U.S. Perspective on Alzheimer's Disease Outcomes Measurement

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International Society for CNS Clinical Trials and Methodology
Advances in Conceptualization of Disease Progression in AD
Session VII. Payers/Policy Issues in AD Progression Trials
Toronto, Canada

Connecting the Payer to the Evidence

- Who is defining value?
- What are their evidence standards?
- How are they using the evidence?

- What should U.S. payers know about AD products?

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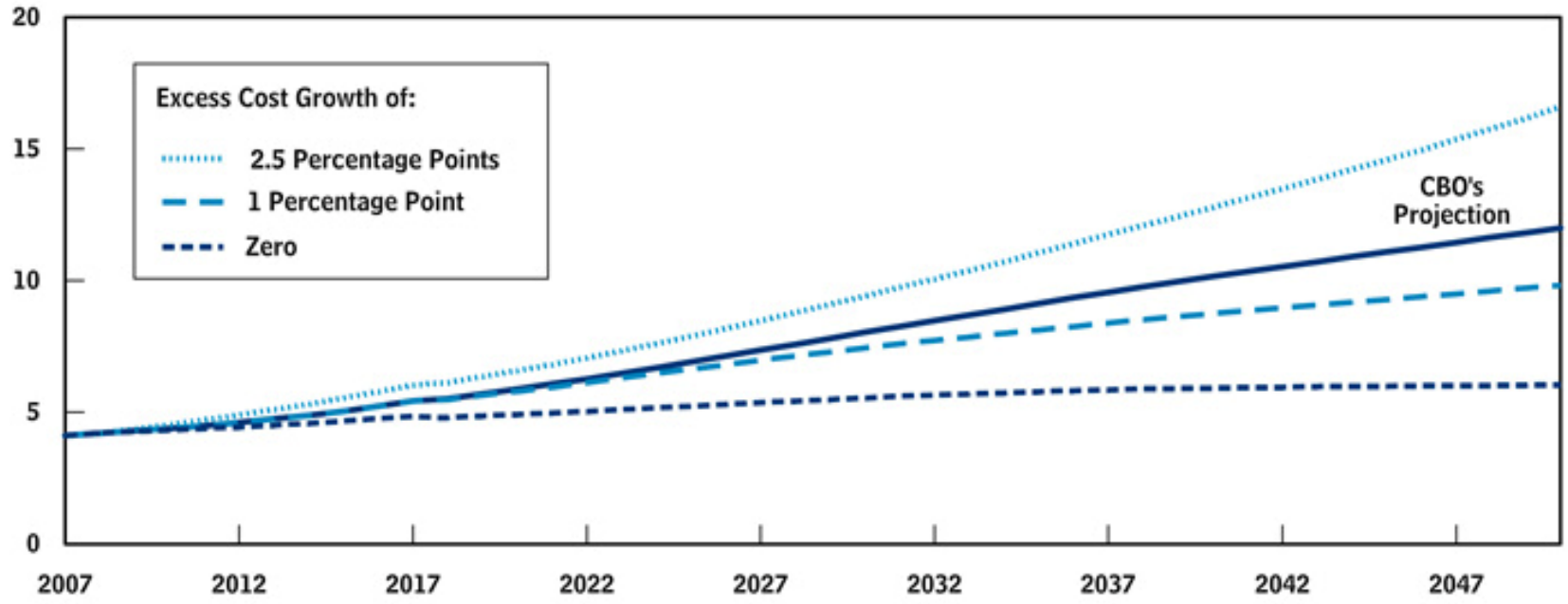
Disclosure

- I work for an organization that provides research and consultation services to a wide range of organizations, including pharmaceutical companies.
- I am involved in development and testing of outcomes measures for cognitive impairment.

It's Going Up

Federal Spending for Medicare and Medicaid as a Percentage of Gross Domestic Product Under Different Assumptions About Excess Cost Growth

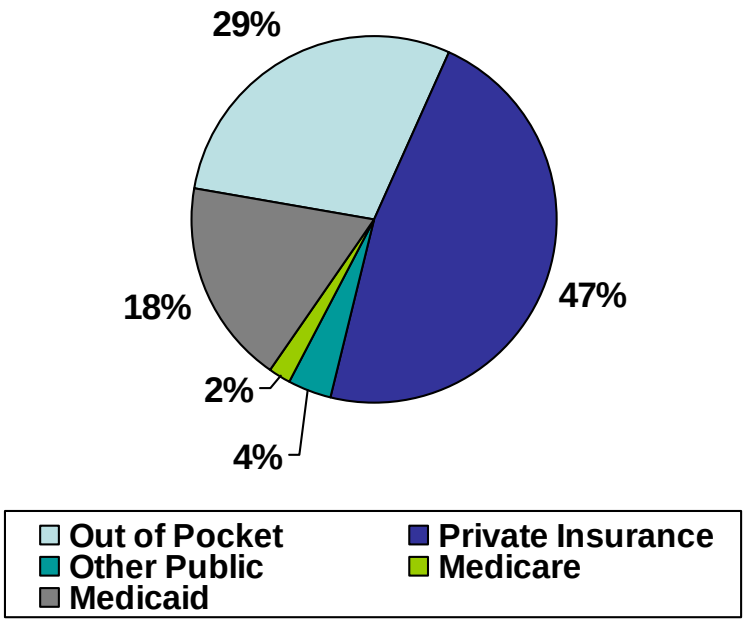


Source: Congressional Budget Office.

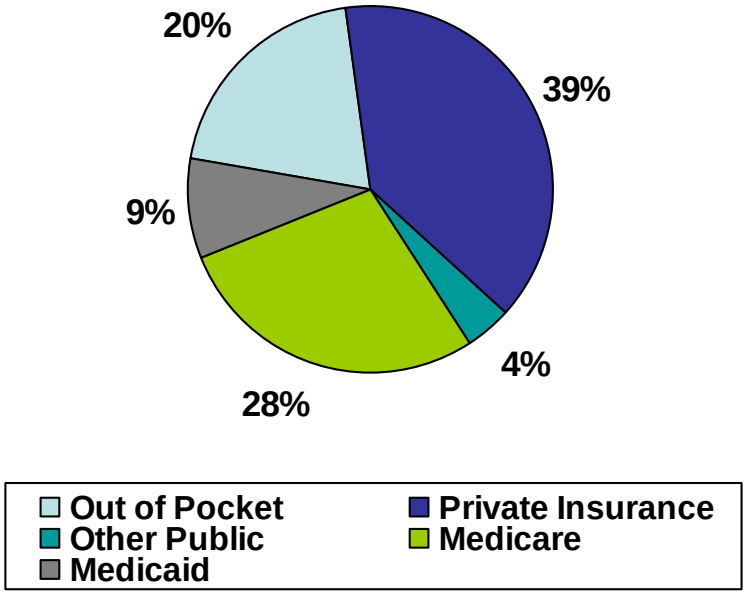
Note: Excess cost growth refers to the number of percentage points by which the growth of annual health care spending per beneficiary is assumed to exceed the growth of nominal gross domestic product per capita.

