Developing Methodological Guidance for Comparative Effectiveness Research

National CER Summit

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Evidence Summary: Radiation Therapy for Clinically Localized Prostate Cancer

Comparisons	Disease specific survival	Freedom from biochemical failure	GU/GI toxicity
No treatment	*insufficient*	*insufficient*	*insufficient*
CyberKnife / EB	*insufficient*	*insufficient*	*insufficient*
SBR / Brachy (HD)	*insufficient*	*insufficient*	*insufficient*
SBR / Brachy (LD)	*insufficient*	*insufficient*	*insufficient*
EB / Brachy (HD)	*insufficient*	*insufficient*	*insufficient*
EB / Brachy (LD)	*insufficient*	*insufficient*	*insufficient*
Brachy HD/LD	*insufficient*	*insufficient*	*insufficient*
Combined mod.	*insufficient*	*insufficient*	*insufficient*
SBR (var)	*insufficient*	*insufficient*	*insufficient*
EB (proton, IMRT)	*insufficient*	*moderate*	*moderate*
Brachy (var)	*insufficient*	*insufficient*	*insufficient*

Source: Tufts Evidence-based Practice Center: Draft AHRQ Technical Assessment, March 25, 2010

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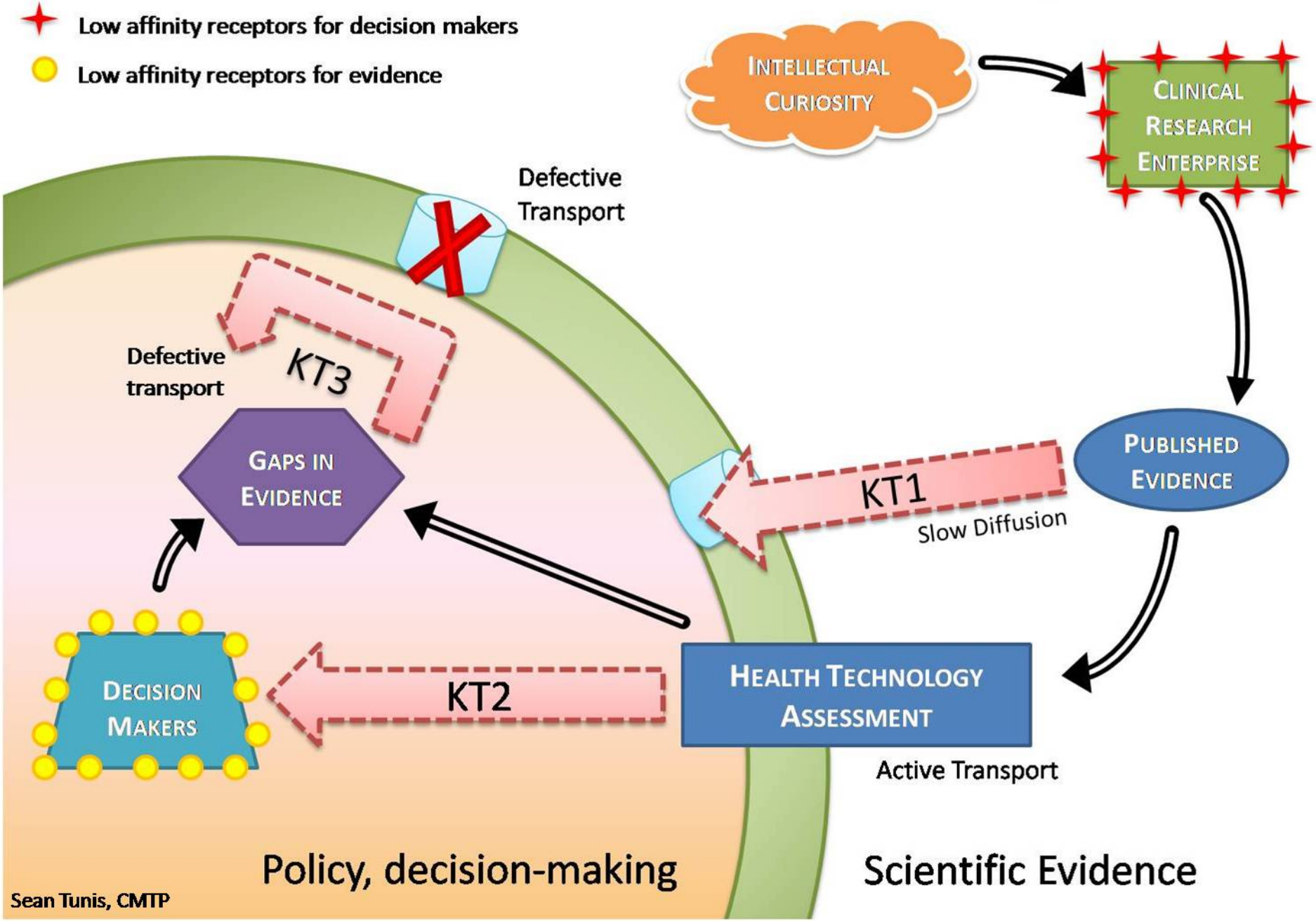
The Evidence Paradox

