Innovation, Uncertainty and Reimbursement Processes in Precision Medicine: The Case of PD-L1

Monday, October 17, 2016

MaRS Discovery District, Toronto

This session was generously sponsored by Merck Canada Inc.

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Meet the Panel

Moderator:

- Barry Stein (Colorectal Cancer Association of Canada)

Speakers:

- Lillian Siu (Princess Margaret Cancer Centre)
- Reiner Banken (Reiner Banken Consulting)
- Scott Gavura (Cancer Care Ontario)

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Session Overview

- Developments in precision medicine provide hope of highly targeted treatments, improving both clinical benefits for patients and effective use of scarce resources in health care. Promising diagnostic tests for selecting groups of patients for treatment are being introduced in health care at an increasingly rapid pace. Early access for high medical need must take into account and manage the uncertainties around value for the patient and for the health system.
- PD-L1 testing in cancer care is the first example where multiple drugs are targeting the same molecular pathway, each drug with its own companion diagnostic test. In spite of the unprecedented collaboration between the different companies involved (Blueprint Project), the drugs are starting to enter the Canadian Health Care System with great uncertainties on the need and benefits for PD-L1 testing and the appropriate choice of a companion diagnostic test for a specific drug.
- The session aims for a dialogue on patient, clinician, health technology assessment and payer perspectives on introducing PD-L1 drugs and companion diagnostics under great uncertainty and a rapidly evolving evidence base.

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Session Timing

15:00	Reiner Banken	Open the session and introduce Barry Stein
15:05	Barry Stein	Introduce session and introduces Lillian
15:10	Lillian Siu	Presentation
15:20	Barry Stein	Introduce Reiner
15:22	Reiner Banken	Presentation
15:32	Barry Stein	Introduce Scott
15:34	Scott Gavura	Presentation
15:44	Barry Stein	Presentation
15:50	All	Comments from presenters : 2 minutes each
16:00	All	Questions from audience
16:13	Barry Stein	Closing of session

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Promises and Challenges of PD-L1 in Clinical Practice

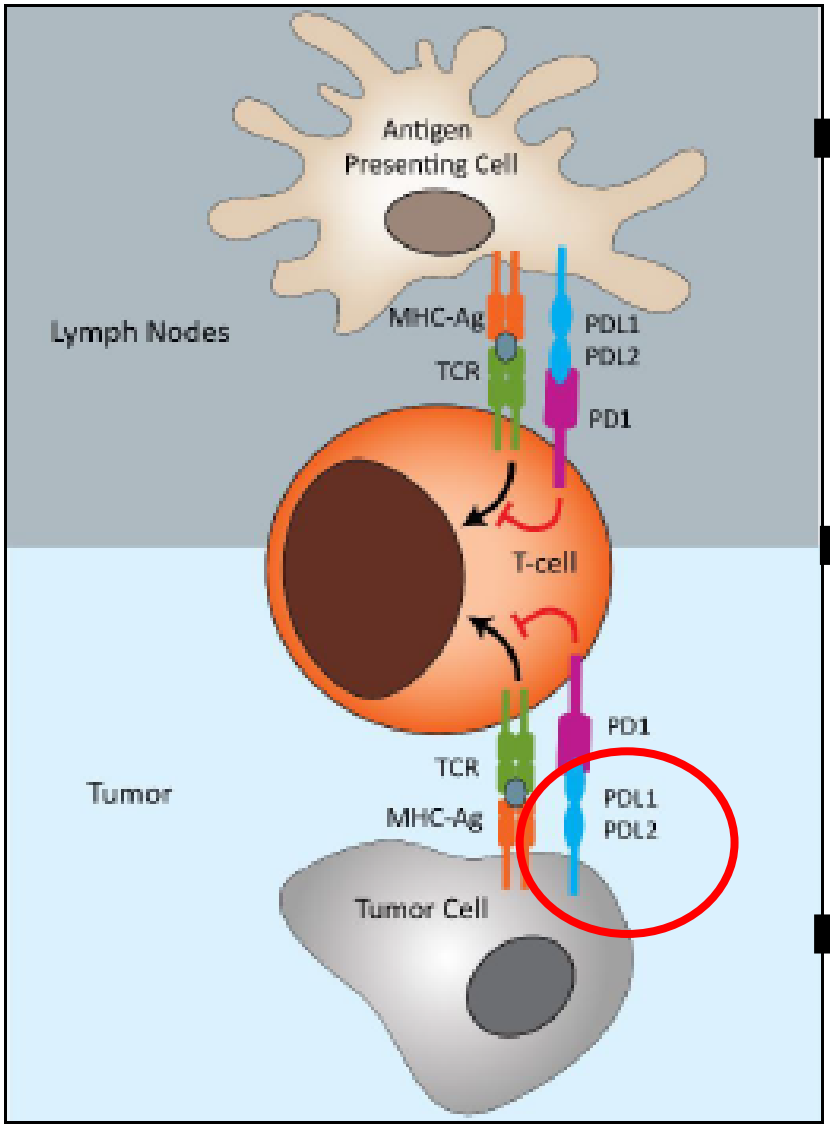
Lillian L. Siu, MD
Princess Margaret Cancer Centre, Toronto, Canada

CAPT 2016, October 17, 2016, MaRS Discovery District

UHN Princess Margaret Cancer Centre

UNIVERSITY OF TORONTO

Interactions Between Antigen Presenting Cells, T Cells and Tumor Cells



Antigen presenting cell

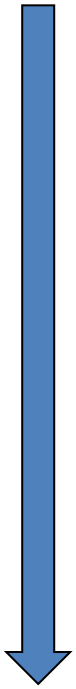
T cell

Tumor cell

Adapted from Zang *et al.* Clinical Cancer Research 2007

Analytical and Clinical Characteristics of Biomarkers

Discovery



Clinical validity:
The test result shows an association with a clinical outcome of interest

Analytical validity:
The test's performance is established to be accurate, reliable, and reproducible

Clinical utility:
Use of the test results in a favorable benefit to risk ratio for the patient

