An Alberta Framework for Evaluation of Companion Diagnostics for Provincial Decision Making & Case study on PD-L1 testing for NSCLC

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Objectives

- Provide background for Alberta context
- Outline proposed framework for assessing CDx for funding
- Briefly describe pilot project on PD-L1 testing for non-small cell lung cancer (NSCLC)
- Share some lessons learned and salient issues

The Saga

May 2013: pCODR recommends funding crizotinib as second-line therapy for patients with ALK-positive advanced non-small-cell lung cancer

“we do need to do something to inform the decision around ALK testing” – Alberta Health/Alberta Health Services

Alberta Health Technologies Decision Process (AHTDP), Alberta Advisory Committee on Health Technologies (AACHT) were engaged

Initial challenge: How do we (Alberta) manage the review of a CDx for a drug that has just been approved by pCODR/CDR?

May 2014: Alberta Workshop on Companion Diagnostics (presentation of environmental scan of international approaches)

Oct 2015: Alberta CDx Working group established

Feb 2016: Meeting with next steps identified – outline possible options with focus on alignment of CDx reviews with those of CADTH for pCODR or CDR

Revised challenge: What process should Alberta institute to ensure that there is adequate information collected on a CDx at the time a recommendation on the accompanying drug is made through pCODR or CDR?

Oct 2016: Proposal prepared by HTPU

Environmental Scan

- France (Haute Autorité de Santé (HAS))
- United Kingdom (National Institute for Health and Clinical Evidence Diagnostics Assessment Programme (DAP))
- Australia (Department of Health's PBAC and MSAC with Health Technology Assessment Access Point for Co-dependent and Hybrid Technologies)
- USA (CMS) – Molecular Diagnostic Program (MolDx); expedited if FDA approved CDx

Processes Across Countries

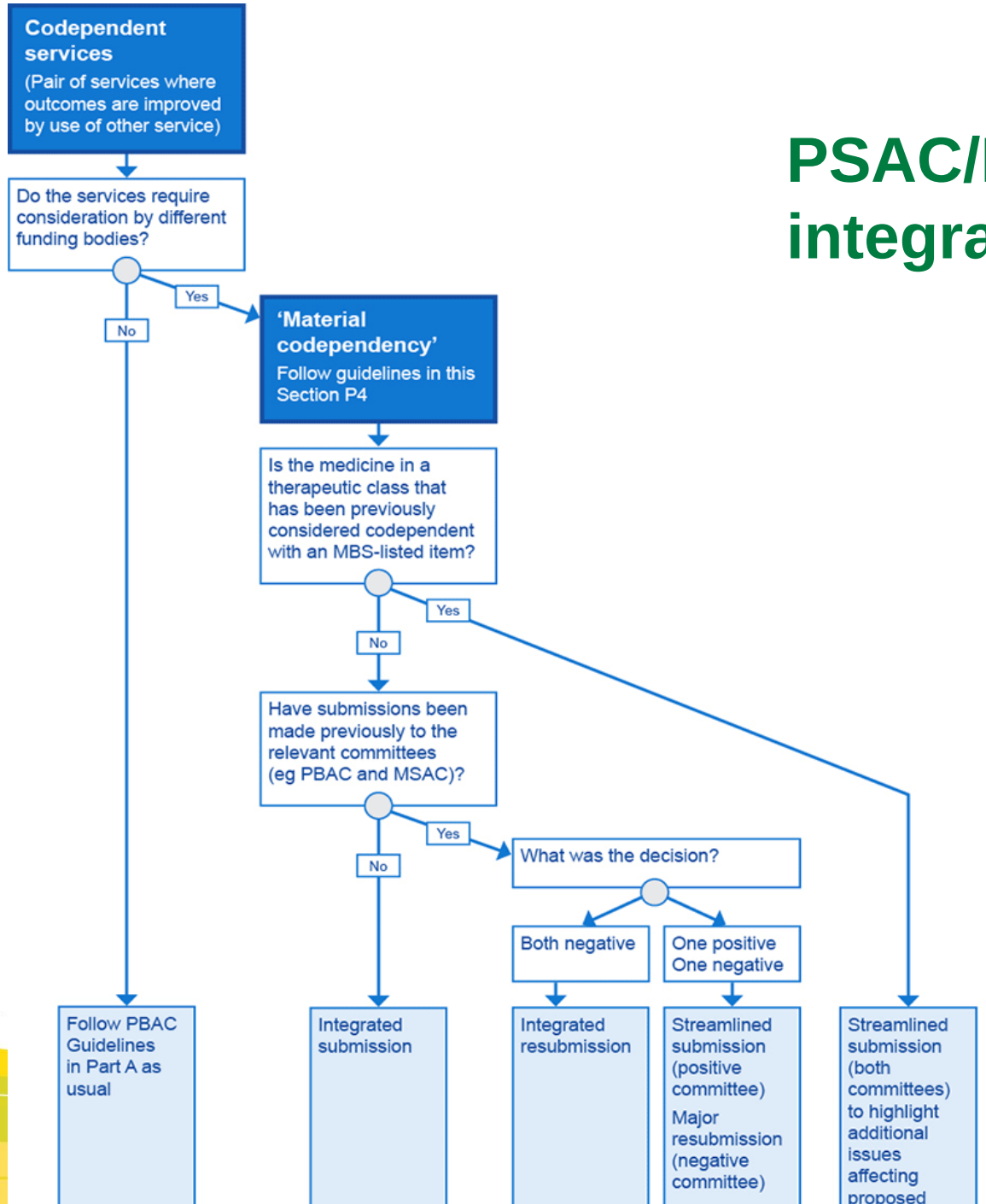
Standard protocol for assessment +/- analytical validity