The Medicare “Part D Shift”

Projected prescription drug spending by payer, 2005



Projected prescription drug spending by payer, 2006



Source: Deutsche Bank, IMSHealth

Rx Coverage in Top 10 Medicare Prescription Drug Plans

	Enrollment	Aricept	Cognex	Exelon	Exelon Patch	Namenda	Razadyne	Razadyne ER
HUMANA	3,012,784	2	3	2	2	2	2	2
UNITED HEALTHCARE	2,694,430	2	3	3	2	2	2	2
PENN LIFE INS CO AND AMER PROG LIFE	1,315,396	2	X	3	3	2	2	2
UNITED HEALTH CARE INS. CO. AND UNITED NEW YORK	1,233,638	2	3	3	3	2	2	2
WELLCARE PRESCRIPTION INSURANCE, INC.	990,686	3	X	2	2	2	2	2
UNICARE LIFE AND HEALTH INSURANCE	725,339	1	X	1	1	1	1	1
ANTHEM INSURANCE	562,391	2	X	2	2	2	2	2
SILVERSCRIPT	555,347	2	3	2	2	2	2	2
HEALTH NET LIFE INS CO/HEALTH NET INS OF NY	524,730	2	X	2	2	2	X	X
RXAMERICA, LLC (Advantage Allegiance)	454,245	2	X	2	X	2	2	2

Source: L. Hefty. UBC Survey of Medicare Prescription Drug Plans. September 2008.
Numbers designate tier coverage; X = not covered.

What's the Contribution of Treatment Cost to

$ No relationship → REGULATORY APPROVAL

FDA – is it safe and effective?

Time horizon: 6-12 months

?

$- - - - - - - ▸ COVERAGE

$——————▸ PAYMENT

Payer – is it relevant to patient care?

Time horizon: 1-2 years

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Connecting the Payer to the Evidence

- Who is defining value?
- What are their evidence standards?
- How are they using the evidence?

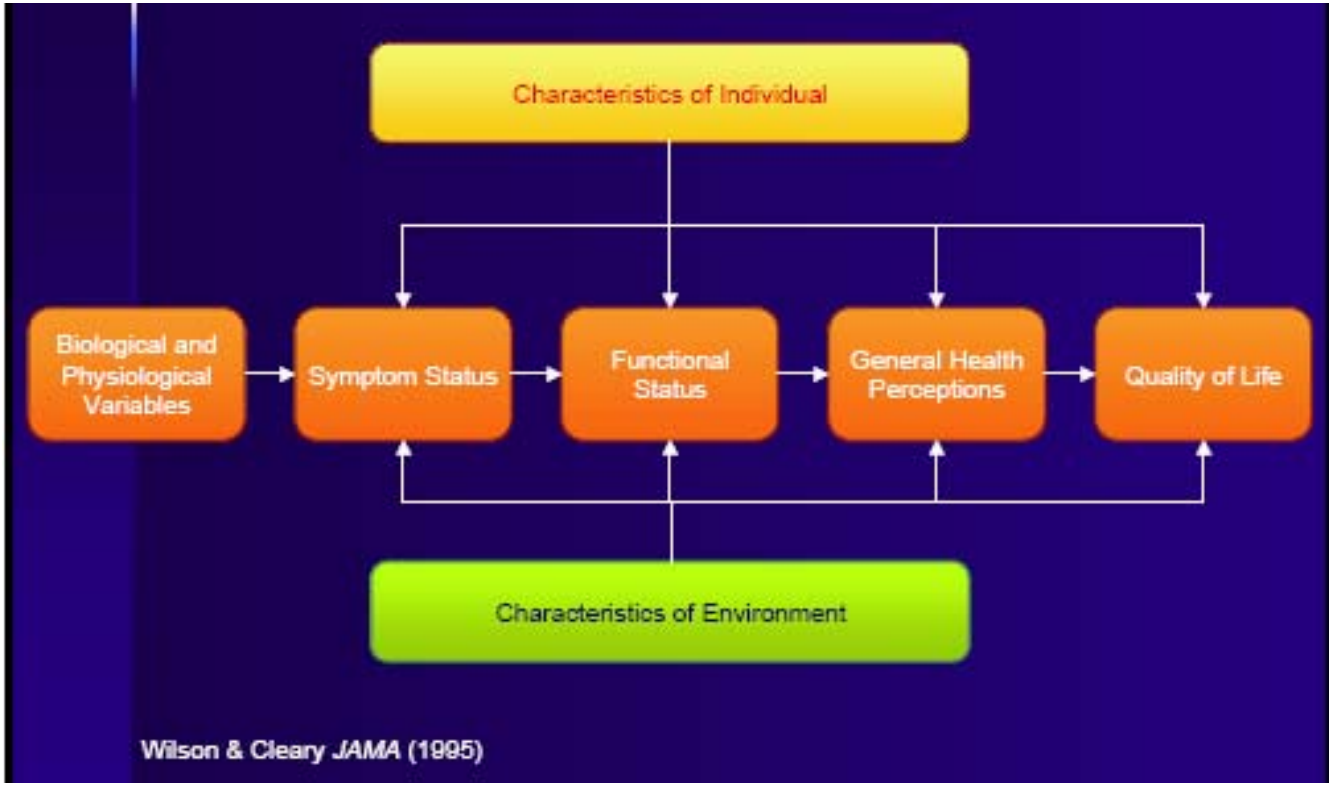
ACP Clinical Practice Guideline:

The evidence is insufficient to compare the effectiveness of different pharmacologic agents for the treatment of dementia.

(Grade: weak recommendation, **low-quality evidence**)

Qaseem et al. AIM 2008

Wilson-Cleary Model of Health Outcomes



"The goal of clinical care is improvement in patient outcomes."

Evidence Eras in the U.S.