Comparison of PD-L1 Assays

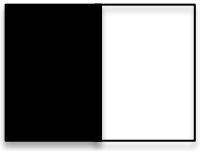
		pembrolizumab (Keytruda, MK-3475)	nivolumab (Opdivo, BMS-936558)	durvalumab (MEDI-4736)	atezolizumab (MPDL3280A, RG7446)
Drug	Manufacturer	Merck Sharp & Dohme	Bristol-Myers-Squibb	MedImmune/ AstraZeneca	Genentech/ Roche
	mAb	humanized IgG4	human IgG4	human Fc-modified IgG1	human Fc-modified IgG1
	Target	PD-1	PD-1	PD-L1	PD-L1
	FDA approved	Melanoma, NSCLC, SCCHN	Melanoma, NSCLC, renal, HD	Bladder*	Bladder, NSCLC*
Companion Diagnostic Assay PD-L1+	IHC assay developer	Dako	Dako	Ventana	Ventana
	Antibody clone	22C3 mouse	28-8 rabbit	SP263 rabbit	SP142
	Expression on	TCs and stroma	TCs	TCs	TICs and TCs
	Cut-off	▪ Melanoma, Bladder, NSCLC: ≥1% TC (or any tumor stroma cell)	▪ NSCLC: ≥1-5% TC ▪ Renal: ≥5% TC	▪ NSCLC, SCCHN: ≥25% TC	▪ Bladder, NSCLC, Breast: IHC 2+ ≥5%-<10% TC or TIC or IHC 3+ ≥10% TC or TIC

* FDA Breakthrough Designation Therapy status

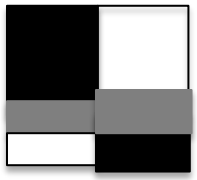
TCs = tumor cells; TIC= tumor-infiltrating immune cells; n/a, not applicable

Hansen, Siu JAMA Oncology, 2016

“Companion” vs “Complementary” Diagnostic



- **Companion Diagnostic:**
  - “Provides information that is essential for the safe and effective use of a corresponding drug or biological product”
  - e.g. PD-L1 IHC 22C3 for pembrolizumab in NSCLC



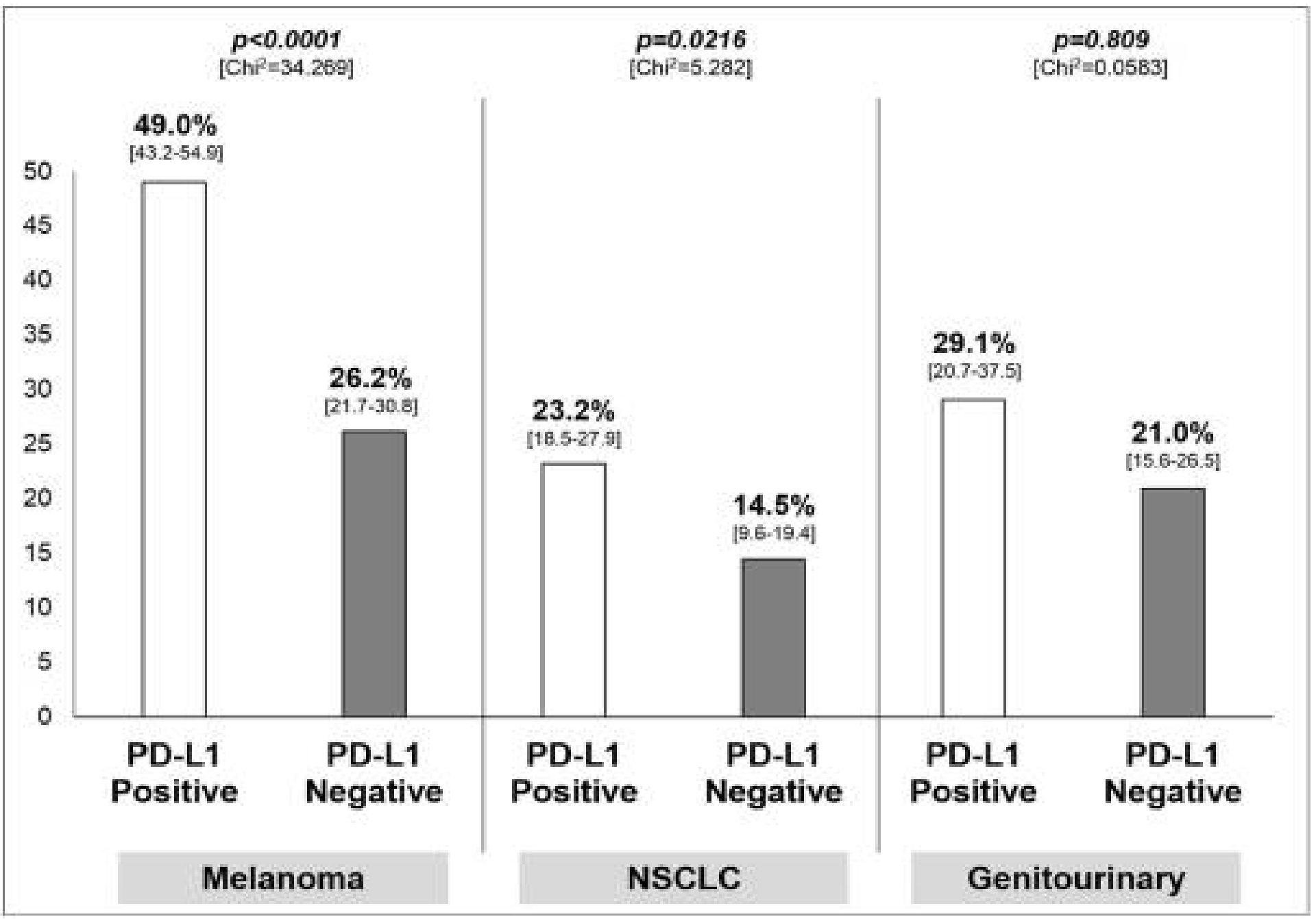
- **Complementary Diagnostic:**
  - ”Not required but aids risk/benefit assessment fro drug use in individual patients”
  - e.g. PD-L1 IHC 28-8 for nivolumab in NSCLC and melanoma, PD-L1 IHC SP142 for atezolizumab in bladder cancer

