CADTH

CADTH METHODS AND GUIDELINES

Guidelines for the Economic Evaluation of Health Technologies: Canada

4TH EDITION

APPENDIX — SPECIFIC GUIDANCE FOR TREATMENTS WITH COMPANION DIAGNOSTICS

Service Line: Methods and Guidelines
Publication Date: September 2019
Report Length: 15 Pages

CADTH

Cite As: *Guidelines for the economic evaluation of health technologies: Canada. 4th ed. Appendix — Specific guidance for treatments with companion diagnostics.* Ottawa: CADTH; 2019 Sep.

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

CADTH

Acknowledgements

Authors

Christopher McCabe, BA, MSc, PhD, Institute of Health Economics

Bethany Shinkins, MSc, DPhil, University of Leeds, Leeds, UK

Karen M. Lee, MA, Director Health Economics, CADTH

Suzanne LaPlante, BPharm, MSc, DLSHTM, Health Economist, CADTH

All authors drafted the guidelines, revised, and approved the final draft.

Contributors

CADTH would like to acknowledge the following individuals for their contributions:
Kim Baird, BA, PMP, provided project management support and helped with organizing the project.

Reviewers

Peer Reviewers

Doug Coyle, MA, MSc, PhD
Professor, School of Epidemiology and Public Health
University of Ottawa
Ottawa, Ontario

Lauren E. Cipriano, PhD
Associate Professor
Ivey Business School and Department of Epidemiology and Biostatistics
University of Western Ontario
London, Ontario

Industry Reviewers

David Shum, PharmD, MBA
Director, Market Access & Pricing
Roche Canada

Iker Martin Nunez, PharmD, MSc
New Product Development Lead
Amgen Canada Inc.

Declan Hamill, LLB, BCL
Vice President, Legal, Regulatory Affairs & Compliance
Innovative Medicines Canada

BIOTECanada[a]

Conflict of Interest Declaration

David Shum and Iker Martin Nunez have declared employment with respective industry.

No conflicts of interest were declared by authors, contributors, or peer reviewers.

[a] The views expressed in this report are those of CADTH and do not necessarily represent the views of BIOTECanada.

CADTH

Table of Contents

Conventions

Companion diagnostic	A test that measures an individual's protein or gene expression or detects genetic variation for the purpose of informing a treatment decision.[1]
False-negative	When an individual with the condition (or target characteristic) is incorrectly identified by a test as not having the condition (or target characteristic).[2]
False-positive	When an individual without the condition (or target characteristic) is incorrectly identified by a test as having the condition (or target characteristic) (adapted from Annemans).[2]
Negative predictive value	The proportion of test negative results that are true-negative.[3]
Positive predictive value	The proportion of test positive results that are true-positive.[3]
Routine practice	A scenario representing current management.
Sensitivity (or true-positive rate)	The probability that an individual with the condition (or target characteristic) has a positive test result (adapted from Annemans).[2]
Specificity (or true-negative rate)	The probability that an individual without the condition (or target characteristic) has a negative test result (adapted from Annemans).[2]
Treat all	A scenario where nobody receives the companion diagnostic, and everyone receives treatment.
True-negative	An individual without the condition (or target characteristic) is correctly identified by a test as not having the condition (or target characteristic) (adapted from Annemans).[2]
True-positive	An individual with the condition (or target characteristic) is correctly identified by a test as having the condition (or target characteristic) (adapted from Annemans).[2]

Introduction

The intent of the following document is to provide additional guidance that pertains specifically to the economic evaluation of treatment and companion diagnostic combinations. The guidance in this document reflects best practices for conducting economic evaluations when assessing these combinations. More detailed guidance may be available when considering specific decision problems (e.g., drug reimbursement reviews) and readers should consult these documents if relevant.