- 1970's: Health Technology Assessment (HTA)
- 1980's: Effectiveness Research
- 1990's: Outcomes Research
- 2000's: Evidence-Based Medicine
- Now: "*Comparative Effectiveness Research*"
- Next?: "Payment for Outcomes"

Early Federal Efforts

- Congress' Office of Technology Assessment
- National Center for Health Tech Assessment
- IOM's Council Health Care Technology
- Agency for Health Care Policy & Research Clinical Guidelines
- Medicare's Cost-Effectiveness Coverage Rule

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U.S. Private Sector Activities Succeeded

- BCBSA's Technology Evaluation Center
- AMA's Diagnostic & Therapeutic Tech Assessment
- American Academy of Physicians' Clinical Efficacy Assessment Project
- ECRI
- AMCP's Format for Formulary Submissions
- Oregon's Drug Effectiveness Review Project (DERP)
- Many others (e.g. Kaiser)

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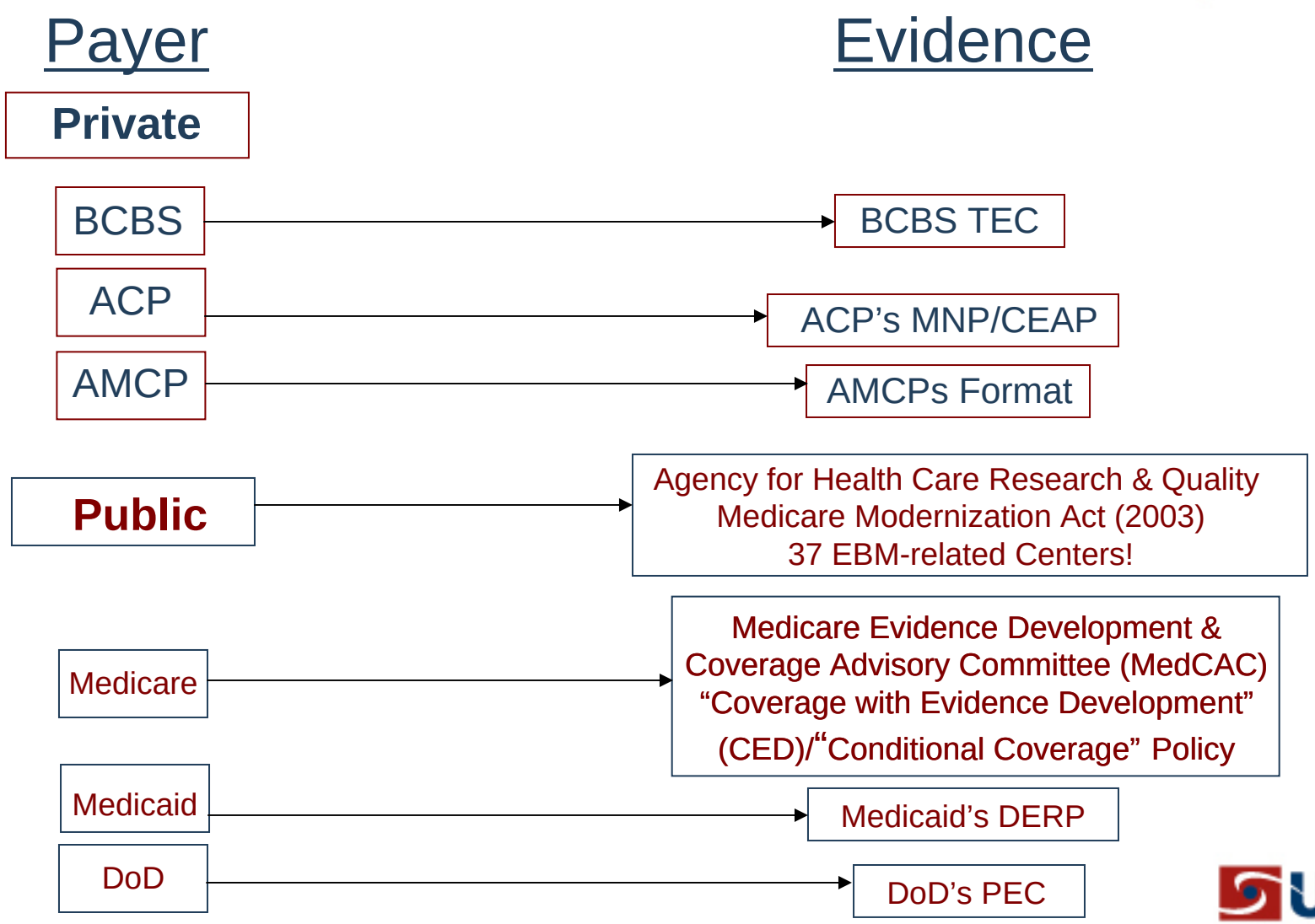
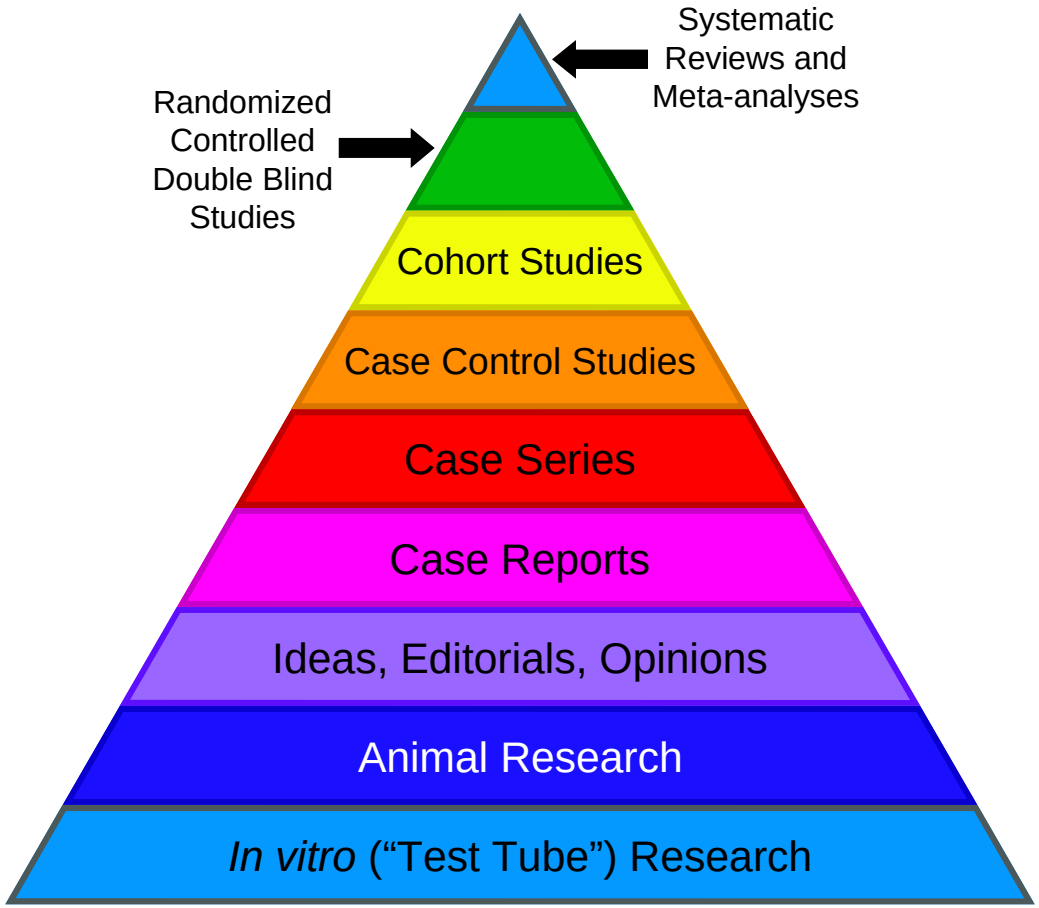
Connecting the Payer to the Evidence

