

CADTH's Proposed Process for the Assessment of Companion Diagnostics

1. Preamble

Companion diagnostics identify subgroups of patients for whom select drugs are likely to be most effective and safe. Based on feedback from participating jurisdictions, and guided by consultations with representatives internationally, across Canada, and among its committees, CADTH has developed a process for the assessment of companion diagnostics through the CADTH Common Drug Review (CDR) and pan-Canadian Oncology Drug Review (pCODR) programs.

2. Background

Companion diagnostics are laboratory tests that aim to measure the expression of a specific biomarker.¹ They guide optimal clinical management by identifying subpopulations of patients who are most likely to benefit from a given drug. These tests are distinct from other emerging molecular diagnostic techniques, such as whole genome sequencing, although most such technologies strive to tailor treatments to the needs of individual patients.

The global market for companion diagnostics is growing. The resulting implications for the Canadian health care system are significant, as there will be an increase in the number of drugs for which there are companion diagnostics. In 2013, the pCODR office reported that, on the horizon for cancer treatment, there were potentially 15 individual drugs and 31 drug-indication pairs linked to 12 different companion diagnostics.² Further, a 2015 survey conducted by CADTH found that 14% of new oncology submissions will have an associated companion diagnostic.³ Of note, these tests are not restricted to oncology drugs, and there are other conditions for which they have been developed, including cystic fibrosis, human immunodeficiency virus, rheumatoid arthritis, and hepatitis C.

The Canadian public reimbursement landscape for companion diagnostics is not well defined. Previous feedback from CADTH's stakeholders has included concerns regarding cross-jurisdictional inconsistency in the processes for approving, funding, and accessing these tests. Hence, there is an important need for pan-Canadian leadership in the development and implementation of a centralized process to inform public reimbursement decision-making for companion diagnostics.

3. Overview of the Proposed Process

3.1. Preparation

CADTH consulted representatives from the Pharmaceutical Benefits Advisory Committee and the Medical Services Advisory Committee in Australia, which has implemented a national health technology assessment (HTA) framework for co-dependent technologies.⁴ Further, CADTH consulted representatives across several Canadian jurisdictions to gather insights into their reimbursement decision-making needs and expectations. Last, CADTH sought feedback from its jurisdictional advisory committees and expert review committees.

3.2. Output

The objective of the proposed process is for CADTH to evaluate a submitted drug and its associated companion diagnostic together, rather than either one in isolation. At CADTH, the current HTA process

for an individual drug culminates with an expert committee — the CADTH Canadian Drug Expert Committee (CDEC) for non-oncology drugs, and the pCODR Expert Review Committee (pERC) for oncology drugs — making a public reimbursement recommendation for the given drug. Under the proposed process, the same expert committee would make a public reimbursement recommendation for a drug that considers its associated companion diagnostic as well. These recommendations will be non-binding, and each participating jurisdiction would make its own funding decision based on the CADTH recommendation and other factors, including jurisdictional mandate, priorities, and resources.

3.3. Eligibility

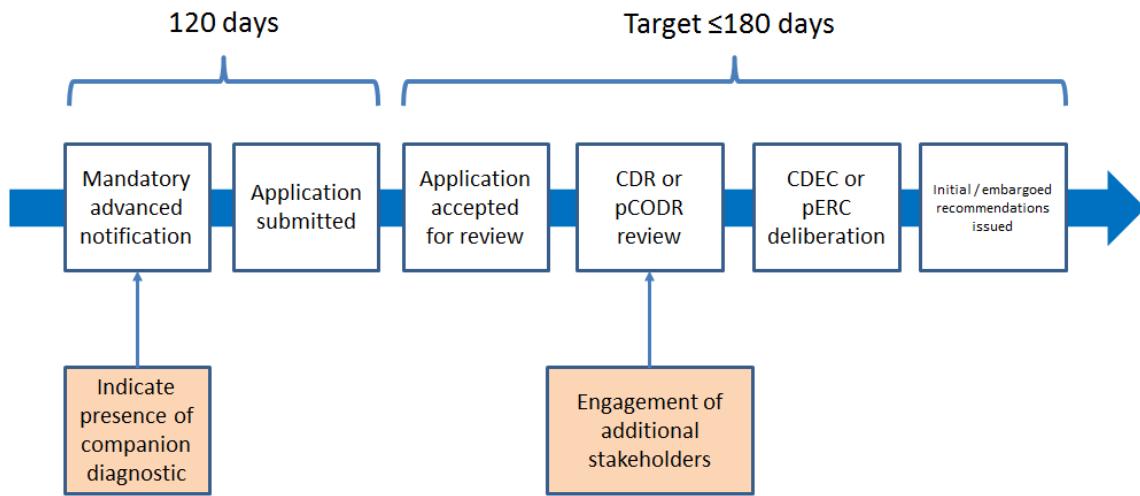
The proposed process would encompass new companion diagnostics associated with drugs that are eligible for review under the CDR and pCODR programs. Of note, a new companion diagnostic is one that is not already reimbursed by most participating jurisdictions across Canada at the time of submission to CADTH.

3.4. Procedure

The proposed process would be integrated into the CDR and pCODR processes, and would **not** increase currently established timelines for completing a review (Figure 1).

When notifying CADTH of a pending drug submission, applicants will be required to indicate the presence of an associated companion diagnostic. CADTH will also require applicants to file a single submission package that pertains to both the drug and the companion diagnostic to the appropriate drug review program. In addition to complying with the current CDR and pCODR submission requirements, applicants will be required to provide CADTH with additional information on the associated companion diagnostic. CADTH will consider producing a submission template to be used by applicants to provide this information in a consistent manner. During the review process, CADTH will engage patients, clinicians, and the participating jurisdictions to gather additional insights into the companion diagnostic (Figure 1).