As a general rule, economic assessments of treatments with companion diagnostics should adhere to CADTH's *Guidelines for the Economic Evaluation of Health Technologies: Canada – 4th Edition*.[4]

Companion diagnostics are tests that measure an individual's protein or gene expression, or that detect genetic variation. Its results are then used to inform treatment decisions.[1] Companion diagnostics can be used for patient selection or treatment monitoring, with the ultimate goal being to improve safety, effectiveness, and patient health outcomes.[5] For the purpose of this guidance, the definition of a companion diagnostic is limited to a test that is used to identify individuals who are most likely to benefit or experience harms from a defined therapeutic intervention. Other scenarios, such as the use of a companion diagnostic to monitor therapeutic response or a comprehensive assessment of the companion diagnostic (when there are multiple potential uses of the companion diagnostic), are beyond the scope of this guidance.

Typically, the performance (accuracy) of diagnostic tests is assessed by comparing the test results with a gold (or reference) standard. For some companion diagnostics, a reference standard may not be available so performance in terms of sensitivity, specificity, true- or false-positive, and true- or false-negative might not be available.[6] Companion diagnostics might be developed at the same time as treatment (e.g., HER2 testing for HER2 inhibitors) or might become available several years after treatment has reached the market (e.g., CYP2C9 testing for warfarin).[7] While in some situations (e.g., launch of first-in-class product), there might be only one type of companion diagnostic available, often times several will be available, each with different sensitivity and specificity. The results might be expressed as a yes/no type of answer or as a series of cut-off values associated with different treatment results. In addition, a sequence of companion diagnostics rather than a single one might be used. These different situations show how companion diagnostics add to the complexity of the economic evaluation. Not only should treatment effect be considered, but so should the performance of the companion diagnostic, the interpretation of its results, and the clinician behavioural response to its results. Furthermore, implementation issues might need to be considered (e.g., when the treatment has been available long before the companion diagnostic, when the delay before obtaining the results is long, when cost is prohibitive). A more detailed description of the challenges related to the economic evaluation of companion diagnostics can be found in the literature.[1,2,7,8]

Guideline Statements

1. Decision Problem

1.1 The decision problem needs to encompass both the treatment and the companion diagnostic and be explicit about the dependency between them to produce clinical benefits.

1.2 The setting(s) in which the companion diagnostic and the treatment are provided must be clearly specified.

1.3 The decision-maker(s) and researchers should determine who is likely to pay for the treatment and the companion diagnostic to determine relevant perspectives.

1.4 The description of the companion diagnostic in the decision problem must be clearly described (e.g., explicit about which version[s] of the companion diagnostic are to be evaluated).

1.5 When scoping the decision problem, factors that impact upon clinician behavioural response to a companion diagnostic result, patient acceptance of the procedure and results, and patient adherence to treatment indicated by the companion diagnostic should be considered to determine whether they are relevant for consideration. Where these items are excluded, justification should be provided.

1.6 There may be several possible ways in which the companion diagnostic can be used within a clinical pathway and/or the results can be interpreted. The decision problem should clearly specify where and when the companion diagnostic will be used in the clinical pathway and how its result will inform the subsequent treatment decision. If there are several possible roles for the companion diagnostic under evaluation, there should be a separate decision problem for each purpose.

1.6.1 In order to guide treatment, an assessment should be made as to the need for subsequent use of the companion diagnostic within the context of the decision problem.

1.6.2 Consider if the companion diagnostic may be used outside of the stated clinical indication; for example, a companion diagnostic that is used to establish whether an individual should receive treatment may then be used to monitor for negative reaction. Where such monitoring is outside of the clinical indication for the companion diagnostic and beyond the scope of the decision problem, monitoring using the companion diagnostic should be excluded from the analysis.

2. Types of Evaluation

2.1 As indicated in CADTH's *Guidelines for the Economic Evaluation of Health Technologies: Canada – 4th Edition*,[4] the economic evaluation should be a cost-utility analysis with outcomes expressed as quality-adjusted life-years (QALYs).

2.2 All key clinical outcomes and costs from the companion diagnostic and treatment must be accounted for in the reference case. These might include:

- clinician adherence to the use of the companion diagnostic
- clinician adherence to the indicated treatment (based on the results of the companion diagnostic)

- patient adherence to the indicated treatment
- all key clinical outcomes from the companion diagnostic and treatment
- increased and/or avoided complications.