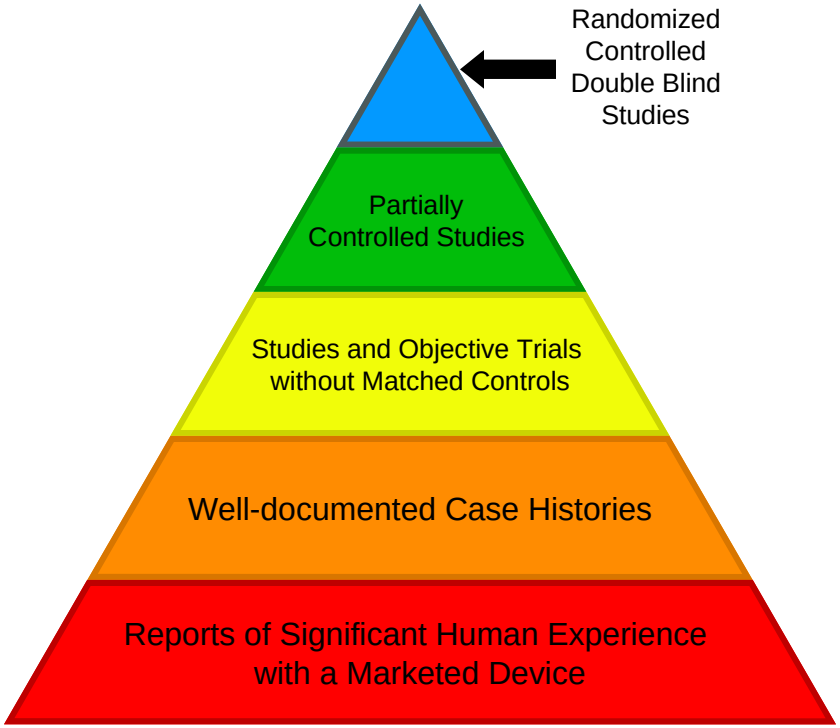


But What Do They Call “Evidence”? The Evidence Hierarchy

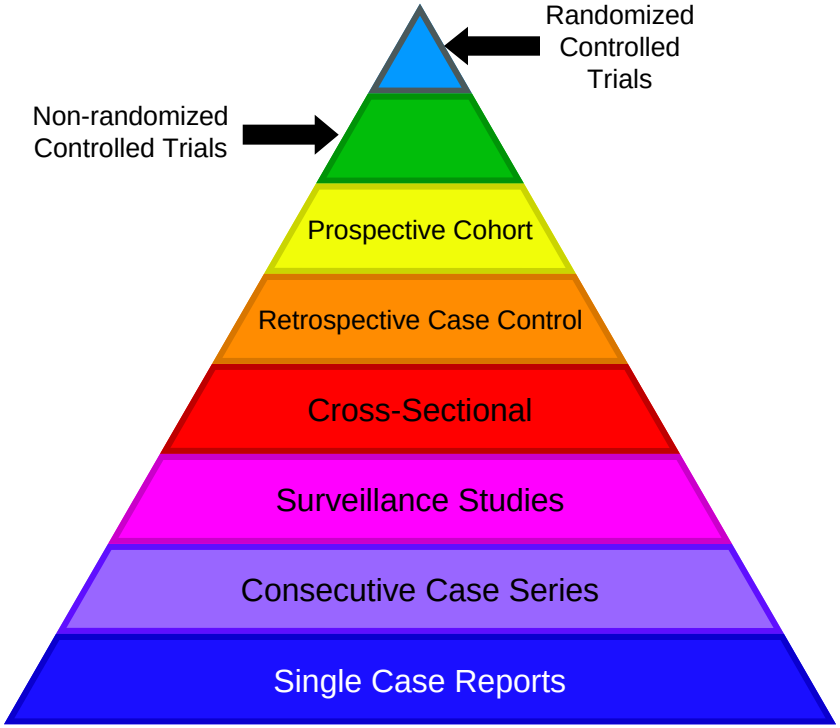


U.S. Regulatory and Payer Evidence Hierarchies

FDA

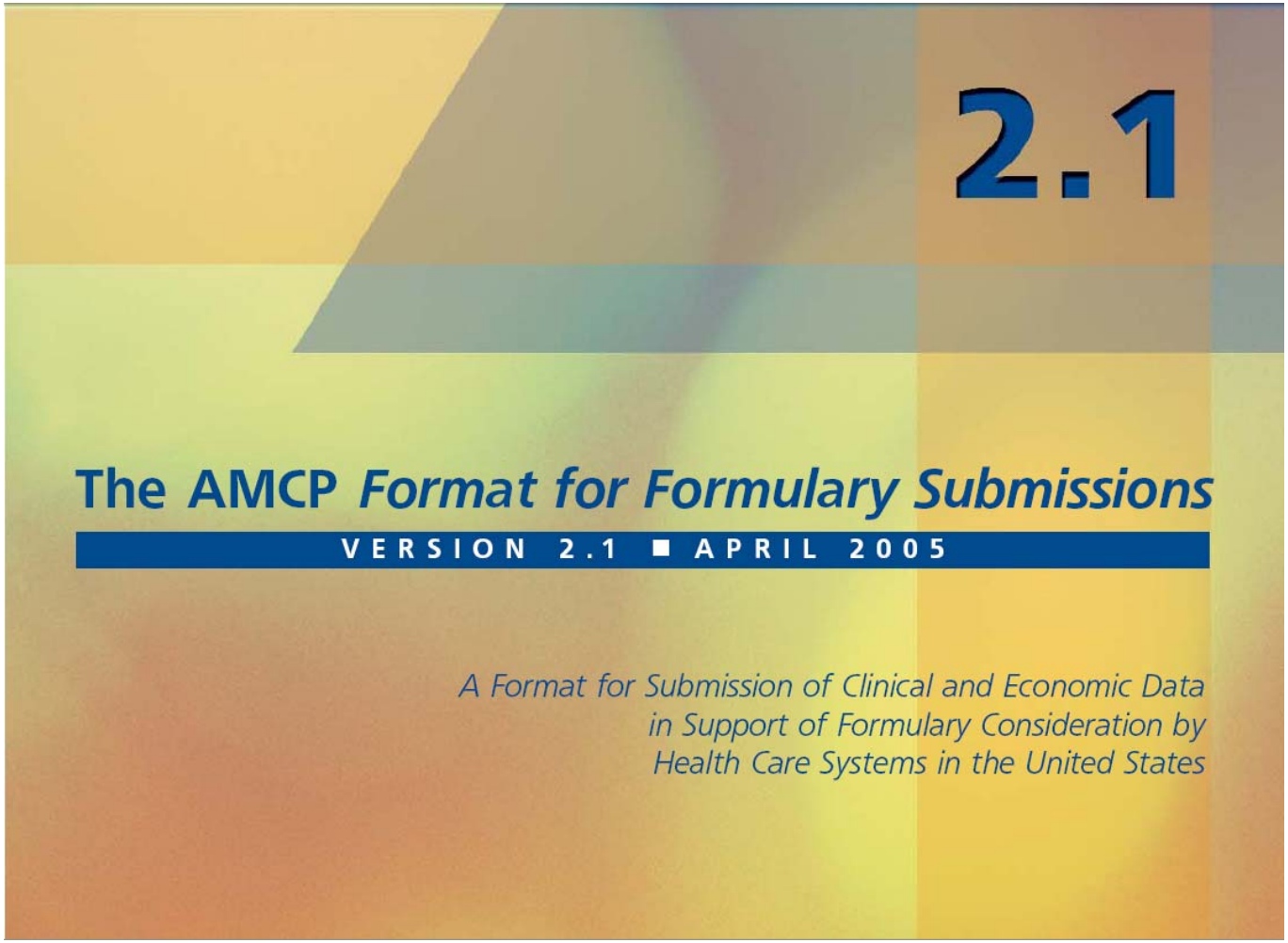


CMS

