in Appendices for some reports suggesting this information may be perceived as less critical to report. A benefit of POCTs unrelated to delay and not investigated in this review is the reduction in secondary tests required. This is an important feature of any new test, improving the testing process for patients and reducing resource use. How POCTs influence the number of tests patients undergo and the cost implications could also be investigated further.

5. Conclusion

This study has shown that many published economic evaluations of POCTs have failed to capture the advantages of increased access and speed to diagnosis and treatment on patient outcomes, and the reductions in patient anxiety and cost that can affect both the health services and patients themselves. We therefore suggest that more should be done to ensure that the methods used in model-based economic evaluations of POCTs adequately consider the impact POCTs have on diagnostic and treatment pathways through changes in testing setting and timing.

Acknowledgment

K.B. completed this work while funded by National Institute for Health Research (NIHR) Research Methods Fellowship (NIHR-RMFI-2013-04-009) and subsequently supported by NIHR Fellowship programme (NIHR-CDF-2015-08-013). J.J.D. received support as an NIHR Senior Investigator and is supported by the NIHR Birmingham Biomedical Research Center at the University Hospitals Birmingham NHS Foundation Trust and the University of Birmingham. The funding sources had no role in the study design; the collection, analysis and interpretation of data; writing the report or in the decision to submit the article for publication. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR, or the Department of Health.

Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jclinepi.2018.11.003.

References

[1] Schünemann HJ, Oxman AD, Brozek J, Glasziou P, Jaeschke R, Vist GE, et al. Grading quality of evidence and strength of recommendations for diagnostic tests and strategies. BMJ 2008; 336(7653):1106−10.

[2] Ferrante di Ruffano L, Davenport C, Eisinga A, Hyde C, Deeks JJ. A capture-recapture analysis demonstrated that randomized controlled trials evaluating the impact of diagnostic tests on patient outcomes are rare. J Clin Epidemiol 2012;65:282−7.

[3] Ferrante di Ruffano L, Dinnes J, Sitch AJ, Hyde C, Deeks JJ. Test-treatment RCTs are susceptible to bias: a review of the methodological quality of randomized trials that evaluate diagnostic tests. BMC Med Res Methodol 2017;17:35.

[4] Ferrante di Ruffano L, Dinnes J, Taylor-Phillips S, Davenport C, Hyde C, Deeks JJ. Research waste in diagnostic trials: a methods review evaluating the reporting of test-treatment interventions. BMC Med Res Methodol 2017;17:32.

[5] National Institute for Health and Clinical Excellence (2011). Diagnostics assessment programme manual. Manchester: National Institute for Health and Clinical Excellence; 2011. Available at www.nice.org.uk.

[6] AHRQ. In: Chang SM, Matchar DB, Smetana GW, Umscheid CA, editors. Methods guide for medical test reviews, AHRQ Publication No. 12-EC017. Rockville, MD: Agency for Healthcare Research and Quality; 2012. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm.

[7] Van den Bruel A, Cleemput I, Aertgeerts B, Ramaekers D, Buntinx F. The evaluation of diagnostic tests: evidence on technical and diagnostic accuracy, impact on patient outcome and cost-effectiveness is needed. J Clin Epidemiol 2007;60:1116−22.

[8] Fang C, Otero HJ, Greenberg D, Neumann PJ. Cost-utility analyses of diagnostic laboratory tests: a systematic review. Value Health 2011;14(8):1010−8.

[9] Dowdy DW, Cattamanchi A, Steingart KR, Pai M. Is scale-up worth it? Challenges in economic analysis of diagnostic tests for tuberculosis. PLoS Med 2011;8(7):e1001063.

[10] Schito M, Peter TF, Cavanaugh S, Piatek AS, Young GJ, Alexander H, et al. Opportunities and challenges for cost-efficient implementation of new point-of-care diagnostics for HIV and tuberculosis. J Infect Dis 2012;205(Suppl 2):S169−80.

[11] Pai M, Flores LL, Hubbard A, Riley LW, Colford JM. Nucleic acid amplification tests in the diagnosis of tuberculous pleuritis: a systematic review and meta-analysis. BMC Infect Dis 2004;4(1):6.