List of FDA Cleared or Approved Companion Diagnostic Devices

Drug Name	Device Trade Name
Trastuzumab Pertuzumab	**HER2** FISH PharmDx Kit
	HERCEPTEST
Trastuzumab	INSITE **HER-2/NEU** KIT
	Bond Oracle **Her2** IHC System
	SPOT-LIGHT **HER2** CISH Kit
	HER2 CISH PharmDx Kit
	INFORM **HER2** DUAL ISH DNA Probe Cocktail
	PATHVYSION **HER2** DNA Probe Kit
	PATHWAY **ANTI-HER2/NEU** (4B5) Rabbit Monoclonal Primary Antibody
Olaparib	**BRACA**nalysis CDx™
Imatinib	DAKO **C-KIT** PharmDx

Drug Name	Device Trade Name
Gefitinib	Therascreen® **EGFR** RGQ PCR Kit
Afatinib	
Erlotinib	cobas **EGFR** Mutation Test
Crizotinib	VENTANA **ALK** (D5F3) CDx Assay
	VYSIS **ALK** Break Apart FISH Probe Kit
Cetuximab and Panitumumab	cobas® **KRAS** Mutation Test
Vemurafenib	COBAS 4800 **BRAF V600** Mutation Test
Trametinib Dabrafenib	THxID™ **BRAF** Kit

http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm



Carbognin L, et al. PLoS One. 2015, 10(6):e0130142.

PD-L1 Assays

Challenges:

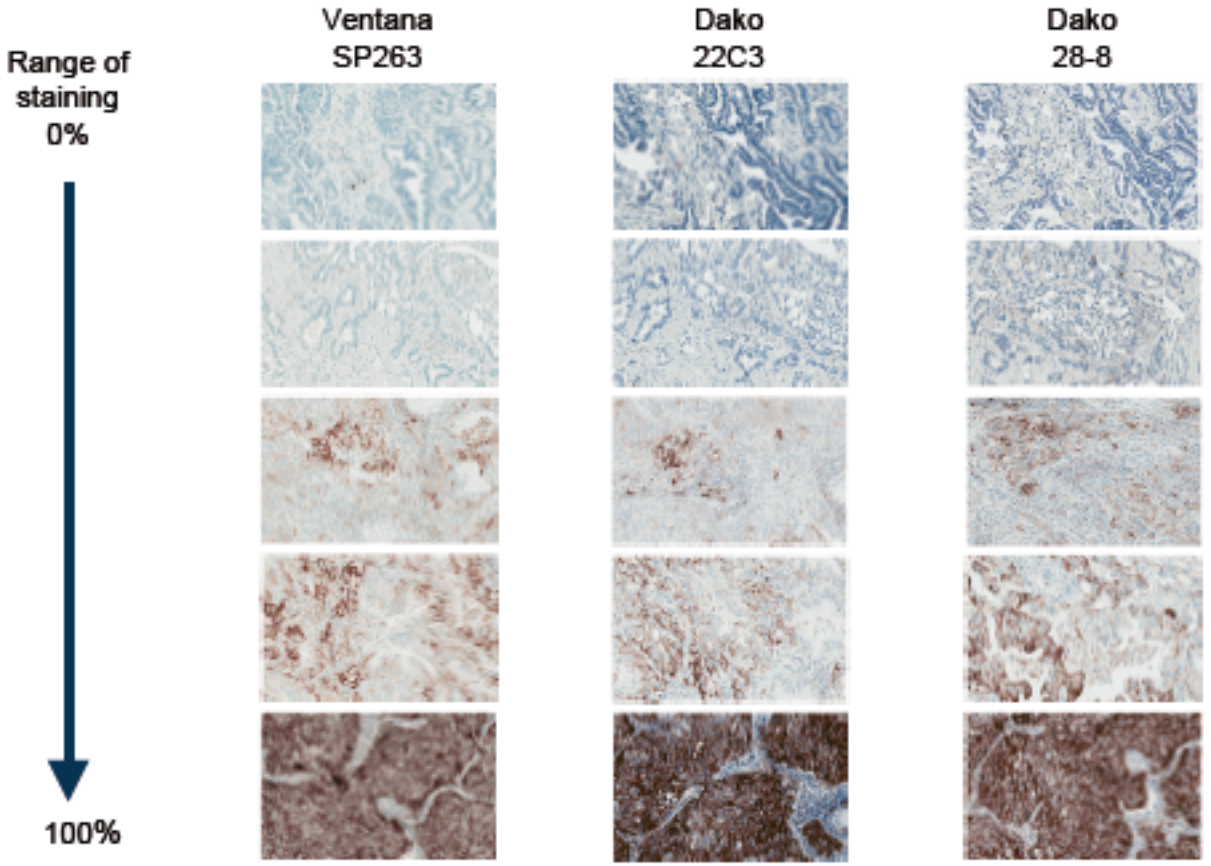
- Different antibodies being used
- Variable definitions for biomarker positivity (which cells/tissue components, different staining thresholds used as cut-offs)
- Lack of standardization and harmonization
- Challenging to make comparisons across trials that used different assays with different definitions

Blueprint and Other PD-L1 Comparative Projects

PD-L1 Membrane Staining

- All three PD-L1 assays showed similar patterns of staining (**Figure 1**)

Figure 1. IHC Images from the Three Diagnostic Assays



The Blueprint Project: Harmonizing Companion Diagnostics Across a Class of Targeted Therapies, AACR 2016; Ratcliffe et al AACR 2016

An HTA perspective on Innovation, Uncertainty and Reimbursement: The case of PD-L1

Canadian Association for Population Therapeutics Annual Conference
Toronto, October, 17th, 2016

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Conflicts of interest

- Work in a governmental HTA agency for many years.
- Work as a consultant with different companies over the last 12 months.
- Recent work with Roche Diagnostics on PD-L1 in Canada.