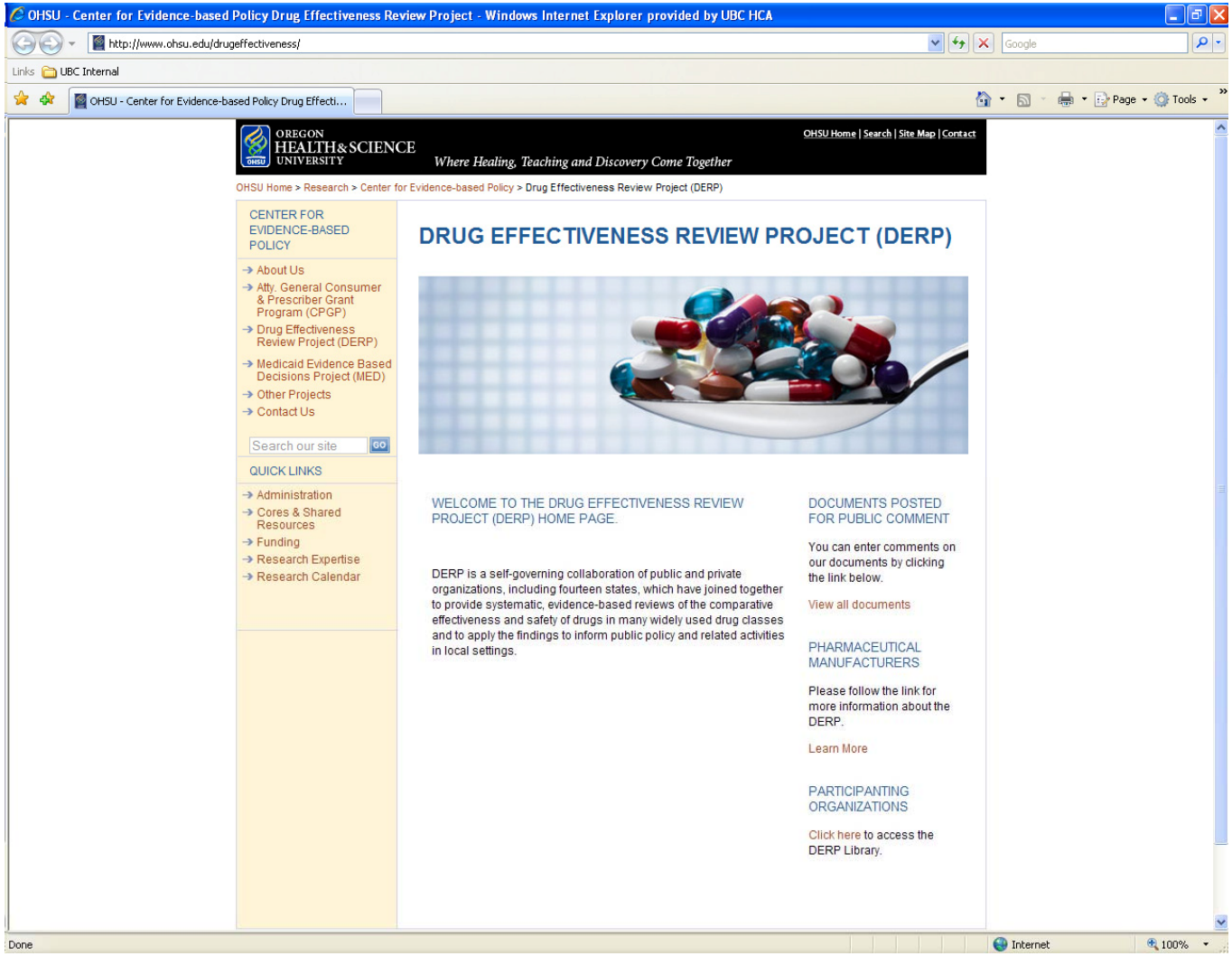


Source: de Lissovoy 2007

AMCP


2.1
The AMCP Format for Formulary Submissions
VERSION 2.1 ■ APRIL 2005
A Format for Submission of Clinical and Economic Data
in Support of Formulary Consideration by
Health Care Systems in the United States

