Coverage With Evidence Development: The Ontario Experience

Evidence Generation for Genomic Diagnostic Test Development

Institute Of Medicine Workshop

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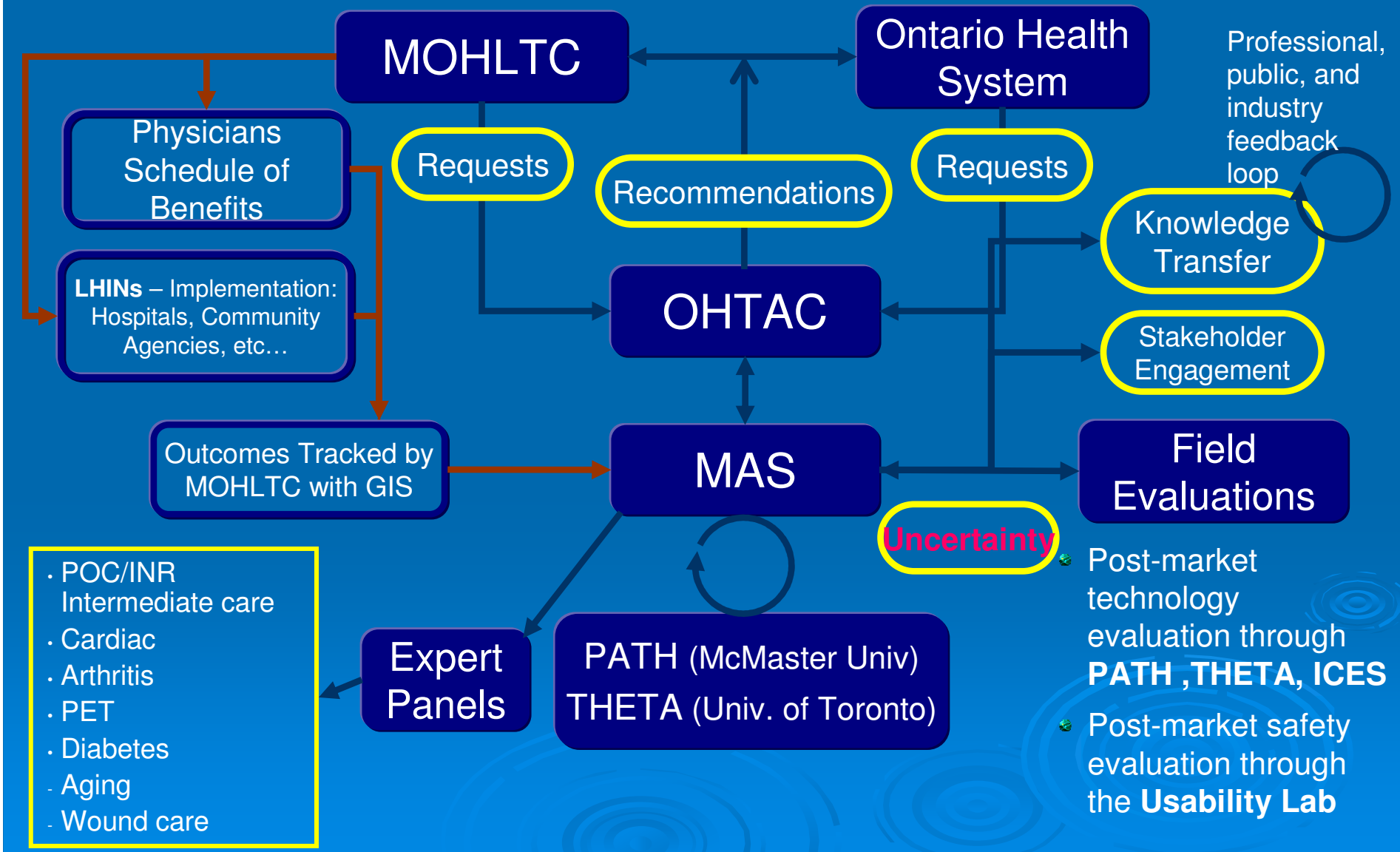
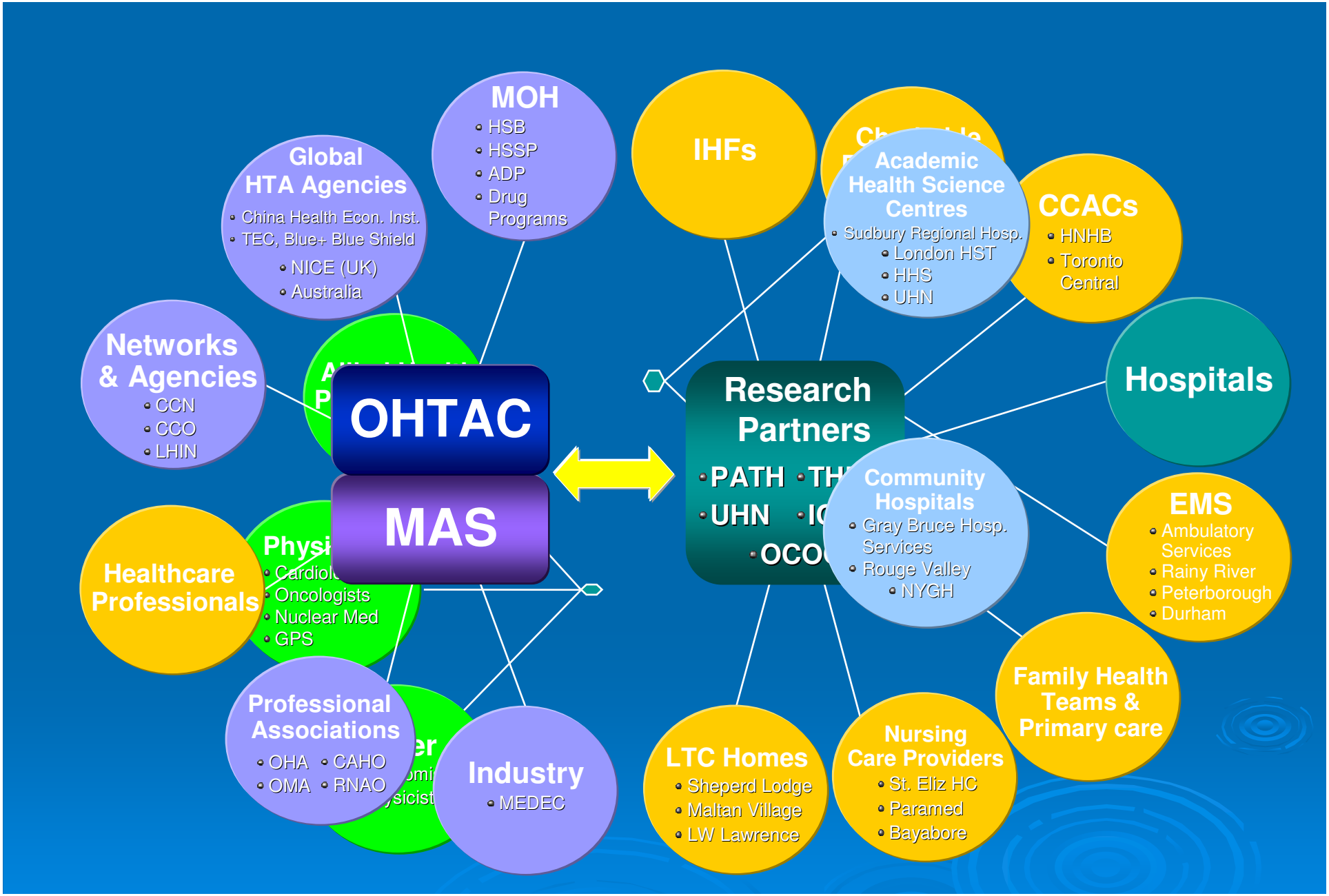
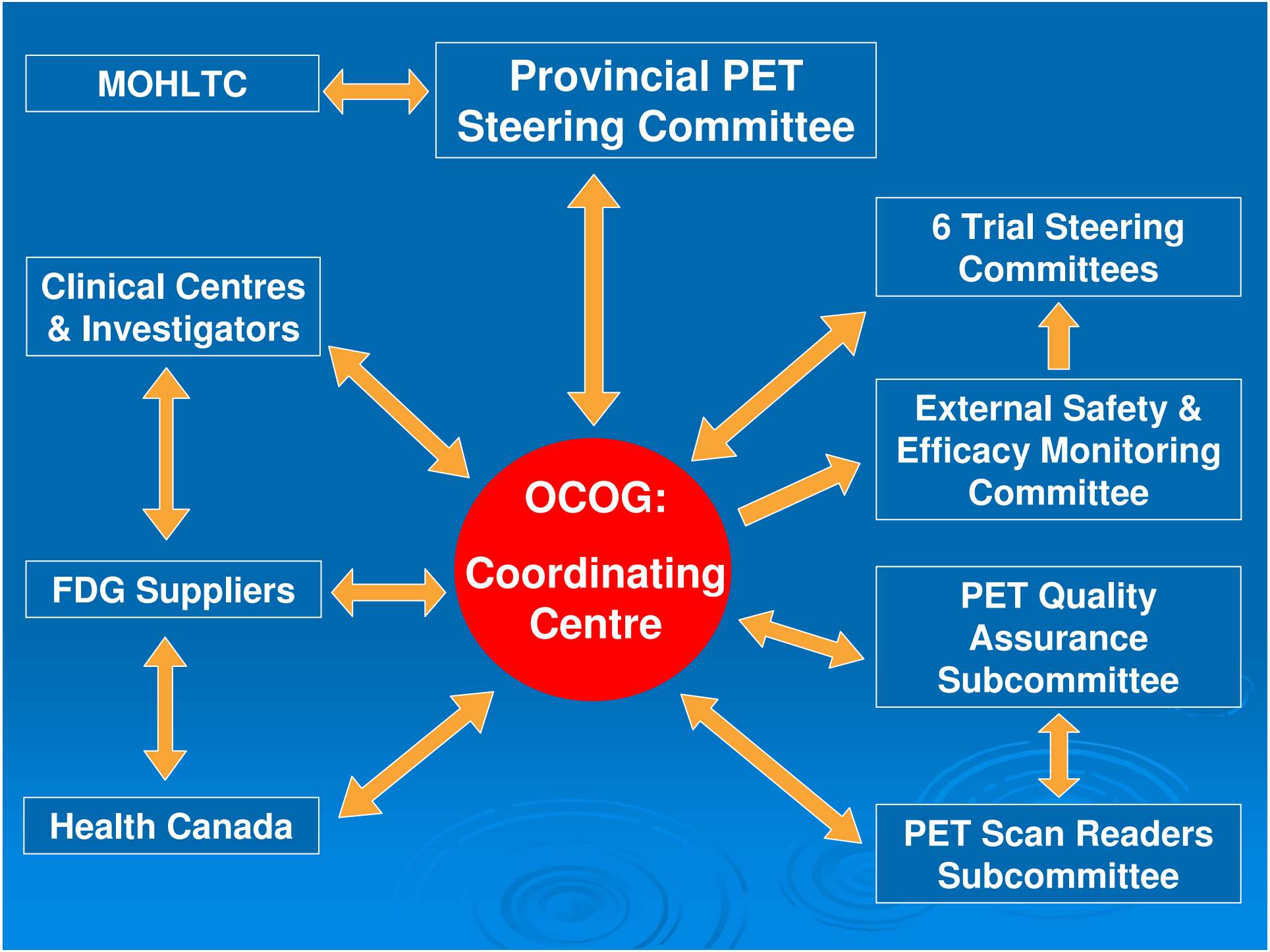
MAS/OHTAC Associated Structures & Linkages