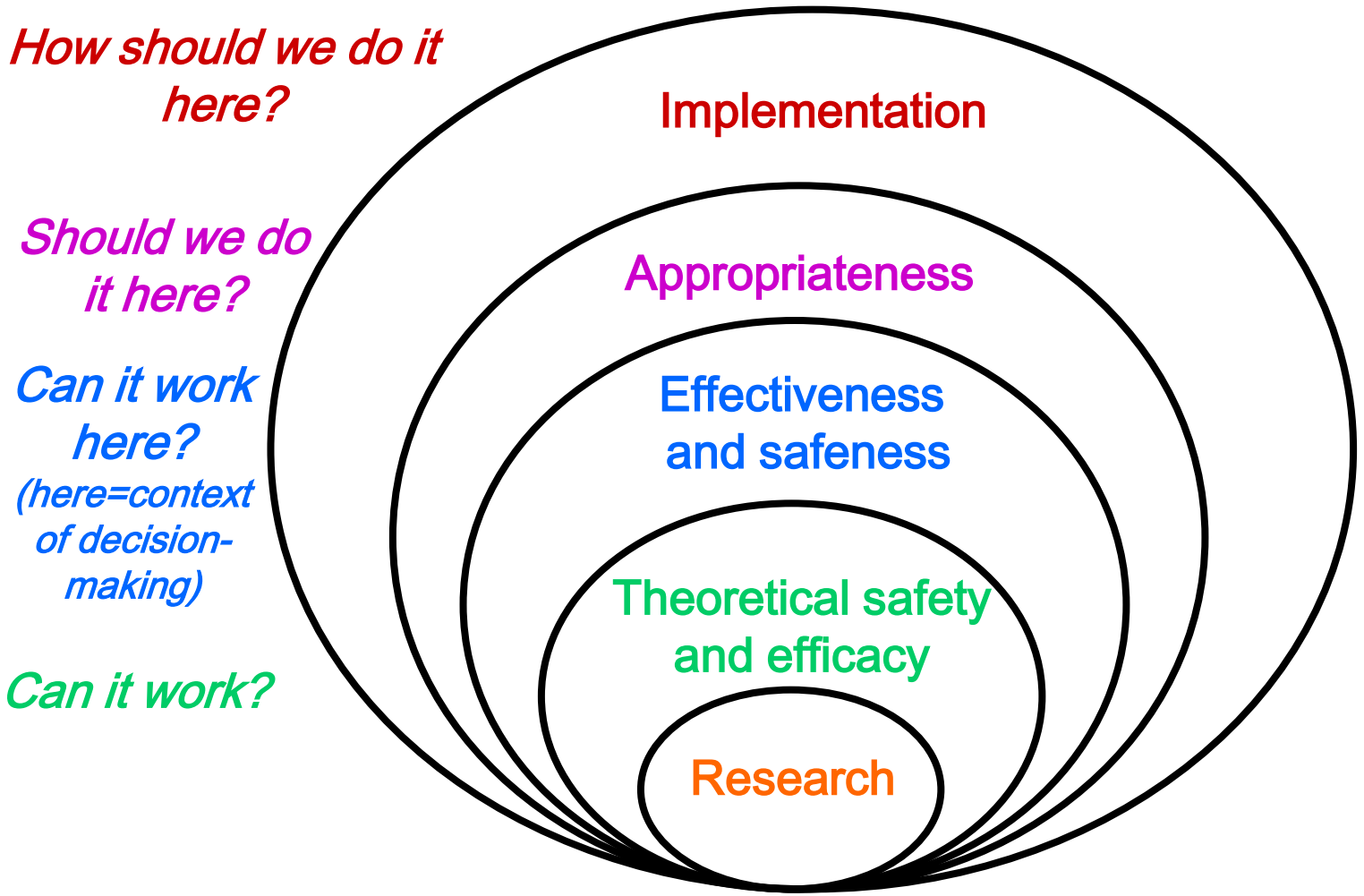
The origin of Health Technology Assessment

Request of the US Congress Senate Committee on Human Resources to OTA in 1974: « whether a reasonable amount of justification should be provided before costly new medical technologies and procedures are put into general use»

Decisions based on needs expressed by physicians

Decisions based on (informed by) a formal and transparent assessment of the evidence

Reasoning in HTA



- HTA depends on available primary studies.
- HTA must deal with uncertainties in knowledge.
- HTA can be a hurdle or an enabler for innovations.

Adapted from Health technology assessment of medical devices. WHO Medical device technical series, 2011. Available at: http://whqlibdoc.who.int/publications/2011/9789241501361_eng.pdf

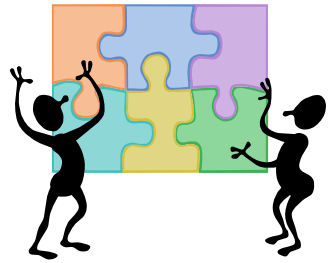
The case of PD-L1

- PD-L1 assays inform decision-making for PD-L1 immunotherapies for an increasing array of cancers.
- Rapidly evolving knowledge on the role of PD-L1 immunotherapies in treatment algorithms and the place of PD-L1 assays (ex resistance).
- Different commercial PD-L1 assays for different PD-L1 drugs and laboratory developed PD-L1 tests (30 to 50% in the US)
- Patient benefits with PD-L1 immunotherapies, increased for PD-L1 positive cancers
- Immunotherapies costing around 10 000$ per month, PD-L1 assays around 100$ for each test

Decision-making for introducing PD-L1 tests

1. Mandatory HTA process only in Québec. HTA informing central decision-making processes. No decision-making at the hospital level.
2. Fragmented decision-making at the provincial and the hospital level in Ontario, centralised assessment process if dedicated funding. HTA if involvement of HQO.
3. Ad hoc assessment of companion and complementary diagnostics. No integrated assessment frameworks for assays and drugs
4. No evidence development pathways in health systems in Canada (such as real world evidence development, coverage with evidence development, adaptive pathways, living labs)

Challenges



- How to provide patient access to PD-L1 assays for patient and for health systems benefit?
    - How to introduce PD-L1 tests under evolving uncertainties of analytic and clinical validity and clinical utility?
        - How to develop dynamic HTA systems linked to collaborative, patient-centered evidence-development pathways?