If there are additional outcomes of interest for a broader perspective beyond the decision problem, these could be considered in a scenario analysis or discussed.

2.3 Key clinical outcomes that could not be included in the evaluation need to be fully described, alongside justifications for why the outcomes were excluded.

3. Target Population

3.1 In the reference case, the target population(s) for the companion diagnostic and subsequent treatment decision should be consistent with the decision problem.

3.2 The result(s) of the companion diagnostic may lead to the identification of distinct subgroups of the population (e.g., phenotypic, risk factors, or molecular characteristics) for which estimates of costs and outcomes associated with the treatment differ (e.g., treatment efficacy differs according to companion diagnostic result level categories). In this case, stratified analyses with results presented for each subgroup should be provided in the reference case. Otherwise, the analysis should be for the entire target population.

3.3 Spillover effects may be a consideration if health effects occur outside of those tested (e.g., if genetic information is shared between biological relatives). If there is evidence of health effects on individuals outside of those included in the target population(s) specified in the decision problem, these should be justified and addressed in a scenario analysis.

4. Comparators

4.1 Fully describe all companion diagnostic and treatment combinations. Explicitly state how the result(s) of the companion diagnostic inform the subsequent treatment decision.

4.2 All (mutually exclusive and collectively exhaustive) decision alternatives should be considered and the choice of comparator(s) justified. This includes no test/no treatment, no test/treat everyone, and potentially various treatment policies in response to test results informed by different cut points, the potential to include additional clinical information in the final treatment decision, and the potential to include patient or physician preferences in the final treatment decision. “Treat all” and “routine practice” comparisons should always be considered as potential comparators when scoping the decision problem.

4.3 Consider whether there are alternative diagnostics (including those currently used in practice) that could be substituted for the companion diagnostic named in the decision problem, as this diagnostic could be used as a relevant comparator. Justification should be provided where these are not considered in the analysis.

4.4 The positioning and role of the companion diagnostic should be consistent with the decision problem. If there are multiple roles for the companion diagnostic to be evaluated, this should be addressed by specifying separate decision problems (as mentioned in guideline statement 1.6).

5. Perspective

5.1 In the reference case, the perspective should be that of the publicly funded health care payer (see guideline statement 1.3).

5.2 In case of multiple public payers, a cost breakdown by payer (e.g., acute in-hospital care, outpatient care, home services, drug formulary, cancer agency, long-term care) should be included to provide information to decision-makers.

6. Time Horizon

No additional recommendations. Refer to Section 6 of CADTH's *Guidelines for the Economic Evaluation of Health Technologies: Canada – 4th Edition*.[4]

7. Discounting

No additional recommendations. Refer to Section 7 of CADTH's *Guidelines for the Economic Evaluation of Health Technologies: Canada – 4th Edition*.[4]

8. Modelling

8.1 Identify the relevant clinical pathways to be compared, which include all relevant companion diagnostic and treatment alternatives and combinations. The number of pathways that need to be modelled may be extensive if companion diagnostic(s) is (are) being used for multi-level patient stratification.

8.2 The model should capture the impacts of the companion diagnostic and treatment interventions on the natural history of the condition. If there is a lack of evidence for the downstream health consequences of detecting and treating condition earlier, this should be clearly stated. Any modelling assumptions regarding natural history, shifts in staging of the condition, and subsequent response to treatment need to be explicit and made with caution. Uncertainty in assumptions (e.g., potential for over-diagnosis and over-treatment) should be considered in scenario analyses.

9. Effectiveness

9.1 All evidence for each identified relevant clinical pathway to be compared should be identified. This may include the companion diagnostic, the corresponding treatment, the combination of the treatment and the companion diagnostic, the treat-all option, and the routine practice option.