Multidisciplinary advisory committees +/- input from patients, caregivers, diagnostics industry

Assessments performed by: independent groups (e.g. NICE DAP, MolDx), sponsors of technology (PBAC/MSAC; with critical appraisal]), or staff within review commissioning organization (HAS)

Duration: <6 months PBAC/MSAC, >12 months DAP, various HAS

PSAC/MSAC – mostly an integrated approach



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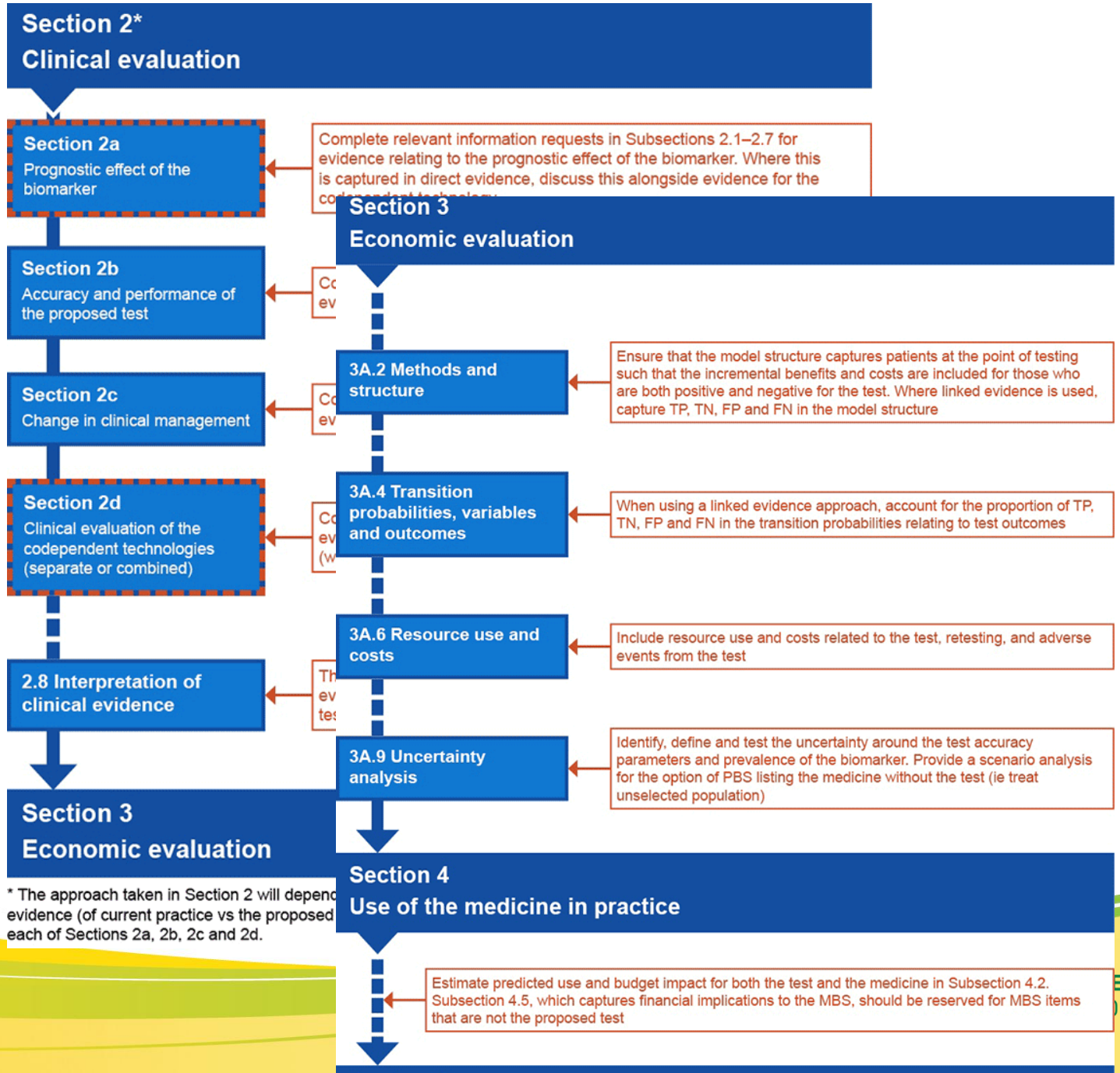
Section 2*
Clinical evaluation
Section 2a
Prognostic effect of the biomarker
Complete relevant information requests in Subsections 2.1–2.7 for evidence relating to the prognostic effect of the biomarker. Where this is captured in direct evidence, discuss this alongside evidence for the
Section 2b
Accuracy and performance of the proposed test
Section 2c
Change in clinical management
Section 2d
Clinical evaluation of the codependent technologies (separate or combined)
2.8 Interpretation of clinical evidence
Section 3
Economic evaluation
* The approach taken in Section 2 will depend
evidence (of current practice vs the proposed
each of Sections 2a, 2b, 2c and 2d.
Section 3
Economic evaluation
3A.2 Methods and structure
Ensure that the model structure captures patients at the point of testing such that the incremental benefits and costs are included for those who are both positive and negative for the test. Where linked evidence is used, capture TP, TN, FP and FN in the model structure
3A.4 Transition probabilities, variables and outcomes
When using a linked evidence approach, account for the proportion of TP, TN, FP and FN in the transition probabilities relating to test outcomes
3A.6 Resource use and costs
Include resource use and costs related to the test, retesting, and adverse events from the test
3A.9 Uncertainty analysis
Identify, define and test the uncertainty around the test accuracy parameters and prevalence of the biomarker. Provide a scenario analysis for the option of PBS listing the medicine without the test (ie treat unselected population)
Section 4
Use of the medicine in practice
Estimate predicted use and budget impact for both the test and the medicine in Subsection 4.2. Subsection 4.5, which captures financial implications to the MBS, should be reserved for MBS items that are not the proposed test

NICE

NICE Technology Appraisals programme and/or Diagnostics Assessment Programme (2010)

Several have gone through TA e.g. trastuzumab for early-stage HER2 positive breast cancer – clear desire to be pragmatic and not delay decisions on drugs

DAP used when 1) drug has already been assessed, 2) multiple test options are in use