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A Payer's Perspective: Innovation, Uncertainty and Reimbursement Processes in Precision Medicine in Oncology

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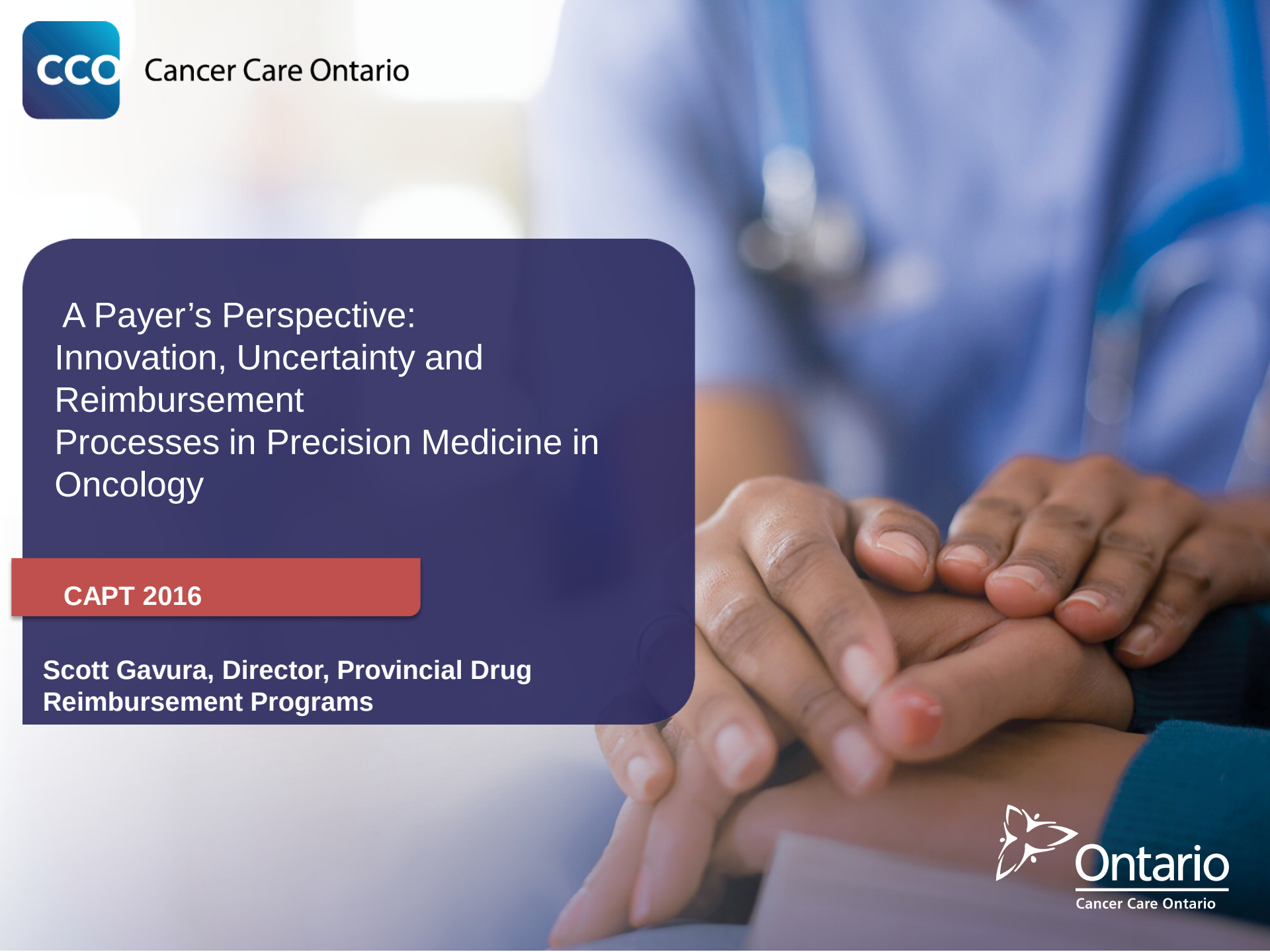
Scott Gavura, Director, Provincial Drug Reimbursement Programs