MOH
HSB
HSSP
ADP
Drug Programs
IHFs
Global HTA Agencies
China Health Econ. Inst.
TEC, Blue+ Blue Shield
NICE (UK)
Australia
Academic Health Science Centres
Sudbury Regional Hosp.
London HST
HHS
UHN
CCACs
HNHB
Toronto Central
Networks & Agencies
CCN
CCO
LHIN
OHTAC
MAS
Research Partners
PATH
UHN
Hospitals
Community Hospitals
Gray Bruce Hosp. Services
Rouge Valley
NYGH
EMS
Ambulatory Services
Rainy River
Peterborough
Durham
Healthcare Professionals
Oncologists
Nuclear Med
GPS
Professional Associations
OHA
CAHO
OMA
RNAO
Industry
MEDEC
LTC Homes
Sheperd Lodge
Maltan Village
LW Lawrence
Nursing Care Providers
St. Eliz HC
Paramed
Bayabore
Family Health Teams & Primary care


MOHLTC
Provincial PET Steering Committee
6 Trial Steering Committees
Clinical Centres & Investigators
External Safety & Efficacy Monitoring Committee
OCOG: Coordinating Centre
FDG Suppliers
PET Quality Assurance Subcommittee
Health Canada
PET Scan Readers Subcommittee