60 week timeline, no apparent coordination with technology appraisals

E.g. gene expression profiling and expanded IHC for guiding chemotherapy in early breast cancer (2013), EGFR-TK testing for NSCLC (2013), **no others related to CDx identified on website of 29 assessments**

Byron et al. Clin Can Res 2014 20(6): 1469

Information Requirements

- **Clinical Effectiveness**
  - ***Analytical validity –*** *may include agreement between multiple tests*
  - ***Clinical validity –*** *especially if need to compare multiple tests without comparative utility*
  - ***Clinical utility*** **(impact of test results on clinical decision-making that leads to improved health outcomes) -** linked evidence approaches as necessary with evidence on prognosis and marker-enriched trials etc used
  - ***Local practice*** (e.g., testing strategies currently used in the province, number of tests performed, and external quality assessment schemes in place)

- **Economic Implications**
  - ***Cost-effectiveness of different testing strategies, +/- test***
  - ***Budget impact analysis***

- **System implications**
  - **Capacity of local laboratories to perform testing strategy identified as most clinically and cost-effective through the assessment**

Proposed Structure and Principles for Alberta Framework:

Five guiding principles: Patient-centered, Evidence-based, Transparent, Efficient, Quality

Information: STEP (**S**ocial and system demographics, **T**echnical effectiveness (and accuracy) review, **E**conomic evaluation & budget impact, **P**olicy considerations)

Decision making considerations: 1) Clinical need, 2) Health impact, 3) Affordability, 4) Implementation feasibility, and 5) Relevant social/ethical/legal considerations.

Timeline: ~6 months (at notice of submission of drug with CDx to CADTH); comprehensive for components assessed, but depth of analysis may need to vary, and limit stakeholder input to CDx Working Group and that provided within CADTH pCODR/CDR and other reports

Funding options & assessments: To be determined

Saga Cont.

Dec 2016: Decision to proceed with pilot using *PD-L1 biomarker IHC testing for advanced NSCLC*

April 2017: proposal & initiation of project

October 2017: S & T steps almost completed

Tumor PD-L1 as Companion Dx with PD-1/PD-L1 inhibitors for 1L or 2L treatment in advanced NSCLC in Alberta: Pilot assessment