9.2 Clinical effects should be obtained from the specific population being considered (e.g., effectiveness of treatment for true-positive patients should be gleaned from populations who test positive and receive treatment, and not just studies considering treatment alone without testing). Similarly, the effects for false-positive patients should be reflective of the specific population. In the absence of linked companion diagnostic-treatment effectiveness data, explicit reporting of the patient population from which included effectiveness data has been obtained, and how it relates to the characteristics of the population affected by the decision, is required. The implications of the uncertainty attributable to using treatment-only effectiveness estimates must be described.

Linking Evidence via Decision-Analytic Modelling

9.3 When there are no clinical studies that follow patients from diagnosis to downstream health outcomes (i.e., clinical utility studies of the companion diagnostic), different types of evidence can be linked together via decision-analytic modelling.

9.4 Linking evidence is meaningful when the evidence for the proposed companion diagnostic(s) and for the proposed treatment(s) has been generated in similar patient populations that reflect the target population.

9.5 Evidence of companion diagnostic and treatment performance should be selected in a comprehensive and unbiased manner, using appropriate methods of systematic literature review.

9.6 There are likely to be multiple factors in addition to the outcome of the diagnostic that may influence a treatment decision and adherence to treatment. If it is assumed in the model that the results from the companion diagnostic solely determine the treatment decision, evidence to support this should be provided (for examples, see Lo et al. [2010]).[9] Otherwise, explicit consideration of the impact of clinician and patient preferences on treatment decisions should be included in the model structure (for examples, see Paulden et al. [2013]).[10]

9.7 If relevant, the uptake rate of the companion diagnostic should be included in the model structure and supported by evidence. If this evidence is not available but the uptake rate is relevant, then a scenario analysis should be reported using a range of possible uptake rates.

Companion Diagnostic Accuracy

9.8 In order to avoid spectrum bias, evidence of companion diagnostic accuracy should be generated in the population to receive the companion diagnostic in clinical practice as defined in the decision problem. If accuracy data has come from a different patient population, there needs to be evidence of its portability from the population in which it was developed to the population to which it is applied. This may be possible to obtain from subgroup analyses within diagnostic accuracy studies (for examples, see Lachs et al. [1992]).[11]

9.9 In some situations, there is no reference standard for the companion diagnostic or the reference standard is unclear (e.g., biomarker correlating with treatment response or disease progression).[6] However, when such a standard exist, the choice of the reference standard should be consistent with the agreed definitions (i.e., “the best available method for establishing the presence or absence of disease target condition.”)[12] If a single reference standard test is not available or is unacceptable for the requested use and/or requested population, select the next best alternative based on which test is most likely to produce the most accurate estimation of disease status. If multiple reference standard tests are appropriate or possible, alternative reference standard tests can be explored in a scenario analysis. If there are concerns about the accuracy of the reference standard test used in the model, analysts should acknowledge and provide discussion.

9.10 Often, the results from companion diagnostics are produced on a continuous scale, rather than as a binary “positive” or “negative” result. When multiple companion diagnostics, be it binary or continuous, are combined, a continuous probability score is typically produced. Cut-offs are then typically selected to facilitate the categorization of patients as either “positive” or “negative” for

treatment decisions. Adjusting the cut-off of a companion diagnostic will change performance characteristics and, consequently, the clinical- and cost-effectiveness of treatment decisions, as well as their budget impact. Ideally, data will be available to examine the effect on cost-effectiveness of changing the companion diagnostic cut-off. While performance data may not be available at different cut-offs, when analysts have access to receiver operating characteristic curves, or ideally, patient-level data, every effort should be made to extract performance data for a range of cut-offs to enable decision-makers to understand the scope for optimizing the cost-effectiveness of the companion diagnostic and treatment combination by varying the cut-off.

9.11 Where a meta-analysis of accuracy data is undertaken to produce evidence to parameterize the model, adherence with best practice in the statistical methods used (as outlined in the *Cochrane Handbook for Diagnostic Test Accuracy Reviews*)[13] is required.