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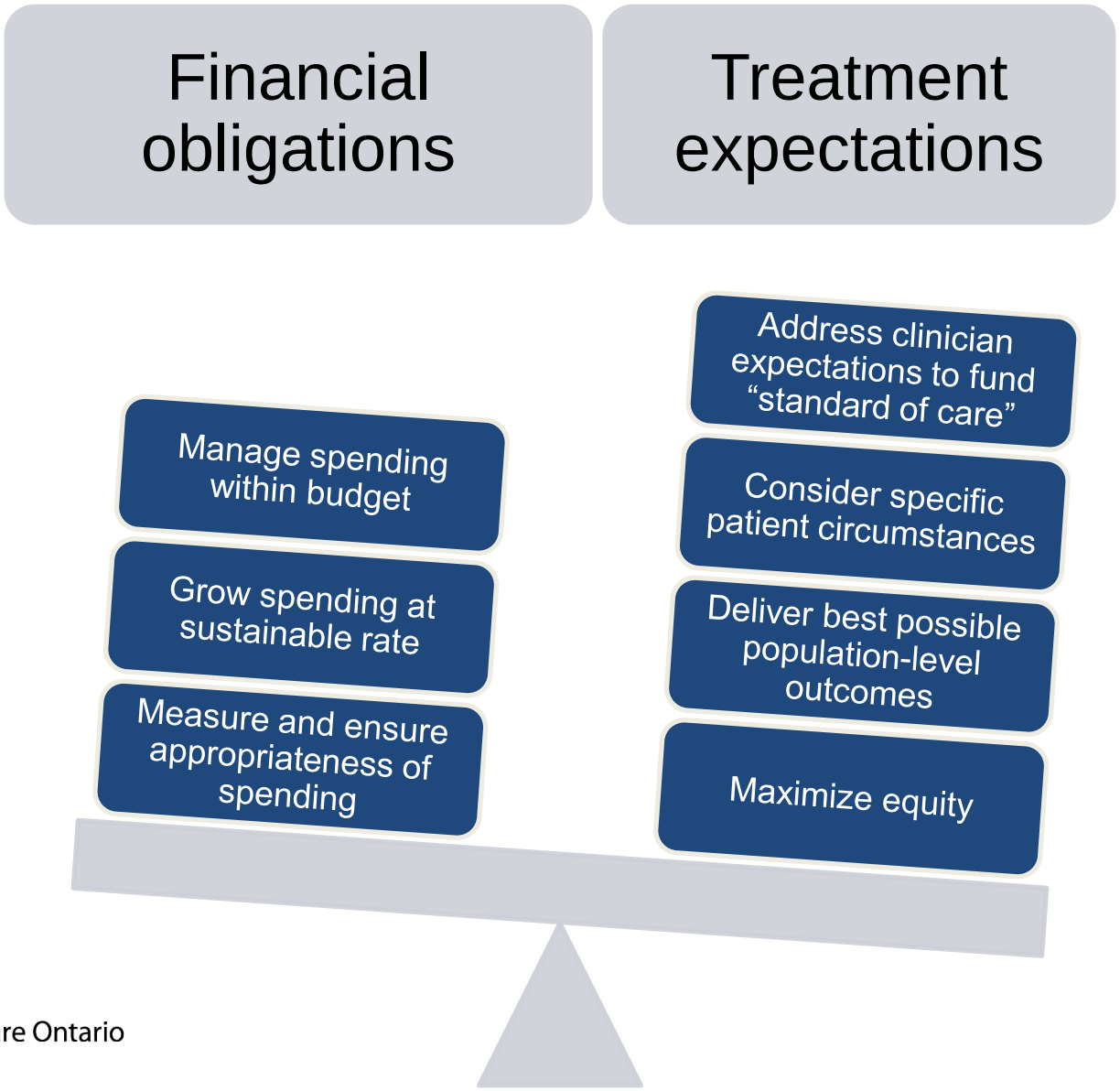
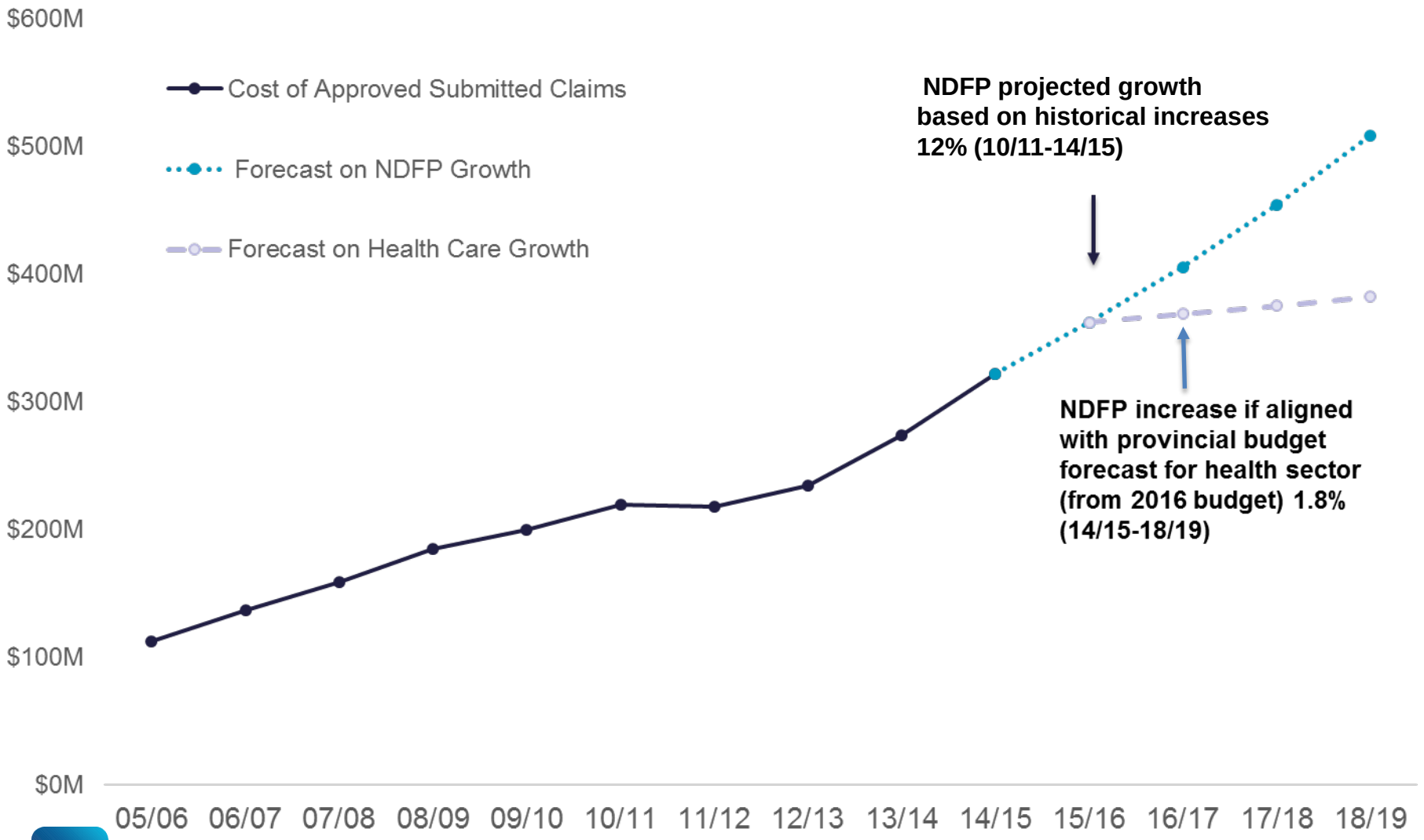
Disclosures

The speaker has no financial or other conflicts of interest to report.

Balancing funding obligations and demands



The sustainability challenge



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Drug costs for claims approved under the New Drug Funding Program.

Implementation challenges

- Drug-specific funding decisions in face of uncertainty
- Multiple new entrants, simultaneously
  - Further increasing uncertainty
- Need to ensure testing in place, simultaneously with drug funding
  - Unique drug/test pairing increases challenge.

The result: Complexity of incorporating adaptive pathways into population-level funding programs

Can we collect and use real-world evidence?

- The vision: a “learning” health system/reimbursement system
  - Ideally, link payment to outcomes **realized** vs. **expected/anticipated**
- Validate assumptions we made during our assessment
  - Possible to confirm clinical- and cost-effectiveness?
- Increase overall confidence in our reimbursement decisions
  - Resolve uncertainty remaining from decision-making process

Can RWE do all this?

- Insufficient information often available to demonstrate a new treatment provides a meaningful clinical benefit.
- Rapid introduction of new therapies means study population may not be representative of target population (e.g., exposure to other therapies)
- Evolving understanding of PD-L1 expression and relationship with tumor response

What data could RWE encompass?