Uncertainty Drives CED/Field Evaluations

- May be caused by e.g.:
  - Low quality evidence
  - ? Incremental net benefit
  - ? Generalizability
  - Safety issues
- For non-drug technologies compounded by:
  - Less rigorous licensing requirements
  - Diffusion pressure
    - Short market exclusivity
    - Early adoption to profile innovation agenda

Recognizing Uncertainty - Effect of GRADE

GRADE (Quality of Evidence Following Systematic Review)	**Will Further Research Change Confidence in the Estimate?**	**Level of Uncertainty**
High	Very unlikely	**Certainty** ↓ **Uncertainty**
Moderate	Likely	
Low	Very likely	
Very Low	Any estimate of effect is very uncertain	

Delayed Uptake to Address Uncertainty Through Post-Market Assessment

- CMS - **Coverage with Evidence Development (CED)** (Tunis SR, Pearson SD, 2006)
- NICE - Only-In-Research program and registries (Chalkidou 2007)
- MSAC – Interim funding e.g. capsular endoscopy
- BCBS sponsored RCT to assess dose-intensive chemotherapy with bone marrow support in breast cancer (Stadtmauer et al 2000)
- Ontario's Field Evaluation Program informs decision making through post-market assessments (Goeree and Levin 2004); (Levin et al 2010)

Ontario Field Evaluation Studies

- Post-market assessment of real world performance
- Addresses residual uncertainty following systematic review
- Improves decision making prior to long-term commitments
- Collaboration between:
  - Medical Advisory Secretariat MAS (Levin et al)
  - Program for the Assessment of Technologies in Health PATH (Goeree et al), McMaster University
  - Toronto Health Economic and Technology Assessment Collaboration THETA (Krahn et al), University of Toronto
  - Usability and Human Factors Laboratory (Easty et al) UHN
  - Ontario Clinical Oncology Group OCOG (Levine et al), CCO and McMaster U
  - Institute of Clinical Evaluative Sciences ICES (Henry et al)
- For uncertainty in incremental net benefit there is (an option) value to delaying decisions and waiting for further evidence ***(Eckerman and Willan, 2006)***
- Alternative - passive diffusion and intuitive decision making

Summary of Ontario Field Evaluations (FE)

- 38 completed or ongoing since 2003:
  - 8 RCTs
  - 17 observational
  - 7 registry
  - 2 polls
  - 4 decision analytic models
- 19 completed
  - Affected decision-making 88%
  - 10 (53%) were CED
  - All CEDs shaped diffusion curve
  - Safety alerts from 3 FEs
  - Published in international peer-reviewed journals in 8/13 (62%) to date (data undergoing analysis in 3)
  - Contributed to >$500M cost avoidance associated with OHTAC recommendations

TECHNOLOGY (N)	FE OVERSEEN BY	TYPE OF STUDY	REASON FOR FE	RESULT	POLICY DECISION
Drug eluting stents (DES) (21,000)	PATH, with ICES,	Prospective pragmatic registry	Generalisability of RCT evidence and cost effective analysis	Only effective in patients at high risk for restenosis	Funded 30% conversion from bare-metal to DES (90% in U.S.A.)
Endovascular abdominal aortic aneurysm repair (EVAR) (160)	PATH and single AHSC	Prospective observation	Safety assessment of endoleak	No endoleak. CE only for high surgical risk	Funded for high but not low surgical risk
Multifaceted primary care diabetes program	PATH, with Oxford University,	Before-after study using micro simulation economic model	Prioritize investments according to downstream effects and CE following systemic review of diabetes strategy.	Most CE were bariatric surgery, MDT. Least insulin infusion pumps for type II	Bariatric program funded and additional funding for MDT. Insulin infusion pumps for type 2 on hold
64-slice CT angiography (CTA) v coronary angiography (CA) (175)	PATH, with cardiologists, radiologists, selected AHSCs	Patients for CA also underwent CTA	Uncertainty re-indications for use, CE and QA parameters	Sensitivity lower than reported, reducing CE	OHTAC recommended slow diffusion until sensitivity issue resolved