Drug Effectiveness Review Project



Coverage with Evidence Development

- July 2006 CMS guidance:

  National Coverage Determinations with Data Collection as a Condition of Coverage:

  Coverage with Evidence Development (CED)

  - PET (FDG) for Dementia and Neurodegenerative Diseases

http://www.cms.hhs.gov/CoverageGenInfo/03_CED.asp

Conditional Coverage/(P4O)

Conditional Reimbursement	Coverage linked to production of further evidence ("coverage with evidence development")
P4O	Coverage/price linked to patient outcomes (e.g. treatment response, treatment outcome)

Efficacy and **Effectiveness**

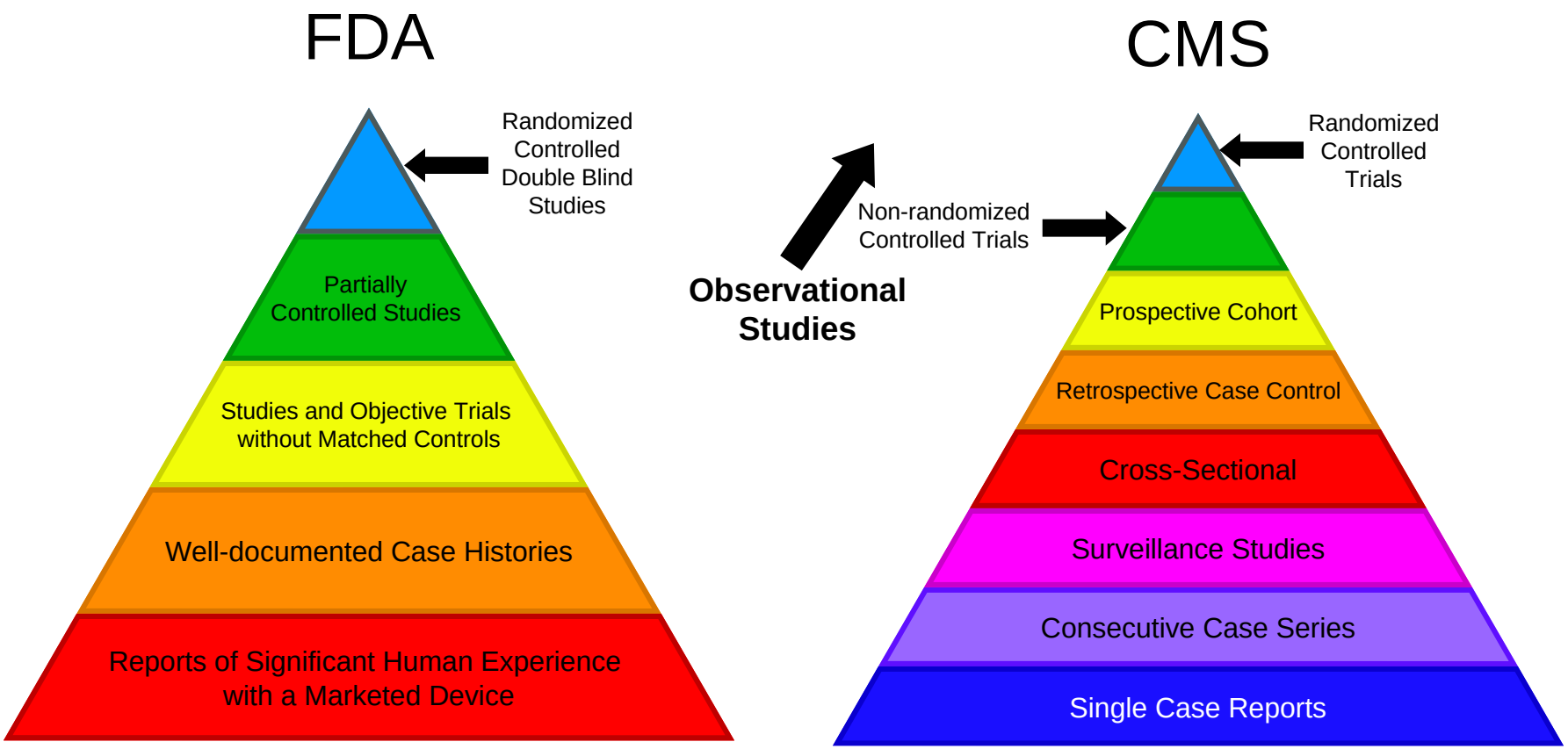
Effectiveness and Efficacy: Observational vs. Randomized Controlled Trials

	Observational Trial	RCT
Population	Heterogeneous	Homogeneous
Treatment	Heterogeneous: actual clinical care	Homogeneous: artificially controlled clinical care
Internal validity	Low	High
External validity	High	Lower
Selection bias	Low	High
Confounding bias	High	Low
Treatment compliance	May be low	Designed to be high