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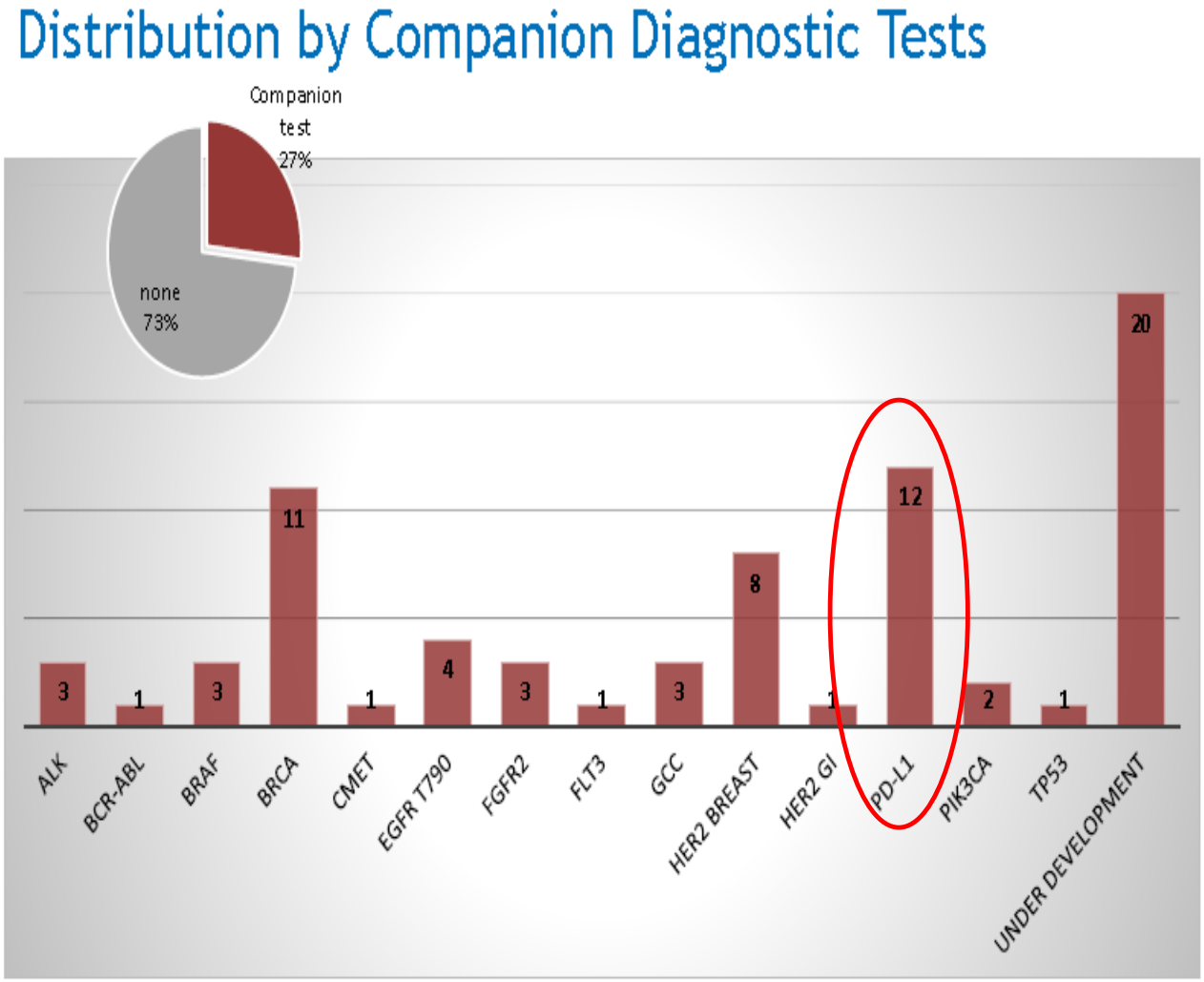
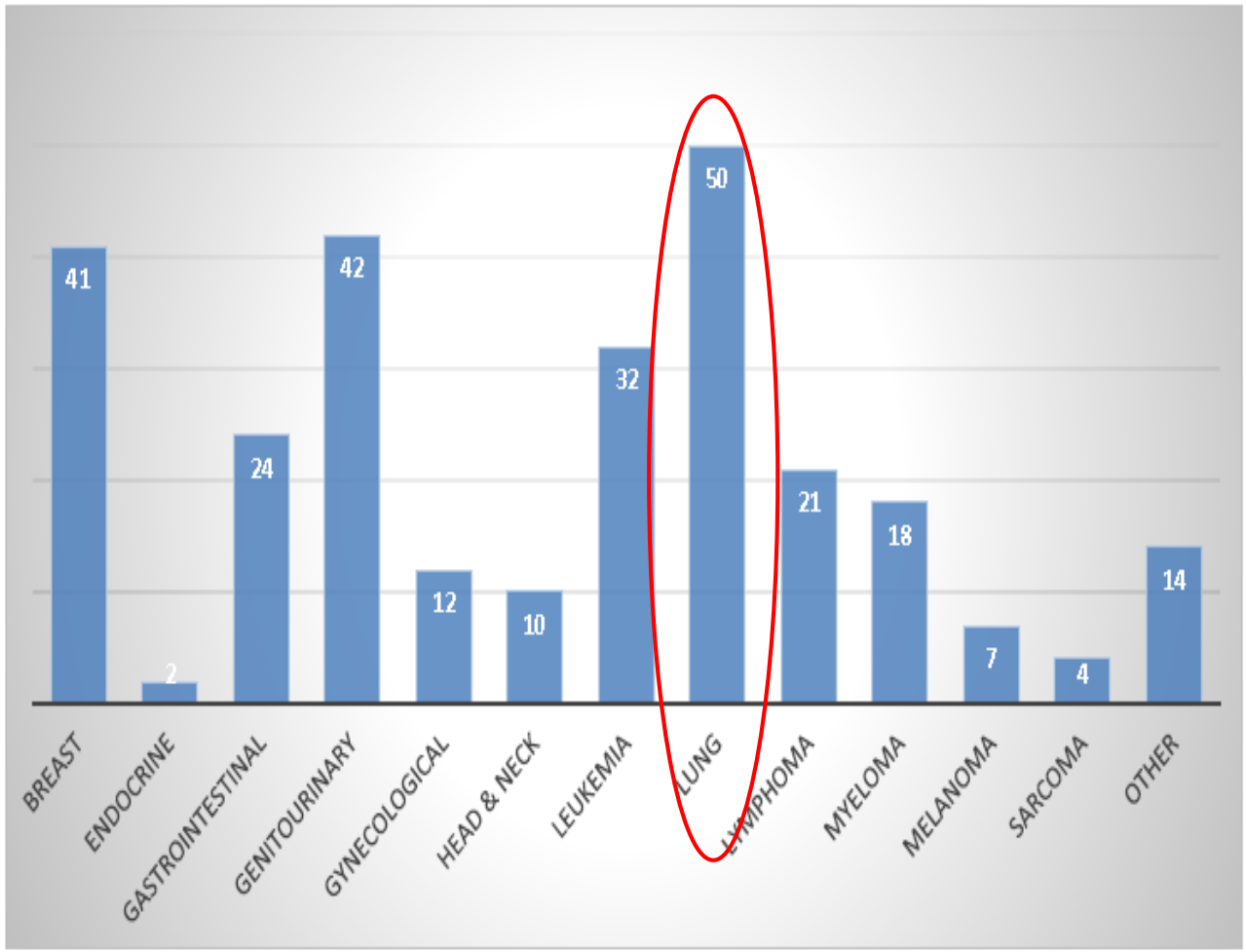
Cancer Drug Pipeline Mar 2017
CADTH
pCODR
https://www.cadth.ca/sites/default/files/pcodr/cancer-drug-pipeline-tracking-info-2017.pdf