- 18,000+ RCTs published each year
- Tens of thousands of other clinical studies
- Systematic reviews intended to inform clinical and health policy decisions routinely conclude that evidence is inadequate

The CER Hypothesis

- Gaps in evidence reflect insufficient engagement of decision makers (patients, clinicians, payers) in selecting research questions and designing studies

Molecular Basis of Uncertainty



PCORI and CER methods

- "Within two years of enactment (with periodic updates) the methodology committee would determine a process to establish and maintain detailed methodological standards for comparative clinical effectiveness studies. The standards would provide criteria for study designs that balance generalizability, timeliness and other factors."

PCORI Methods - Process

- "The process for developing and updating such guidance shall include input from all relevant experts, stakeholders, and decision makers, and shall provide opportunities for public comment."

Categories of CER Methods

- Systematic reviews of existing research
- Decision modeling, with or without cost information
- Retrospective analysis of existing clinical or administrative data
- Prospective non-experimental studies, including registries
- Experimental studies, including randomized clinical trials (RCTs)

Methods Balance in CER

- Many CER studies will require a conscious effort to sacrifice internal validity in order to increase relevance, feasibility and timeliness
  - Including patients with hx of substance abuse in trials of anti-depressants
  - Intensity of QA in radiation oncology studies
  - Allowing MD choice of alternative to CCTA for dx of CAD
  - Use of reduced wound size rather than complete closure to compare wound treatments

Methodological Guidance for CER

- "Effectiveness Guidance Documents"
- Analogous to FDA-guidance
- Recommendations for study design reflecting information needs of patients, clinicians, payers
- Targeted to product developers, clinical researchers
- Aligned with regulatory guidance
- Balance validity with relevance, feasibility, timeliness
- Objective is to provide "reasonable confidence of improved health outcomes"

Elements of Study Design

- Patients
- Interventions
- Comparators
- Outcomes
- Timing
- Setting

Review Methods vs Methods Guidance

- Evidence review: "What was the relative importance of outcomes measured; which were pre-specified primary outcomes and which were secondary"
- EGD: "Acceptable outcomes for breast cancer prognosis include distant recurrence at 5 or 10 years, disease free survival, disease specific mortality, and overall survival"

EGD Development Process

- Begin with systematic reviews, HTA, etc
- Content experts generate initial draft recommendations
- Technical working group refines draft recs
- Expert - stakeholder advisory group meeting to discuss draft recommendations
- Revised recs circulated for public comment
- Final methods recommendations posted

CER Methods Guidance Underway

- Non-invasive cardiac imaging
- Treatment for atrial fibrillation
- Off-label indications for oncology drugs
- Molecular diagnostics in oncology
- Treatments for chronic wounds
- Pragmatic phase III pharmaceutical trials
- HTA-payer methods guidance
  - International harmonization of scientific advice

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