9.12 The consequence of a false-positive companion diagnostic result should be fully modelled. If individuals are treated unnecessarily, then the reduction in treatment effectiveness; any harm from the treatment, including avoidable anxiety; and the associated resource consumption should be included in the model. It is possible that individuals with a false-positive result will not go through the entire treatment cycle as their true disease status becomes evident over time or based on treatment response. If this is the case, then this should also be recognized in the model.

9.13 For false-negative companion diagnostic results, the likelihood that patients will not receive the same treatment as true-positive cases, and the associated consequences from this, need to be fully modelled. This should include consideration of the health and resource use implications of any “lost treatment options” due to delayed diagnosis.

9.14 If multiple tests or platform tests are being utilized, the analysis will need to take explicit account of the probability of incidental findings, and their impact on health care resource utilization and health outcomes (for examples, see Xiong et al. [2006]).[14]

9.15 Where co-dependent accuracy statistics, such as sensitivity and specificity, are being used to inform model parameters, the correlation between the two parameters should be built into the model by using paired distributions.

9.16 If multiple companion diagnostics are being used in sequence, or in combination with each other, the changes to the case-mix after each companion diagnostic and the inter-dependency between performance characteristics should, where possible, be incorporated into the modelling. Where this is not possible, this issue should be highlighted as a key weakness in the Discussion section of the report, along with a narrative account of whether it is possible to describe the direction of effect on this inter-dependency on the findings. Scenario analysis should be considered where primary data are not available.

9.17 To model the performance of the companion diagnostic, transition probabilities are guided by rates of true- and false-positives as well as true- and false-negatives from the companion diagnostic. This should be applied to the model, the source(s) should be reported, and quality of the information assessed. Strengths and weaknesses of the sources of information should be presented in the Discussion section.

10. Measurement and Valuation of Health

10.1 In the reference case, QALY should be used as the method of capturing the value of the combined health effect of the treatment and companion diagnostic.

10.2 When applying utilities, health states and the time spent in each health state across the whole clinical pathway should be considered for all different companion diagnostic outcomes (e.g., false- and true-positive, false- and true-negative).

11. Resource Use and Costs

11.1 Include the cost of companion diagnostic(s) undertaken on all patients for whom the treatment is being considered, in addition to the costs arising from the diagnostic information produced and subsequent treatment decisions. The cost components to include will depend on the perspective of the analysis. The analyst should also consider whether the companion diagnostic will be provided as part of an existing panel of tests, will be added to an existing panel of tests, or will be available as a test on its own. The following provides a reminder of some of the key cost components for consideration when undertaking an analysis from the perspective of a publicly funded health care payer.

11.1.1 Costs associated with the diagnostic: companion diagnostic cost, including the costs of sampling and consultations regarding results; costs of re-testing for non-assessable results; and costs for adverse events associated with testing. If a fee is not available for the companion diagnostic, a health care provider approach (micro costing) may be used to estimate the health care costs. This would include the costs of infrastructure, staff, material, quality assurance for testing, and the costs of collecting, storing, and retrieving the samples. Furthermore, if capital investment is required, this should also be accounted for (with appropriate amortization).

11.1.2 Costs associated with treatment(s): treatment (drug, routine care) and administration, monitoring, other concomitant drugs, and drug-related adverse events (including for those where the result was false-positive).

11.1.3 Cost components associated with the downstream impact of companion diagnostic and treatment interventions: change in the number of inpatient admissions, accident and emergency attendances, outpatient clinic visits, etc.

11.2 Depending on the perspective of the decision problem, additional costs that are driven by companion diagnostic(s) and treatments in terms of availability (e.g., limited capacity or wait lists) and location (e.g., need to travel, need to send in samples) should be incorporated into the analyses, or at a minimum should be described and their implications discussed.

11.3 Ensure that all additional resources required for uptake and training are included in the costs.

11.4 Ensure any one-off or long-term costs and associated systems costs (e.g., tailoring or maintaining electronic health records) are included, or their exclusion clearly justified.

11.5 Where costs are anticipated to decrease over time (e.g., capital acquisition, training or learning curves), this could be explored in scenario analyses or described in the Discussion section.