TECHNOLOGY (N)	OVERSEEN BY	TYPE OF STUDY	REASON FOR FIELD EVALUATION	RESULT	POLICY DECISION
PET to stage locally advanced NSCLC (310)	OCOG	RCT	Clinical utility in decision re-combined modality Rx	Terminated by efficacy & safety cmmtee	PET insured for this indication
PET to stage early NSCLC (322)	OCOG	RCT	Resolve inconsistencies to inform decision re- access	PET reduces futile thoracotomy rates	PET insured for this indication
PET to stage breast cancer (320)	OCOG	Prospective cohort	Compare PET to sentinel lymph node biopsy	No utility in staging	Not insured
PET for colorectal cancer metastatic to liver (400)	OCOG	RCT	Clinical utility in decision for metastatectomy	Accrual completed February 2010	Awaiting results
PET for head and neck cancer (400)	OCOG	Prospective cohort	Clinical utility pre surgery following radiation therapy	No clinical utility	Not insured
Extracorporeal photopheresis (EP) (120)	PATH with AHSC	Prospective observational	Basis for decision re-funding for GvH and Sezary	Effective in GvH. Inconclusive for Sezary	Insured for GvH. Inconclusive for Sezary - small vol. after backlog dealt with

Gene Expression Profiling (Oncotype DX®) for Guiding Adjuvant Chemo in Early Breast Cancer

- MAS/THETA analysis - Not final, posted for public engagement
  - Low quality evidence for prognostic value
  - Very low quality evidence for predictive value for CMF benefit
- Quality concerns:
  - Studies designed as retrospective subgroup analyses of RCTs and lack of differences could be attributed to type 2 error
  - Data not specific to HER-2/neu-negative women
  - Limitations in statistical analyses
- Markov modeling (probabilistic sensitivity analysis) showed that testing all early stage lymph-node negative women with breast cancer is cost-effective with ICER of $23,983 per QALY
  - However, assumptions need verification, clinical data of low quality
- Uncertainty re- economic model and preference by oncologists that this be tested in real-time in Ontario

CED Proposed for Oncotype-DX® Testing in Breast Cancer

- Q 1: How does ODX change treatment?
  - Prospective cohort study - Does RS change treatment recommended and received in ER+ LN- patients who are candidates for chemo?
- Q 2: How does the ODX compare to traditional factors?
  - Electronically-collected data for age, tumor size, grade, ER, PR, HER-2/neu will allow measuring correlations between RS and traditional risk classification
- Q 3: Impact of ODX on breast cancer distant recurrence?
  - Patient and administrative data from the cohort study
- Will be informed by results from e.g.:
  - TAILORx trial. Main study question - is it safe to withhold chemo in intermediate RS? RS of 11 to 25 randomized to endocrine therapy versus endocrine plus chemo.? Recruitment > 10,000 completed in October 2010

EGFR Mutation Testing in NSCLC

1. Predictive effect of mutated EGFR based on retrospective subgroup analysis of archived specimens from IPASS RCT studying first-line *gefitinib* v chemo.

   Longer PFS for:

   - Gefitinib v chemo in EGFR mutation positive
   - Chemo v gefitinib in EGFR mutation negative

2. Predictive effect of mutated EGFR through retrospective analysis of archived specimens from BR21 RCT of second/third-line *erlotinib* v placebo:

   - BR.21 showed 23% response for erlotonib v placebo
   - Improved non-significant survival advantage of erlotinib in EGFR positive and negative (HR 0.55 and 0.74)
   - ? type II error (sample size (16% of original study population), very low event rates. Study not powered to examine predictive effect of mutation)
   - Pattern of practice to use erlotinib irrespective of EGRF status

- Decision to recommend funding EGFR testing for:
  - gefitinib for first line treatment
  - monitor responses to erlotinib by EGFR mutation status

K-*ras* Mutation Testing in Colon Cancer

- Predictive effect of K-*ras* based on retrospective subgroup analysis of tumor specimens between two arms of an RCT
- Cetuximab in wild-type K-*ras* improved OS and PFS but no difference between the groups for mutated K-*ras* treated with cetuximab
- Moderate quality evidence of effectiveness
- Economic analysis - adding K-*ras* testing to cetuximab or penatumumab was a dominant cost-effective strategy

- Decision to recommend funding K-*ras* testing

Factors that are Likely to Affect CED Design

- Event rates and natural history of disease (time horizon)
- Pre or post diffusional study. It is easier to shape a diffusion curve than to bend a diffused curve. Pre-diffusional preferred
- Diffusion pressures
  - Rapid market penetration driven by short market exclusivity (non-drugs)
  - Public, political, industry and professional pressures
- Feasibility
  - Funding
  - Complexity of study design and execution
  - Compliance with policies and legal issues
  - End-user participation and buy-in
  - Willingness by payer to withdraw or increase access based on results
- Innovative approaches are essential to expedite CEDs