- Treatment data / Rx claims data
- Outcomes data
- Genomic data
- Socioeconomic data
- Patient-generated data (e.g., PRO's)

What barriers exist?

- There's a lack of consensus on the implementation approach.
- There's an incremental cost to collecting, cleaning maintaining and analyzing datasets developed expressly for RWE use.
  - Build this into implementation plans?
- We lack a common framework (across multiple stakeholders, gov't and non gov't) that defines how RWE data will be integrated and used.

Cancer Care Ontario

A Payer's Perspective: Innovation, Uncertainty and Reimbursement Processes in Precision Medicine in Oncology

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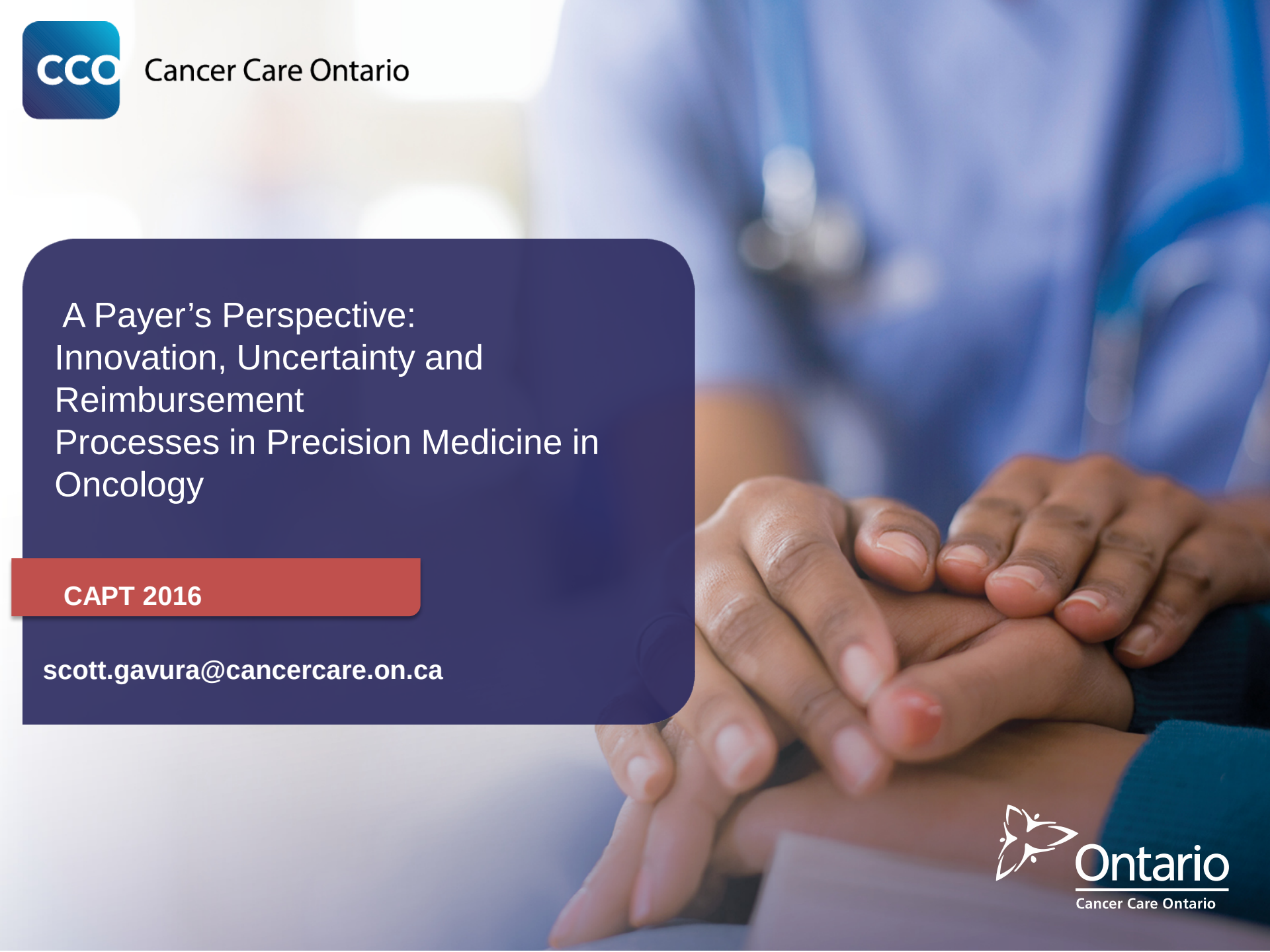

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Immuno-Oncology Policy

TO REIMBURSE PD-L1 PREDICTIVE BIOMARKERS … OR NOT?

THAT IS THE QUESTION.

CAPT
Toronto
October 17, 2016

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Colorectal Cancer Association of Canada

Immuno-oncology Therapies

Enabling The Body's Immune System To Fight Cancer

- Immunotherapy targets the body's immune system, rather than the tumour itself. Selectively recognises & targets cancer cells, not healthy cells.

- Gives long-lasting memory to the immune system, enabling it to continually adapt to the cancer over time & provide durable, long-term response to cancer with fewer side effects.

- Several drugs have already been developed and many more are in pre-clinical and clinical development stage targeting advanced melanoma, lung, bladder, prostate, colorectal and pancreatic cancer, providing hope for patients in some cases where no effective treatments were previously available.

- **How can we ensure patient access to this new and possibly game changing technology?**

Colorectal Cancer Association of Canada

Policymakers, Regulatory Authorities, Health Professionals & Patients Require A Better Understanding of IO In Cancer Treatment

- The complexity of immuno-therapy drugs, the high number of patients and the high costs of these drugs necessitate a better understanding of IO drugs and their predictive biomarkers being used in clinical practice to identify the appropriate patient for the right drug.

- IO therapies and their predictive biomarkers are somewhat imprecise and variable, but are being integrated into cancer plans and policies.

- Need to ensure alignment between regulatory and reimbursement authorities taking into account the benefits of IO.