[12] Clerc O, Greub G. Routine use of point-of-care tests: usefulness and application in clinical microbiology. Clin Microbiol Infect 2010; 16(8):1054−61.

[13] Jahn UR, Van Aken H. Near-patient testing: point-of-care or point of costs and convenience? Br J Anaesth 2003;90:425−7.

[14] Price CP. Regular review - point of care testing. Br Med J 2001; 322(7297):1285−8.

[15] Drummond MF, Sculpher M, Torrance G, O'Brien B, Stoddart G. Methods for the economic evaluation of health care programmes. New York: Oxford University Press; 2005.

[16] Loubiere S, Moatti JP. Economic evaluation of point-of-care diagnostic technologies for infectious diseases. Clin Microbiol Infect 2010;16(8):1070−6.

[17] Trevino EA, Weissfeld AS. The case for point-of-care testing in infectious-disease diagnosis. Clin Microbiol Newsl 2007;29(23):177−9.

[18] Gutierres SL, Welty TE. Point-of-care testing: an introduction. Ann Pharmacother 2004;38:119−25.

[19] Dissemination CfRa. How are studies identified for NHS EED. Available at http://www.crd.york.ac.uk/crdweb/searchstrategies.asp. Accessed July , 2014.

[20] Dowdy DW, O'Brien MA, Bishai D. Cost-effectiveness of novel diagnostic tools for the diagnosis of tuberculosis. Int J Tuberc Lung Dis 2008;12(9):1021−9.

[21] Abimbola TO, Marston BJ, Date AA, Blandford JM, Sangrujee N, Wiktor SZ. Cost-effectiveness of tuberculosis diagnostic strategies to reduce early mortality among persons with advanced HIV infection initiating antiretroviral therapy. J Acquir Immune Defic Syndr 2012;60(1):e1−7.

[22] Albert H. Economic analysis of the diagnosis of smear-negative pulmonary tuberculosis in South Africa: incorporation of a new rapid test, FASTPlaqueTB, into the diagnostic algorithm. Int J Tuberc Lung Dis 2004;8(2):240−7.

[23] Alonso S, Tachfouti N, Najdi A, Sicuri E, Picado A. Cost-effectiveness of diagnostic-therapeutic strategies for paediatric visceral leishmaniasis in Morocco. BMJ Glob Health 2017;2(3):e000315.

[24] Choi HW, Miele K, Dowdy D, Shah M. Cost-effectiveness of Xpert(R) MTB/RIF for diagnosing pulmonary tuberculosis in the United States. Int J Tuberc Lung Dis 2013;17(10):1328−35.

[25] Giraldez-Garcia C, Rubio B, Gallegos-Braun JF, Imaz I, Gonzalez-Enriquez J, Sarria-Santamera A. Diagnosis and management of acute pharyngitis in a paediatric population: a cost-effectiveness analysis. Eur J Pediatr 2011;170(8):1059−67.

[26] Jankovic SM, Kostic M. Cost-effectiveness of introducing point-of-care test for detection of level of glycogen phosphorylase in early diagnostic algorithm of acute coronary syndrome. Value Health Reg Issues 2016;10:79−84.

[27] Khaparde S, Raizada N, Nair SA, Denkinger C, Sachdeva KS, Paramasivan CN, et al. Scaling-up the Xpert MTB/RIF assay for the detection of tuberculosis and rifampicin resistance in India: an economic analysis. PLoS One 2017;12(9):e0184270.

[28] Klepser DG, Bisanz SE, Klepser ME. Cost-effectiveness of pharmacist-provided treatment of adult pharyngitis. Am J Manag Care 2012;18(4):e145−54.

[29] Langley I, Lin H-H, Egwaga S, Doulla B, Ku C-C, Murray M, et al. Assessment of the patient, health system, and population effects of Xpert MTB/RIF and alternative diagnostics for tuberculosis in Tanzania: an integrated modelling approach. Lancet Glob Health 2014;2(10):e581−91.