The Tradeoffs

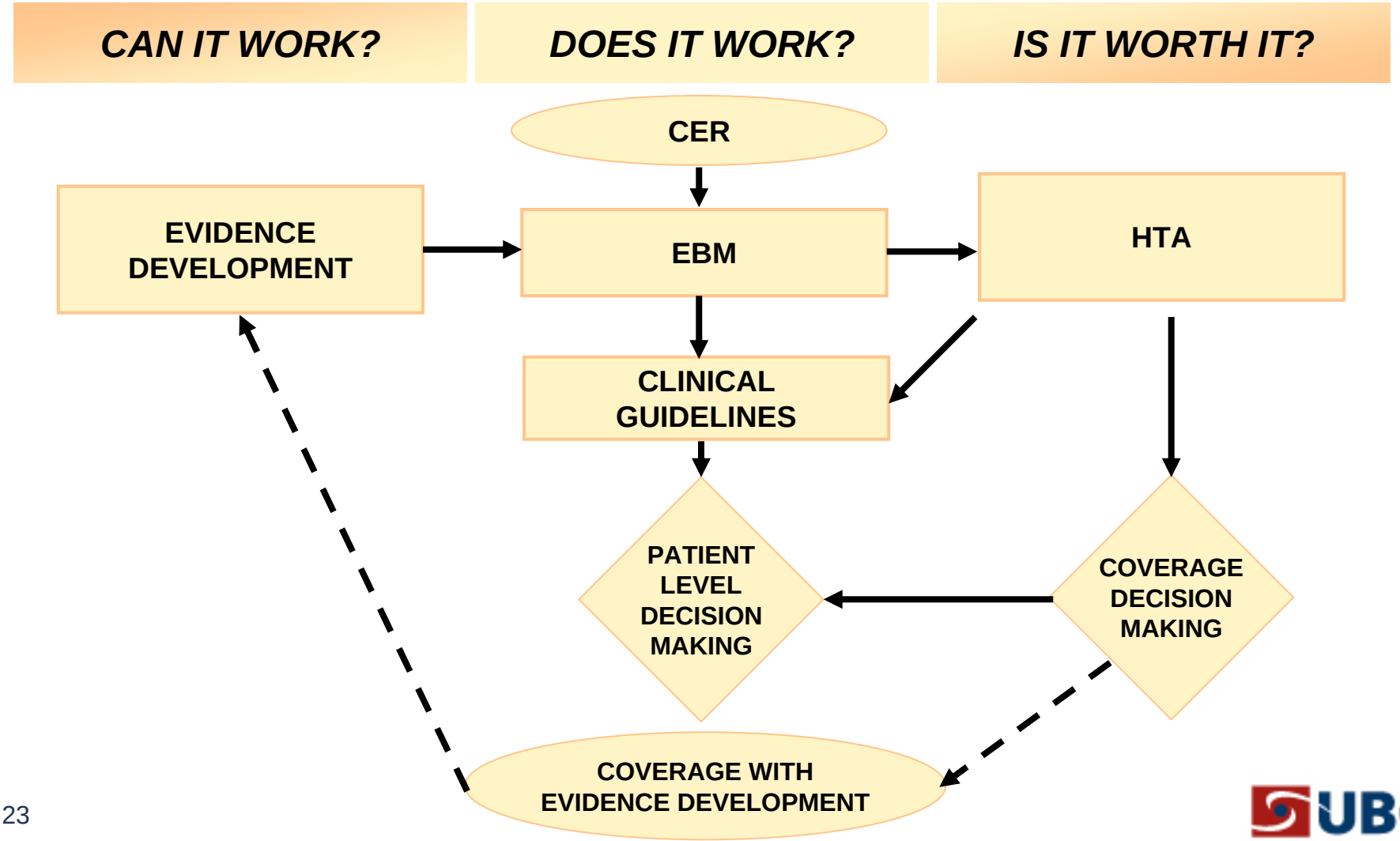
"…despite the magnificent scientific achievements of randomized clinical trials, the foundation for a basic science of patient care will also require major attention to the events and observations that occur in the ordinary circumstances of clinical practice… **a project that satisfies the priorities of one viewpoint will almost inevitably displease the other side**." (Feinstein 1983)

Who values what?

