Coverage With Evidence Development: The Ontario Experience

Evidence Generation for Genomic Diagnostic Test Development

Institute Of Medicine Workshop

Leslie Levin MD FRCP (Lon), FRCP
Head, Medical Advisory Secretariat
Ontario Ministry of Health and Long-Term Care
Professor of Medicine, University of Toronto
Outcomes Tracked by MOHLTC with GIS

Physicians Schedule of Benefits

LHINs – Implementation: Hospitals, Community Agencies, etc…

Requests

Recommendations

Ontario Health System

Requests

Knowledge Transfer

Stakeholder Engagement

Field Evaluations

Uncertainty

Post-market technology evaluation through PATH, THETA, ICES

Post-market safety evaluation through the Usability Lab

• POC/INR Intermediate care
  • Cardiac
  • Arthritis
  • PET
  • Diabetes
  • Aging
  • Wound care

Expert Panels

PATH (McMaster Univ)

THETA (Univ. of Toronto)
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

<table>
<thead>
<tr>
<th>GRADE (Quality of Evidence Following Systematic Review)</th>
<th>Will Further Research Change Confidence in the Estimate?</th>
<th>Level of Uncertainty</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Very unlikely</td>
<td>Certainty</td>
</tr>
<tr>
<td>Moderate</td>
<td>Likely</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>Very likely</td>
<td></td>
</tr>
<tr>
<td>Very Low</td>
<td>Any estimate of effect is very uncertain</td>
<td>Uncertainty</td>
</tr>
</tbody>
</table>
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
<table>
<thead>
<tr>
<th>TECHNOLOGY (N)</th>
<th>FE OVERSEEN BY</th>
<th>TYPE OF STUDY</th>
<th>REASON FOR FE</th>
<th>RESULT</th>
<th>POLICY DECISION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug eluting stents (DES) (21,000)</td>
<td>PATH, with ICES,</td>
<td>Prospective pragmatic registry</td>
<td>Generalisability of RCT evidence and cost effective analysis</td>
<td>Only effective in patients at high risk for restenosis</td>
<td>Funded 30% conversion from bare-metal to DES (90% in U.S.A.)</td>
</tr>
<tr>
<td>Endovascular abdominal aortic aneurysm repair (EVAR) (160)</td>
<td>PATH and single AHSC</td>
<td>Prospective observation</td>
<td>Safety assessment of endoleak</td>
<td>No endoleak. CE only for high surgical risk</td>
<td>Funded for high but not low surgical risk</td>
</tr>
<tr>
<td>Multifaceted primary care diabetes program</td>
<td>PATH, with Oxford University,</td>
<td>Before-after study using micro simulation economic model</td>
<td>Prioritize investments according to downstream effects and CE following systemic review of diabetes strategy.</td>
<td>Most CE were bariatric surgery, MDT. Least insulin infusion pumps for type II</td>
<td>Bariatric program funded and additional funding for MDT. Insulin infusion pumps for type 2 on hold</td>
</tr>
<tr>
<td>64-slice CT angiography (CTA) v coronary angiography (CA) (175)</td>
<td>PATH, with cardiologists, radiologists, selected AHSCs</td>
<td>Patients for CA also underwent CTA</td>
<td>Uncertainty re-indications for use, CE and QA parameters</td>
<td>Sensitivity lower than reported, reducing CE</td>
<td>OHTAC recommended slow diffusion until sensitivity issue resolved</td>
</tr>
<tr>
<td>TECHNOLOGY (N)</td>
<td>OVERSEEN BY</td>
<td>TYPE OF STUDY</td>
<td>REASON FOR FIELD EVALUATION</td>
<td>RESULT</td>
<td>POLICY DECISION</td>
</tr>
<tr>
<td>----------------------------------------------</td>
<td>-------------</td>
<td>---------------</td>
<td>------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------</td>
<td>----------------------------------------</td>
</tr>
<tr>
<td>PET to stage locally advanced NSCLC (310)</td>
<td>OCOG</td>
<td>RCT</td>
<td>Clinical utility in decision re-combined modality Rx</td>
<td>Terminated by efficacy &amp; safety cmmttee</td>
<td>PET insured for this indication</td>
</tr>
<tr>
<td>PET to stage early NSCLC (322)</td>
<td>OCOG</td>
<td>RCT</td>
<td>Resolve inconsistencies to inform decision re- access</td>
<td>PET reduces futile thoracotomy rates</td>
<td>PET insured for this indication</td>
</tr>
<tr>
<td>PET to stage breast cancer (320)</td>
<td>OCOG</td>
<td>Prospective cohort</td>
<td>Compare PET to sentinel lymph node biopsy</td>
<td>No utility in staging</td>
<td>Not insured</td>
</tr>
<tr>
<td>PET for colorectal cancer metastatic to liver (400)</td>
<td>OCOG</td>
<td>RCT</td>
<td>Clinical utility in decision for metastatectomy</td>
<td>Accrual completed February 2010</td>
<td>Awaiting results</td>
</tr>
<tr>
<td>PET for head and neck cancer (400)</td>
<td>OCOG</td>
<td>Prospective cohort</td>
<td>Clinical utility pre surgery following radiation therapy</td>
<td>No clinical utility</td>
<td>Not insured</td>
</tr>
<tr>
<td>Extracorporeal photopheresis (EP) (120)</td>
<td>PATH with AHSC</td>
<td>Prospective observational</td>
<td>Basis for decision re-funding for GvH and Sezary</td>
<td>Effective in GvH. Inconclusive for Sezary</td>
<td>Insured for GvH. Inconclusive for Sezary - small vol. after backlog dealt with</td>
</tr>
</tbody>
</table>
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