- **The PD-L1 (Programmed-death ligand1) protein is at the center of clinical decisions for selecting patients who are most likely to benefit from immuno-therapy in connection with checkpoint blockade drugs.**

Colorectal Cancer Association of Canada

PD-L1, New Combinations & Future Biomarkers

- The next 5 -10 years will see an increasing role for immunotherapy and select predictive biomarkers will be vital in determining the appropriate responders.

- For those that do not respond, we may be able to turn non immunogenic tumours into ones that that become amenable to immunotherapy by doing such things such as combining anti PD-L1 therapies with MEK* inhibitors in Microsatellite-Stable mCRC patients…providing more hope for patients.

- PD-L1 predictive biomarkers are under fire and attention is beginning to turn the possibility of other biomarkers such as TMB (Tumour Mutational Burden).
- **At present however, selecting patients based on PD-L1 expression, however imperfect, seems to be the most significant marker for some types of cancer such as NSCLC as highlighted at the recent ESMO 2016 annual meeting.**

Colorectal Cancer Association of Canada

*A MEK inhibitor is a drug that inhibits mitogen activated protein kinase enzymes MEK1 and or MEK2. They have the potential for treatment in KRAS/BRAF mutated CRC.

ANTI PD-L1 THERAPY AT ITS BEST

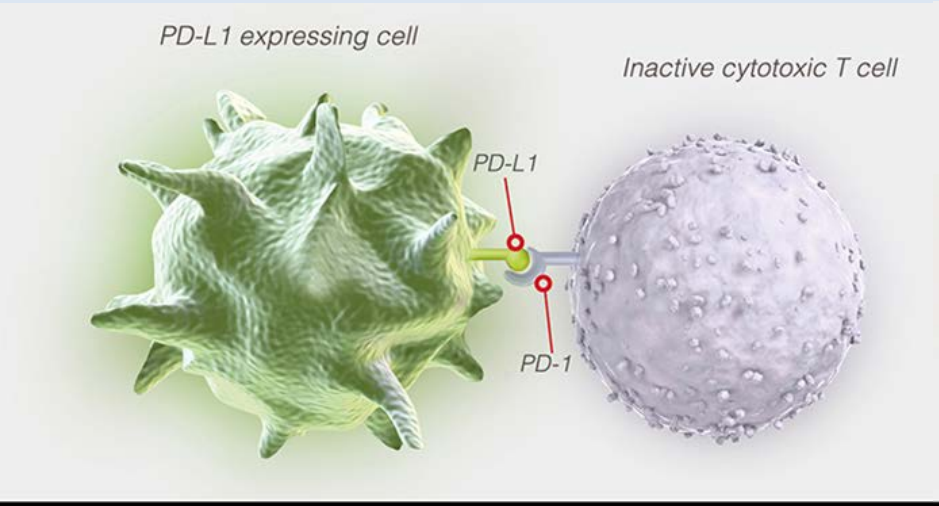

Figure 1: Inactivation of T cells limits damage to normal tissue.

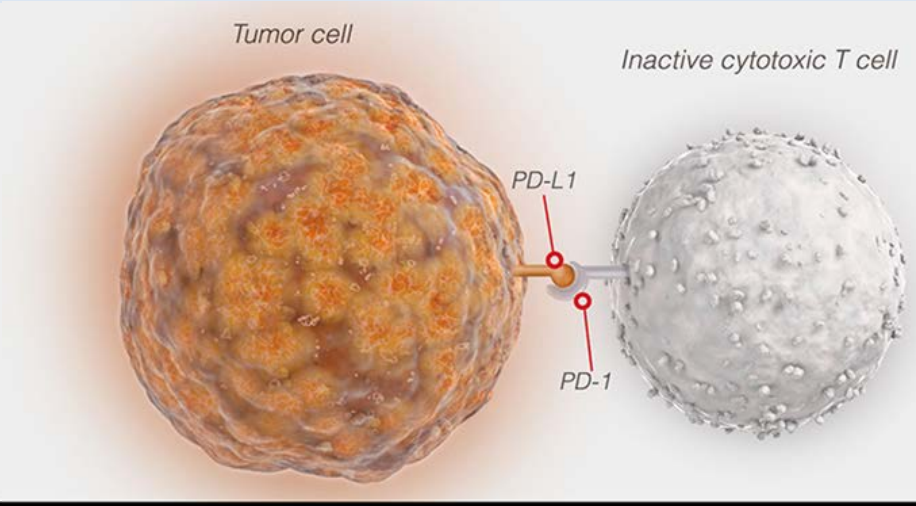

Figure 2: Inactivation of T cells reduces tumor cell death and elimination.

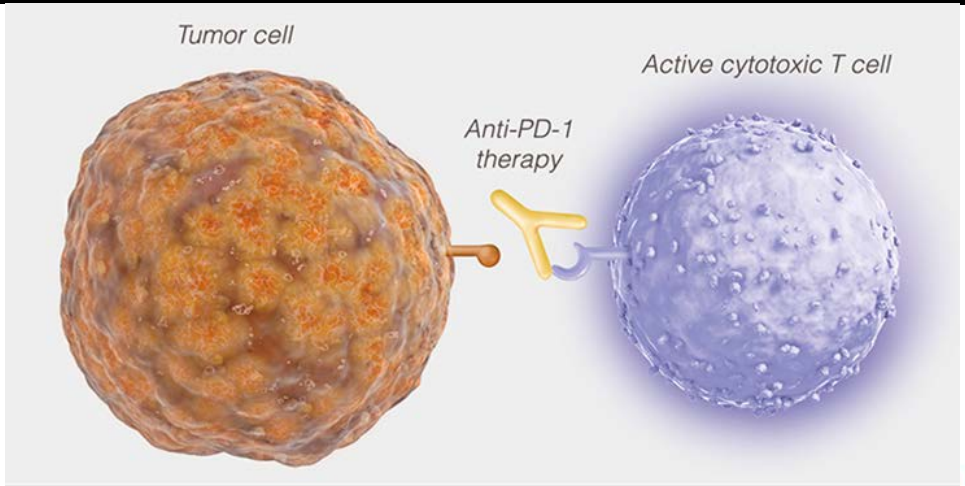

Figure 3: Blocking the PD-1/PD-L1 interaction enables active T cells and tumor cell death and elimination.

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