[30] Meyer-Rath G, Schnippel K, Long L, MacLeod W, Sanne I, Stevens W, et al. The impact and cost of scaling up GeneXpert MTB/RIF in South Africa. PLoS One 2012;7:e36966.

[31] Nelson RE, Stockmann C, Hersh AL, Pavia AT, Korgenksi K, Daly JA, et al. Economic analysis of rapid and sensitive polymerase chain reaction testing in the emergency department for influenza infections in children. Pediatr Infect Dis J 2015;34(6):577−82.

[32] Rajalahti I, Ruokonen EL, Kotomäki T, Sintonen H, Nieminen MM. Economic evaluation of the use of PCR assay in diagnosing pulmonary TB in a low-incidence area. Eur Respir J 2004;23(3):446−51.

[33] Schroeder LF, Robilotti E, Peterson LR, Banaei N, Dowdy DW. Economic evaluation of laboratory testing strategies for hospital-associated Clostridium difficile infection. J Clin Microbiol 2014; 52(2):489−96.

[34] Tesfaye A, Fiseha D, Assefa D, Klinkenberg E, Balanco S, Langley I. Modeling the patient and health system impacts of alternative xpert MTB/RIF algorithms for the diagnosis of pulmonary tuberculosis in Addis Ababa, Ethiopia. BMC Infect Dis 2017;17(1):318.

[35] Turner KME, Round J, Horner P, Macleod J, Goldenberg S, Deol A, et al. An early evaluation of clinical and economic costs and benefits of implementing point of care NAAT tests for Chlamydia trachomatis and Neisseria gonorrhoea in genitourinary medicine clinics in England. Sex Transm Infect 2014;90:104−11.

[36] Ward MJ, Self WH, Singer A, Lazar D, Pines JM. Cost-effectiveness analysis of early point-of-care lactate testing in the emergency department. J Crit Care 2016;36:69−75.

[37] You JHS, Lui G, Kam KM, Lee NLS. Cost-effectiveness analysis of the Xpert MTB/RIF assay for rapid diagnosis of suspected tuberculosis in an intermediate burden area. J Infect 2015;70(4):409−14.

[38] You JHS, Tam LP, Lee NLS. Cost-effectiveness of molecular point-of-care testing for influenza viruses in elderly patients at ambulatory care setting. PLoS One 2017;12(7):e0182091.