Distribution by Tumour Site

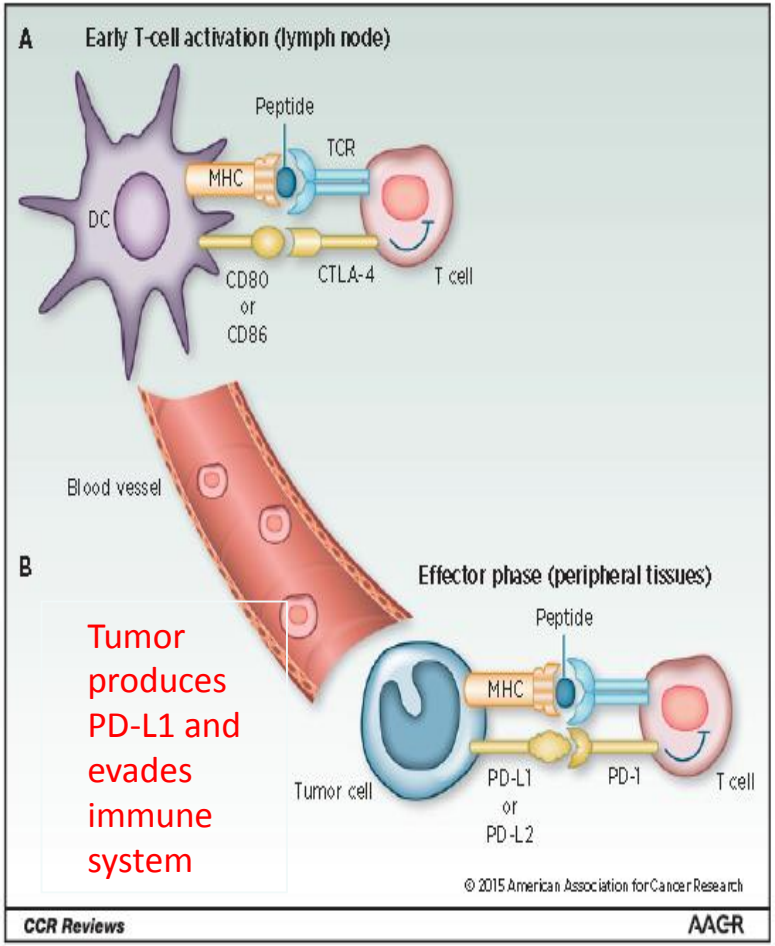


PD-1 Pathway and PD-L1

Tumor cell production of PD-L1 leads to their evasion of the immune response

Freeman 2000; Latchman 2001; Dong 2002

Therapeutic antibodies, *checkpoint inhibitors*, against PD-L1 or PD-1 act to restore an immune attack on tumor cells



Clin Cancer Res; 21(5) March 1, 2015

Companion Diagnostics (CDx)

Must offer sufficient ***clinical utility***, encompassing prediction of response for ***patient-important clinical outcomes*** as compared with an ***appropriate standard of care*** and ability to ***guide decisions*** by patients and clinicians. Poste et al., 2012; Williams et al., 2012; Khoury et al., 2009; Rogowski et al., 2009

Key evidence criteria

(i) There are no implications as a prognostic marker (e.g. no association with response without treatment or with SOC)

(ii) There is a *differential* response for those with a negative test result

(iii) The test has *sufficient* analytical and clinical validity

Current PD-1/PD-L1 inhibitors & immunohistochemistry tests serving as CDx (required) or "complementary diagnostics"

Drug	Pembrolizumab (with CDx)	Nivolizumab	Atezolizumab	Durvalumab	Avelumab
Diagnostic assay	Dako 22C3 antibody w/ EnVision FLEX visualization system on Automated Link 48 staining platform with DakoLink software	Dako 28-8 antibody w/ Dako EnVision FLEX visualization system on Dako Automated Link 48 staining platform with DakoLink software	Ventana SP142 w/ Benchmark Ultra with OptiView Universal DAB Detection Kit and OptiView Amplification Kit	Ventana SP263 antibody w/ Benchmark Ultra with OptiView Universal DAB Detection Kit	Proprietary assay with 73-10 antibody (Dako)
Scoring method	% tumor cells with membrane staining at any intensity	% tumor cells with membrane staining at any intensity	% tumor cell *or* % area with tumor-infiltrating immune cells	% tumor cells with membrane staining	% tumor cells with membrane stained at any (1 & 5%) and moderate-to-high intensity (25%)
Thresholds in trials	<1%, ≥1%-49%, ≥50%	<1%, ≥1%, ≥5%, ≥10%	≥1-<5%, ≥5-49%, ≥10% (IC only), ≥50% (TC)	≥25%	≥1%, ≥5%, ≥25% (moderate-to-high intensity)

Policy Questions

Should PD-L1 testing be provided through the publicly funded healthcare system in Alberta?

What is the appropriate use of PD-L1 testing in Alberta's publicly funded healthcare system?

Social and system demographics

What is the *burden of illness and anticipated need* for PD-L1 testing for NCSLC in Alberta?

Is PD-L1 testing *anticipated to be used within clinical practice* for NSCLC to inform treatment decisions in Alberta? Where does PL-L1 testing currently fit within the treatment algorithms for NSCLC, and how will it alter care?

What is the *capacity for PD-L1 testing in Alberta*, including use of tests included in clinical trials and other available commercial or LDTs? Would the capacity change in the future depending on the patient populations indicated for PD-L1 testing?

Technical effects and effectiveness

Are currently available PD-L1 assays *analytically valid*?

Is *clinical validity* specific to PD-L1/PD-1 inhibitor treatment or is *PD-L1 expression also prognostic for response with current standard of care*?

Does PD-L1 testing provide *clinical utility*, in terms of *patient-important benefits and harms*, for medical decision making with respect to using pembrolizumab or other PD-L1/PD1 inhibitors compared with *standard care*?