12. Analysis

12.1 In line with CADTH's *Guidelines for the Economic Evaluation of Health Technologies: Canada – 4th Edition*,[4] researchers should report disaggregated expected costs and outcomes for each strategy, and incremental costs and outcomes for the whole population and any subgroups identified in the decision problem. The analyses should be conducted and the results reported sequentially.

12.2 Assessments of whether there is a companion diagnostic performance level below which the companion diagnostic should not be used (for example, either false-positives are too great or false-negatives are too great) should always be reported. This may be undertaken using one-way stochastic sensitivity analysis of the performance characteristic parameters, and plotting the performance values that are expected to produce a negative net benefit, alongside the probability that these values will be observed (for examples, see Soares et al. [2018]).[6]

13. Uncertainty

13.1 A comprehensive analysis of uncertainty should be undertaken in line with CADTH's *Guidelines for the Economic Evaluation of Health Technologies: Canada – 4th Edition*.[4]

13.2 Special attention should be given to vary treatment(s) effectiveness, companion diagnostic(s) performance, uptake rate, and the prevalence of patients from the tested population with the condition to be treated.

13.3 The following scenario analyses should be conducted as part of the standard set:

- prevalence of individuals that should receive treatment
- proportion of individuals eligible for companion diagnostic (i.e., lower threshold for using companion diagnostic) where relevant
- rate of companion diagnostic uptake
- diagnostic accuracy (i.e., companion diagnostic performance characteristics such as sensitivity and specificity)
- effectiveness of treatment in all those who subsequently receive the treatment (i.e., those with a true-positive or false-positive)
- heterogeneity in clinical and/or patient behavioural response to companion diagnostic results (i.e., adherence to recommendation from companion diagnostic results)
- impact of clinician preferences on companion diagnostic and treatment decisions (for examples, see Lo et al. [2010][9] and Paulden et al. [2013])[10]
- impact of patient preferences on companion diagnostic and treatment decisions (for examples, see Lo et al. [2010][9] and Paulden et al. [2013]).[10]

13.4 Companion diagnostic technologies may have a less mature evidence base compared with conventional technologies that have been licensed based on large phase III trial programs. As a result, decision-makers may be particularly interested in the value of gathering additional evidence on different components of the decision problem as well as the expected cost-effectiveness of the technology given the current evidence base. Therefore, analysts should consider the provision of expected value of partial information (EVPI) analyses on the companion diagnostic performance and treatment effectiveness parameters to

support the decision-maker's consideration of the contribution of each parameter (or group of parameters) to the total decision uncertainty.

13.4.1 Where significant uncertainties remain in key model parameters, it may be necessary to revisit the economic evaluation at a later stage of the technology life cycle when further data are available (e.g., from ongoing research).

13.4.2 Where the decision problem includes consideration for further research to inform future decisions, to help reduce decision uncertainty, use value-of-information (VOI) analysis may provide the decision-maker with insights into which aspects of the diagnostic technology or treatment could benefit from additional research.

13.5 If spillover effects are explored in a scenario analysis, any differences in the health effects between the populations tested and treated, and those indirectly affected need to be fully described.

14. Equity

No additional recommendations. Please refer to Section 6 of CADTH's *Guidelines for the Economic Evaluation of Health Technologies: Canada – 4th Edition*.[4]

15. Reporting

15.1 Reporting should adhere to the recommendations in CADTH's *Guidelines for the Economic Evaluation of Health Technologies: Canada – 4th Edition*.[4]

15.2 Report results (total cost, total QALYs, incremental costs and QALYs, incremental cost-effectiveness ratio [ICER]) for all perspectives assessed.

15.3 Report results (total cost, total QALYs, incremental costs and QALYs, ICER) by budget holder (e.g., acute in-hospital care, outpatient care, home care services, drug formulary, cancer agency, long-term care) where costs are borne by different decision-makers or payers. At a minimum, treatment costs and companion diagnostic costs must be reported separately from other health care costs.