[39] Howe RS, Kusnier LP. Diagnosis and management of pharyngitis in a pediatric population based on cost-effectiveness and projected health outcomes. Pediatrics 2006;117(3):609−19.
[40] Fauli S, Thue G. Economic consequences of near-patient test results: the case of tests for the Helicobacter Pylori bacterium in dyspepsia. Eur J Health Econ 2008;9(3):221−8.
[41] Kip MMA, Koffijberg H, Moesker MJ, Ijzerman MJ, Kusters R. The cost-utility of point-of-care troponin testing to diagnose acute coronary syndrome in primary care. BMC Cardiovasc Disord 2017;17(1):213.
[42] Scherer LC, Sperhacke RD, Ruffino-Netto A, Rossetti ML, Vater C, Klatser P, et al. Cost-effectiveness analysis of PCR for the rapid diagnosis of pulmonary tuberculosis. BMC Infect Dis 2009;9:216.
[43] Hueston WJ, Benich JJ 3rd. A cost-benefit analysis of testing for influenza A in high-risk adults. Ann Fam Med 2004;2(1):33−40.
[44] Lavelle TA, Uyeki TM, Prosser LA. Cost-effectiveness of oseltamivir treatment for children with uncomplicated seasonal influenza. J Pediatr 2012;160(1):67−73.e6.
[45] Lee BY, McGlone SM, Bailey RR, Wiringa AE, Zimmer SM, Smith KJ, et al. To test or to treat? An analysis of influenza testing and antiviral treatment strategies using economic computer modeling. PLoS One 2010;5:e11284.
[46] Nagase H, Moriwaki K, Kamae M, Yanagisawa S, Kamae I. Cost-effectiveness analysis of oseltamivir for influenza treatment considering the virus emerging resistant to the drug in Japan. Value Health 2009;12(Suppl 3):S62−5.
[47] Rolland E, Checchi F, Pinoges L, Balkan S, Guthmann JP, Guerin PJ. Operational response to malaria epidemics: are rapid diagnostic tests cost-effective? Trop Med Int Health 2006;11(4):398−408.
[48] Rothberg MB, Rose DN. Vaccination versus treatment of influenza in working adults: a cost-effectiveness analysis. Am J Med 2005;118(1):68−77.
[49] Shillcutt S, Morel C, Goodman C, Coleman P, Bell D, Whitty CJ, et al. Cost-effectiveness of malaria diagnostic methods in sub-Saharan Africa in an era of combination therapy. Bull World Health Organ 2008;86(2):101−10.
[50] Uzochukwu BS, Obikeze EN, Onwujekwe OE, Onoka CA, Griffiths UK. Cost-effectiveness analysis of rapid diagnostic test, microscopy and syndromic approach in the diagnosis of malaria in Nigeria: implications for scaling-up deployment of ACT. Malar J 2009;8:265.
[51] Hansen KS, Grieve E, Mikhail A, Mayan I, Mohammed N, Anwar M, et al. Cost-effectiveness of malaria diagnosis using rapid diagnostic tests compared to microscopy or clinical symptoms alone in Afghanistan. Malar J 2015;14:217.
[52] Basu S, Modrek S, Bendavid E. Comparing decisions for malaria testing and presumptive treatment: a net health benefit analysis. Med Decis Making 2014;34:996−1005.
[53] Bell JM, Shields MD, Agus A, Dunlop K, Bourke T, Kee F, et al. Clinical and cost-effectiveness of procalcitonin test for prodromal meningococcal disease-A meta-analysis. PLoS One 2015;10(6):e0128993.
[54] Shen K, Xiong T, Tan SC, Wu J. Oseltamivir treatment for children with influenza-like illness in China: a cost-effectiveness analysis. PLoS One 2016;11(4):e0153664.
[55] Dowdy DW, Lourenço MC, Cavalcante SC, Saraceni V, King B, Golub JE, et al. Impact and cost-effectiveness of culture for diagnosis of tuberculosis in HIV-infected Brazilian adults. PLoS One 2008;3:e4057.
[56] Dowdy DW, Steingart KR, Pai M. Serological testing versus other strategies for diagnosis of active tuberculosis in India: a cost-effectiveness analysis. PLoS Med 2011;8(8):e1001074.
[57] Elwyn G, Taubert M, Davies S, Brown G, Allison M, Phillips C. Which test is best for Helicobacter pylori? A cost-effectiveness model using decision analysis. Br J Gen Pract 2007;57(538):401−3.