What is the *comparative effectiveness between different PD-L1/PD1 inhibitors* versus standard of care, across all NSCLC patients and those at various PG-L1 thresholds?

Economic evaluation

Is testing with PD-L1 for treatment with PD-L1/PD1 inhibitors cost-effective for the current labelling for PD-L1/PD1 inhibitors? Are there differences *between different assays or different drugs* in terms of cost-effectiveness?

What are the *unit and total costs of providing PD-L1 testing to the population for which it is currently indicated*?

What is the *budget impact* for using PD-L1 test(s) with NSCLC treatment as currently indicated?

Who should be responsible for these costs?

Public policy analysis

How do *patients value* PD-L1 testing and their treatment experience with PD-L1/PD1 inhibitors?

What *social, ethical, and legal considerations* are relevant to answering the policy question?

How will resources (e.g. infrastructure, people, training, programs, existing services, etc.) be impacted by different policy decisions?

Is implementation of a policy decision *feasible*? What are potential *approaches*, *facilitators, and barriers* to implementing a policy decision?

Information sources

- CADTH pan-Canadian Oncology Drug Reviews
- Primary literature including grey literature
- NSCLC stats (current and projected) relevant to eligibility for PD-L1 inhibitors
- Drug and CDx currently listed pricing
- Alberta CDx Working group & thoracic oncology
- Clinical trial registries

Progress

- Input from oncology specialists on current clinical algorithm for advanced NSCLC

- Database searches (>3000 citations), study selection and data extraction
  1. Clinical utility, directly provided via RCTs (n=8) or allowing for a linked-evidence approach combining data from single-arm trials (n=8) with data from the control arm in RCTs
  2. Prognostic role of PD-L1 expression in advanced NSCLC (n=20)
  3. Analytical & clinical validity (n=26)
  4. Economic evaluations (n=5)

- Input from CDx Working group members from Oncology IHC laboratory on current and future needs for PD-L1 testing across Alberta

- **Iterative, targeted approach used based on current needs and hierarchy and "directness" of evidence**

Recommended Options

Possible decision may include:

1) Provide to all patients
2) Provide to a subgroup of patients, who meet certain eligibility criteria
3) Provide for an interim period while additional evidence is collected
4) Do not provide

CADTH on Drugs with CDx

Nov 2016 proposal & solicitation of input

June 2017 approved approach released, effective Oct 2017

No independent assessment of CDx, rather

“investigate factors relevant to testing that would inform the implementation of associated drugs under review by CADTH pCODR or CDR”

Component of review	CDx Review Input CADTH	Province	Who needs to be involved
Analytical validity	No	Yes	• HTA unit • AHS Lab • CCLMAC or equivalent for non-cancer
Clinical validity	No	Yes	• HTA unit • AHS Lab • CCLMAC or equivalent for non-cancer
Clinical utility	Yes, but may be limited	Yes	• HTA unit • AHS Lab • Clinicians (e.g., provincial tumor groups) • CCLMAC or equivalent for non-cancer • Provincial pharmacy
Cost-effectiveness	Depends on reporting; fixed	Yes	• HTA unit • AHS Lab and Finance • Provincial pharmacy • CCLMAC or equivalent for non-cancer
Budget impact	Yes, but not specific to jurisdiction	Yes	• HTA unit • AHS Lab and Finance • CCLMAC or equivalent for non-cancer
System feasibility and implementation Patient experiences	Yes, but not specific to jurisdiction	Yes	• HTA unit • AHS Lab and Finance • Provincial pharmacy • CCLMAC • AHS clinical managers/directors

Lessons Learned and Salient Issues

- Stakeholder input essential to refine review scope to context & current decision needs
- Provincial healthcare system context will shape requirements
- Key parameters of analytical validity are very important to consider, even for implementation (e.g., sample timing); caution with proceeding on ‘any valid test’ without including clinical data
- Difficulty assessing value if not aligned/coordinated with provincial drug review
- Ongoing, highly active research area – does this impact confidence in making funding decisions and/or manner in which provinces should make policy decisions?

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