15.4 Report disaggregate results in terms of individual cost components, predicted companion diagnostic outcomes (true- and false-negatives, true- and false-positives), and predicted clinical outcomes (mortality, events, etc.). Results should also be provided in terms of the costs and outcomes for false-positives and false-negatives.

15.5 Report implementation costs, where relevant.

References

1. Byron SK, Crabb N, George E, Marlow M, Newland A. The health technology assessment of companion diagnostics: experience of NICE. *Clin Cancer Res.* 2014;20(6):1469-1476.
2. Annemans L, Redekop K, Payne K. Current methodological issues in the economic assessment of personalized medicine. *Value Health.* 2013;16(6 Suppl):S20-26.
3. Fletcher RH, Fletcher SW, Fletcher GS. *Clinical epidemiology: the essentials.* 5th ed. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2014.
4. Guidelines for the economic evaluation of health technologies: Canada. *(CADTH methods and guidelines)*. 4th ed. Ottawa: CADTH; 2017: https://cadth.ca/sites/default/files/pdf/guidelines_for_the_economic_evaluation_of_health_technologies_canada_4th_ed.pdf. Accessed 2019 Jul 18.
5. Faulkner E, Annemans L, Garrison L, Helfand M, Holtorf AP, Hornberger J, et al. Challenges in the development and reimbursement of personalized medicine-payer and manufacturer perspectives and implications for health economics and outcomes research: a report of the ISPOR personalized medicine special interest group. *Value Health.* 2012;15(8):1162-1171.
6. Soares MO, Walker S, Palmer SJ, Sculpher MJ. Establishing the value of diagnostic and prognostic tests in health technology assessment. *Med Decis Making.* 2018;38(4):495-508.
7. Shabaruddin FH, Fleeman ND, Payne K. Economic evaluations of personalized medicine: existing challenges and current developments. *Pharmgenomics Pers Med.* 2015;8:115-126.
8. Husereau D, Marshall DA, Levy AR, Peacock S, Hoch JS. Health technology assessment and personalized medicine: are economic evaluation guidelines sufficient to support decision making? *Int J Technol Assess Health Care.* 2014;30(2):179-187.
9. Lo SS, Mumby PB, Norton J, Rychlik K, Smerage J, Kash J, et al. Prospective multicenter study of the impact of the 21-gene recurrence score assay on medical oncologist and patient adjuvant breast cancer treatment selection. *J Clin Oncol.* 2010;28(10):1671-1676.
10. Paulden M, Franek J, Pham B, Bedard PL, Trudeau M, Krahn M. Cost-effectiveness of the 21-gene assay for guiding adjuvant chemotherapy decisions in early breast cancer. *Value Health.* 2013;16(5):729-739.
11. Lachs MS, Nachamkin I, Edelstein PH, Goldman J, Feinstein AR, Schwartz JS. Spectrum bias in the evaluation of diagnostic tests: lessons from the rapid dipstick test for urinary tract infection. *Ann Intern Med.* 1992;117(2):135-140.
12. Center for Devices and Radiological Health. Guidance for industry and FDA staff: statistical guidance on reporting results from studies evaluating diagnostic tests. Rockville (MD): U.S. Department of Health and Human Services, Food and Drug Administration; 2007: https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071287.pdf. Accessed 2019 Jul 18.
13. Macaskill P, Gatsonis C, Deeks JJ, Harbord RM, Takwoingi Y. Chapter 10: Analysing and presenting results. In: Deeks JJ, Bossuyt PM, Gatsonis C, eds. *Cochrane handbook for systematic reviews of diagnostic test accuracy. Version 1.0*. London: The Cochrane Collaboration; 2010: https://methods.cochrane.org/sdt/handbook-dta-reviews. Accessed 2019 Jul 18.
14. Xiong T, McEvoy K, Morton DG, Halligan S, Lilford RJ. Resources and costs associated with incidental extracolonic findings from CT colonography: a study in a symptomatic population. *Br J Radiol.* 2006;79(948):948-961.