[58] Sun D, Dorman S, Shah M, Manabe YC, Moodley VM, Nicol MP, et al. Cost utility of lateral-flow urine lipoarabinomannan for tuberculosis diagnosis in HIV-infected African adults. Int J Tuberc Lung Dis 2013;17(4):552−8.
[59] Menzies NA, Cohen T, Lin H-H, Murray M, Salomon JA. Population health impact and cost-effectiveness of tuberculosis diagnosis with Xpert MTB/RIF: a dynamic simulation and economic evaluation. PLoS Med 2012;9(11):e1001347.
[60] Brown J, Paladino JA. Impact of rapid methicillin-resistant Staphylococcus aureus polymerase chain reaction testing on mortality and cost effectiveness in hospitalized patients with bacteraemia: a decision model. Pharmacoeconomics 2010;28:567−75.
[61] Shah M, Dowdy D, Joloba M, Ssengooba W, Manabe YC, Ellner J, et al. Cost-effectiveness of novel algorithms for rapid diagnosis of tuberculosis in HIV-infected individuals in Uganda. AIDS 2013;27:2883−92.
[62] Vassall A, van Kampen S, Sohn H, Michael JS, John KR, den Boon S, et al. Rapid diagnosis of tuberculosis with the xpert MTB/RIF assay in high burden countries: a cost-effectiveness analysis. PLoS Med 2011;8(11):e1001120.
[63] Hughes R, Wonderling D, Li B, Higgins B. The cost effectiveness of Nucleic Acid Amplification Techniques for the diagnosis of tuberculosis. Respir Med 2012;106(2):300−7.
[64] Nshimyumukiza L, Douville X, Fournier D, Duplantie J, Daher RK, Charlebois I, et al. Cost-effectiveness analysis of antiviral treatment in the management of seasonal influenza A: point-of-care rapid test versus clinical judgment. Influenza Other Respir Viruses 2016;10(2):113−21.
[65] Chihota VN, Grant AD, Fielding K, Ndibongo B, van Zyl A, Muirhead D, et al. Liquid vs. solid culture for tuberculosis: performance and cost in a resource-constrained setting. Int J Tuberc Lung Dis 2010;14(8):1024−31.
[66] Schnippel K, Meyer-Rath G, Long L, Stevens WS, Sanne I, Rosen S. Diagnosing Xpert MTB/RIF negative TB: impact and cost of alternative algorithms for South Africa. S Afr Med J 2013;103(2):101−6.
[67] van't Hoog AH, Cobelens F, Vassall A, van Kampen S, Dorman SE, Alland D, et al. Optimal triage test characteristics to improve the cost-effectiveness of the Xpert MTB/RIF assay for TB diagnosis: a decision analysis. PLoS One 2013;8:e82786.
[68] Bisoffi Z, Sirima SB, Meheus F, Lodesani C, Gobbi F, Angheben A, et al. Strict adherence to malaria rapid test results might lead to a neglect of other dangerous diseases: a cost benefit analysis from Burkina Faso. Malar J 2011;10:226.
[69] Cate-Hoek AJ, Toll DB, Buller HR, Hoes AW, Moons KG, Oudega R, et al. Cost-effectiveness of ruling out deep venous thrombosis in primary care versus care as usual. J Thromb Haemost 2009;7(12):2042−9.
[70] Dugas AF, Coleman S, Gaydos CA, Rothman RE, Frick KD. Cost-utility of rapid polymerase chain reaction-based influenza testing for high-risk emergency department patients. Ann Emerg Med 2013;62(1):80−8.
[71] Duriseti RS, Shachter RD, Brandeau ML. Value of quantitative D-dimer assays in identifying pulmonary embolism: implications from a sequential decision model. Acad Emerg Med 2006;13(7):755−66.
[72] Goodacre S, Stevenson M, Wailoo A, Sampson F, Sutton AJ, Thomas S. How should we diagnose suspected deep-vein thrombosis? J Assoc Physicians 2006;99(6):377−88.
[73] Siddiqui MR, Edmunds WJ. Cost-effectiveness of antiviral stockpiling and near-patient testing for potential influenza pandemic. Emerg Infect Dis 2008;14:267−74.
[74] Thokala P, Goodacre SW, Collinson PO, Stevens JW, Mills NL, Newby DE, et al. Cost-effectiveness of presentation versus delayed troponin testing for acute myocardial infarction. Heart 2012;98(20):1498−503.
[75] Udeh BL, Schneider JE, Ohsfeldt RL. Cost effectiveness of a point-of-care test for adenoviral conjunctivitis. Am J Med Sci 2008;336(3):254−64.