Figure 1: Overview of the Proposed Process



CDEC = CADTH Canadian Drug Expert Committee; CDR = CADTH Common Drug Review; pCODR = pan-Canadian Oncology Drug Review; pERC = pCODR Expert Review Committee.

In cases where the manufacturer of a drug is different from that of the companion diagnostic, it will be the responsibility of the drug manufacturer to provide the necessary information on the companion diagnostic. It will not be the responsibility of CADTH to manage the relationship between the manufacturers.

Under the proposed process, at this time, fees for reviewing a drug application that includes a companion diagnostic would be the same as the current fees for drug applications at CADTH.

3.5. Implementation

The implementation of the process for the assessment of companion diagnostics is anticipated on or after Monday, April 3, 2017.

4. Evidentiary Requirements

4.1. General Information

Applicants will be required to provide details on the biomarker of interest, the companion diagnostic, and laboratory services (Table 1).

Table 1: General Information Required for the Assessment of a Companion Diagnostic

Aspect	Details
Biomarker	Description of the biomarker; e.g., rationale for selecting and targeting it with the drug, comparison with other known biomarkers
Companion diagnostic	Description of the main companion diagnostic proposed for use to determine suitability to receive the submitted drug; e.g., bio-specimen requirements, testing protocol in typical clinical pathway, manufacturer Identification of other known commercial companion diagnostic tests in Canada (if available) that may be used with the drug and indication under review, and justification of the selection of the main test
Laboratory services	Description of required laboratory services; e.g., infrastructure requirements, turnaround time for results, training requirements for staff

4.2. Clinical Evidence

Applicants will be required to provide evidence on the analytical validity, clinical validity, and clinical utility of the companion diagnostic (Table 2). In parallel with conducting a standard drug review, CADTH clinical reviewers will critically appraise the submitted clinical evidence on the companion diagnostic, and concurrently produce a Rapid Response report that will summarize and critically appraise relevant information from the published literature. This report will be incorporated into the clinical review report for the drug, and will be posted as an independent document on the CADTH website.

Table 2: Clinical Evidence Required for the Assessment of a Companion Diagnostic

Aspect	Details
Analytical validity	Measures such as accuracy, precision, reliability, and analytical sensitivity and specificity of the companion diagnostic, and how these measures compare with other tests
Clinical validity	Measures such as clinical specificity and sensitivity, positive predictive value, negative predictive value, and likelihood ratios, and how they compare with other tests
Clinical utility	Benefits and risks of using the companion diagnostic, how it will add to the treatment of patients, and how it will change the patient's health outcomes

4.3. Economic Evidence

Applicants will be required to explicitly incorporate the companion diagnostic into their economic analyses of the drug and indication under review, including modelling of the upfront and downstream costs and consequences (e.g., of false-negatives and/or false-positives) associated with the test in any cost-effectiveness analyses. CADTH economic reviewers will critically appraise the submitted evidence.

If more than one commercial companion diagnostic is available in Canada for the drug and indication under review, the applicant should include the main test proposed for use with the drug in the base-case economic analysis. List prices should be provided for both the main test and any additional companion diagnostics available in Canada.

As per normal requirements for economic models submitted to CDR or pCODR, models should be unlocked. To allow for the conduct of sensitivity analyses, the user should be able to implement changes to key inputs in submitted models, including the cost of the companion diagnostic, any additional costs required to perform the test (e.g., technician time), and clinical validity parameters (e.g., sensitivity, specificity) that may affect downstream costs and consequences.

Budget impact analyses (BIAs) should account for the cost of testing with the main companion diagnostic. Applicants will be required to provide BIAs for the drug and associated companion diagnostic in combination and separately, as some jurisdictions fund the two technologies through separate mechanisms.

5. Patient Input

Under the proposed process, CADTH will seek additional input from patient groups on the submitted drug and the associated companion diagnostic to ensure that issues that are important to patients are formally and meaningfully incorporated into the review process. The patient input templates that are currently used within the CDR and pCODR programs will include a dedicated section on companion diagnostics, with accompanying instructions on the type of information that may optimally support CADTH's review of the drug under review and its associated companion diagnostic.

6. Clinician Input

Under the proposed process, CADTH will engage additional experts in pathology and/or laboratory testing who would be able to comment on front-line clinical aspects of the companion diagnostic, such as the consistency of the testing protocol with Canadian guidelines.

7. Jurisdictional Input

Under the proposed process, CADTH will seek additional insights from participating jurisdictions regarding the enablers and barriers to the adoption of the drug under review and the associated companion diagnostic, with an emphasis on understanding issues related to the companion diagnostic; e.g., current availability, frequency and timing of testing, length of time for the analysis, and laboratory infrastructure requirements.

8. 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):1469-76.
2. Performance measures report: partial assessment of pCODR's first years [Internet]. Toronto: Pan-Canadian Oncology Drug Review (pCODR); 2014. Available from: <http://www.pcodr.ca/idc/groups/pcodr/documents/pcodrdocument/pcodr-perform-measures-apr2014.pdf>

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4. Merlin T, Farah C, Schubert C, Mitchell A, Hiller JE, Ryan P. Assessing personalized medicines in Australia: a national framework for reviewing codependent technologies. *Med Decis Making*. April 2013; 333-342.