[76] Zikusooka C, McIntyre D, Barnes K. Should countries implementing an artemisinin-based combination malaria treatment policy also introduce rapid diagnostic tests? Malar J 2008;7(1):176.

[77] Hunter R. Cost-effectiveness of point-of-care C-reactive protein tests for respiratory tract infection in primary care in England. Adv Ther 2015;32(1):69−85.

[78] Penno EC, Crump JA, Baird SJ. Performance requirements to achieve cost-effectiveness of point-of-care tests for sepsis among patients with febrile illness in low-resource settings. Am J Trop Med Hyg 2015;93(4):841−9.

[79] Tawiah T, Hansen KS, Baiden F, Bruce J, Tivura M, Delimini R, et al. Cost-effectiveness analysis of test-based versus presumptive treatment of uncomplicated malaria in children under five years in an area of high transmission in central Ghana.[Erratum appears in PLoS One. 2017 Jan 20;12 (1):e0170848; PMID: 28107534]. PLoS One 2016;11:e0164055.

[80] Oxlade O, Sugarman J, Alvarez GG, Pai M, Schwartzman K. XpertMTB/RIF for the diagnosis of tuberculosis in a remote arctic setting: impact on cost and time to treatment initiation. PLoS One 2016;11(3):e0150119.

[81] Suen SC, Bendavid E, Goldhaber-Fiebert JD. Cost-effectiveness of improvements in diagnosis and treatment accessibility for tuberculosis control in India. Int J Tuberc Lung Dis 2015;19(9):1115−24. i−xv.

[82] Schweitzer J, Ellis C, Young M, Gildenberg S, Altman D. Eosinophilic fasciitis. J Am Acad Dermatol 2017;76:AB122.

[83] Batwala V, Magnussen P, Hansen KS, Nuwaha F. Cost-effectiveness of malaria microscopy and rapid diagnostic tests versus presumptive diagnosis: implications for malaria control in Uganda. Malar J 2011;10:372.

[84] Ansah EK, Epokor M, Whitty CJM, Yeung S, Hansen KS. Cost-effectiveness analysis of introducing RDTs for malaria diagnosis as compared to microscopy and presumptive diagnosis in central and peripheral public health facilities in Ghana. Am J Trop Med Hyg 2013;89(4):724−36.

[85] Hendriksen JM, Geersing GJ, Van Voorthuizen SC, Oudega R, Ten Cate-Hoek AJ, Joore MA, et al. The cost-effectiveness of point-of-care D-dimer tests compared with a laboratory test to rule out deep venous thrombosis in primary care. Expert Rev Mol Diagn 2015;15(1):125−36.

[86] Oliveira M, de Castro Gomes A, Toscano C. Cost effectiveness of OptiMal(R) rapid diagnostic test for malaria in remote areas of the Amazon Region, Brazil. Malar J 2010;9(1):277.

[87] Oliveira MR, Giozza SP, Peixoto HM, Romero GA. Cost-effectiveness of diagnostic for malaria in extra-amazon region, Brazil. Malar J 2012;11:390.

[88] Theron G, Pooran A, Peter J, van Zyl-Smit R, Kumar Mishra H, Meldau R, et al. Do adjunct tuberculosis tests, when combined with Xpert MTB/RIF, improve accuracy and the cost of diagnosis in a resource-poor setting? Eur Respir J 2012;40(1):161−8.

[89] Lubell Y, Reyburn H, Mbakilwa H, Mwangi R, Chonya S, Whitty CJ, et al. The impact of response to the results of diagnostic tests for malaria: cost-benefit analysis. BMJ 2008;336:202−5.

[90] Andrews JR, Lawn SD, Dowdy DW, Walensky RP. Challenges in evaluating the cost-effectiveness of new diagnostic tests for HIV-associated tuberculosis. Clin Infect Dis 2013;57:1021−6.

[91] NICE. National Institute for Health and Clinical Excellence (November 2012). The guidelines manual. London: National Institute for Health and Clinical Excellence; 2012. Available at www.nice.org.uk.

[92] Edejer TT-T, Baltussen R, Adam T, Hutubessy R, Acharya A, Evans D, et al. WHO Guide to Cost-Effectiveness Analysis 2012.

[93] Zwerling A, Dowdy D. Economic evaluations of point of care testing strategies for active tuberculosis. Expert Rev Pharmacoecon Outcomes Res 2013;13:313−25.

[94] Drain PK, Hyle EP, Noubary F, Freedberg KA, Wilson D, Bishai WR, et al. Diagnostic point-of-care tests in resource-limited settings. Lancet Infect Dis 2014;14(3):239−49.

[95] Ferrante di Ruffano L, Hyde CJ, McCaffery KJ, Bossuyt PMM, Deeks JJ. Assessing the value of diagnostic tests: a framework for designing and evaluating trials. BMJ 2012;344:e686.