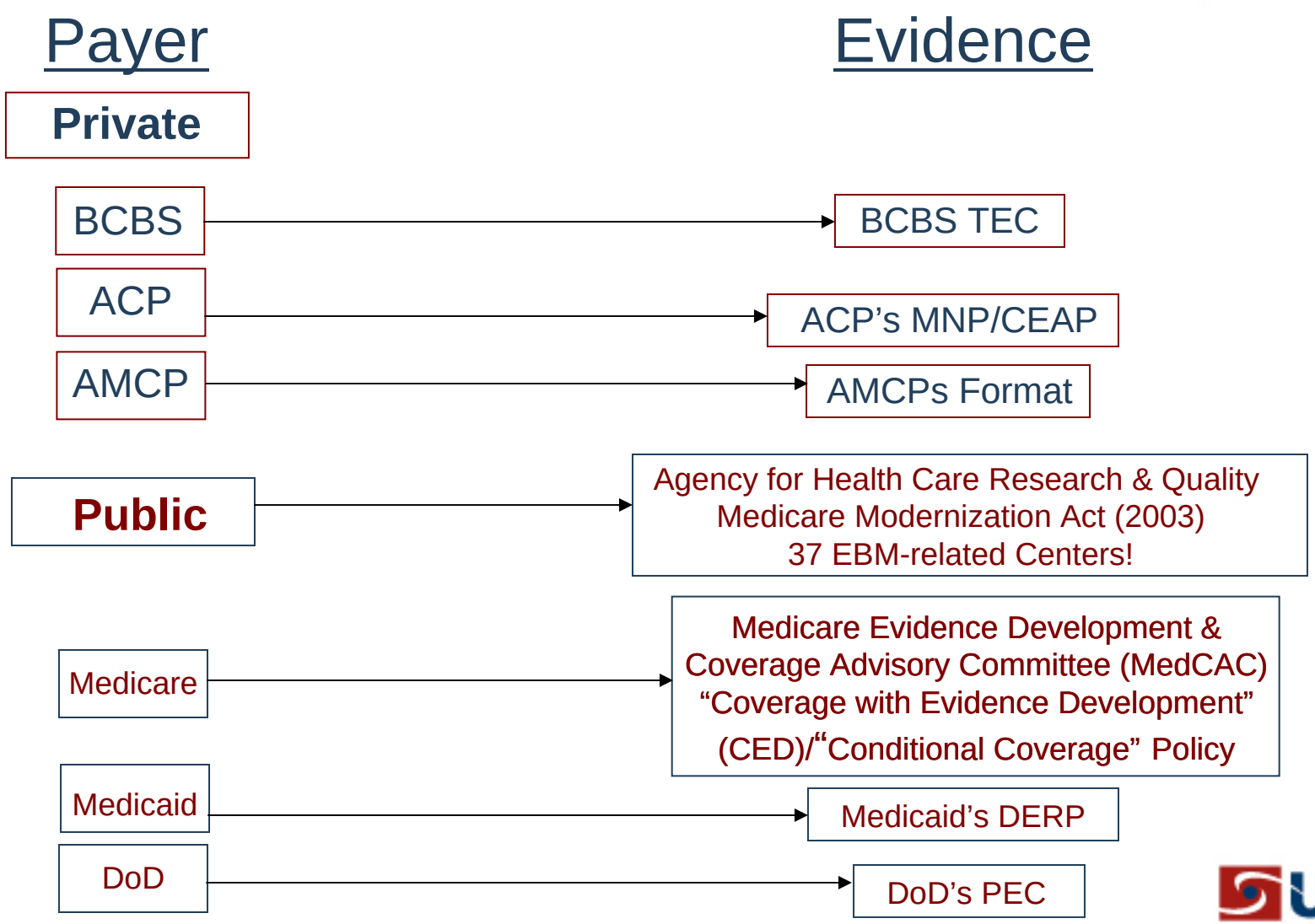


EBM-CER-HTA Relationships

Source: Drummond et al., *IJTAHC*, June, 2008

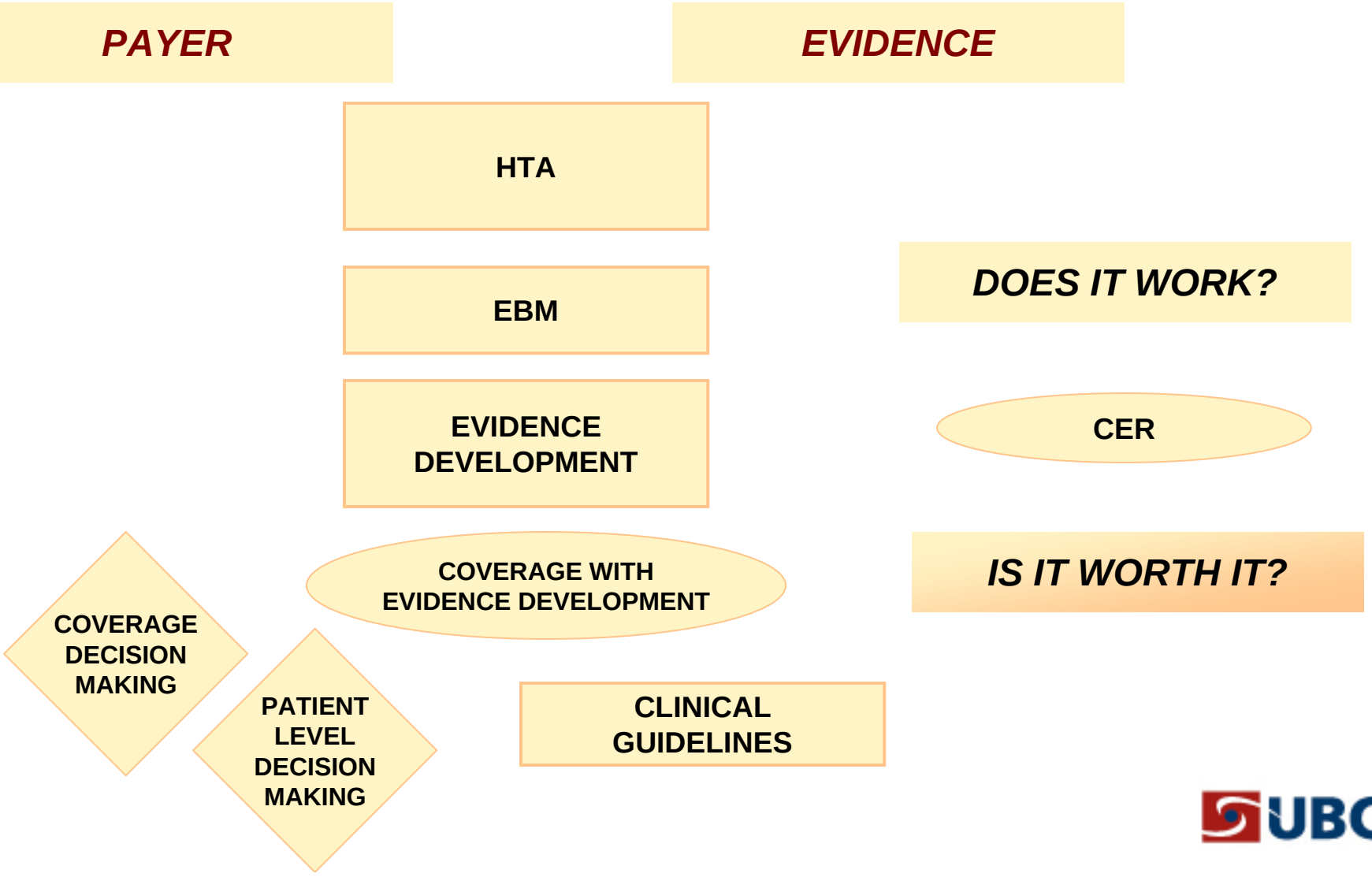


Connecting the Payer to the Evidence



HTA…A

A sideways view on Drummond et al., *IJTAHC*, June, 2008



What Should HTA Be?

"Efforts to curb the inappropriate use of medical technologies… can have only limited success unless they address the paucity of reliable information about their benefits, cost, and value."

- Elements of an objective technology assessment initiative:
  - Administrative independence
  - Dedicated funding
  - Production of objective and timely research
  - Use of reliable methods
  - Widespread dissemination
  - A governance and organizational structure that lend it legitimacy

Emanuel EJ, Fuchs VR, Garber AM. Essential elements of a technology and outcomes assessment initiative. *JAMA.* 2007;298(11):1323-1325

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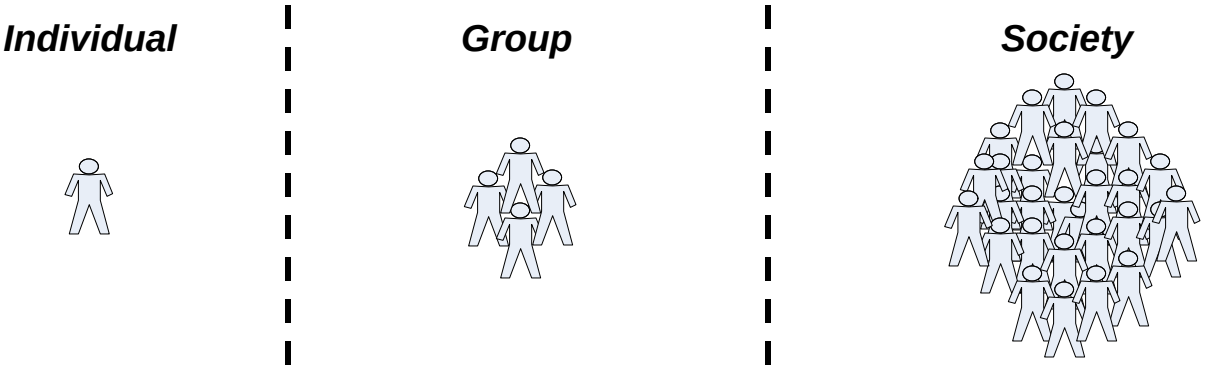
Connecting the Payer to the Evidence

- Who is defining value?
- What are their evidence standards?
- How are they using the evidence?

*What **<u>should</u>** the connection be between the payer and the evidence?*

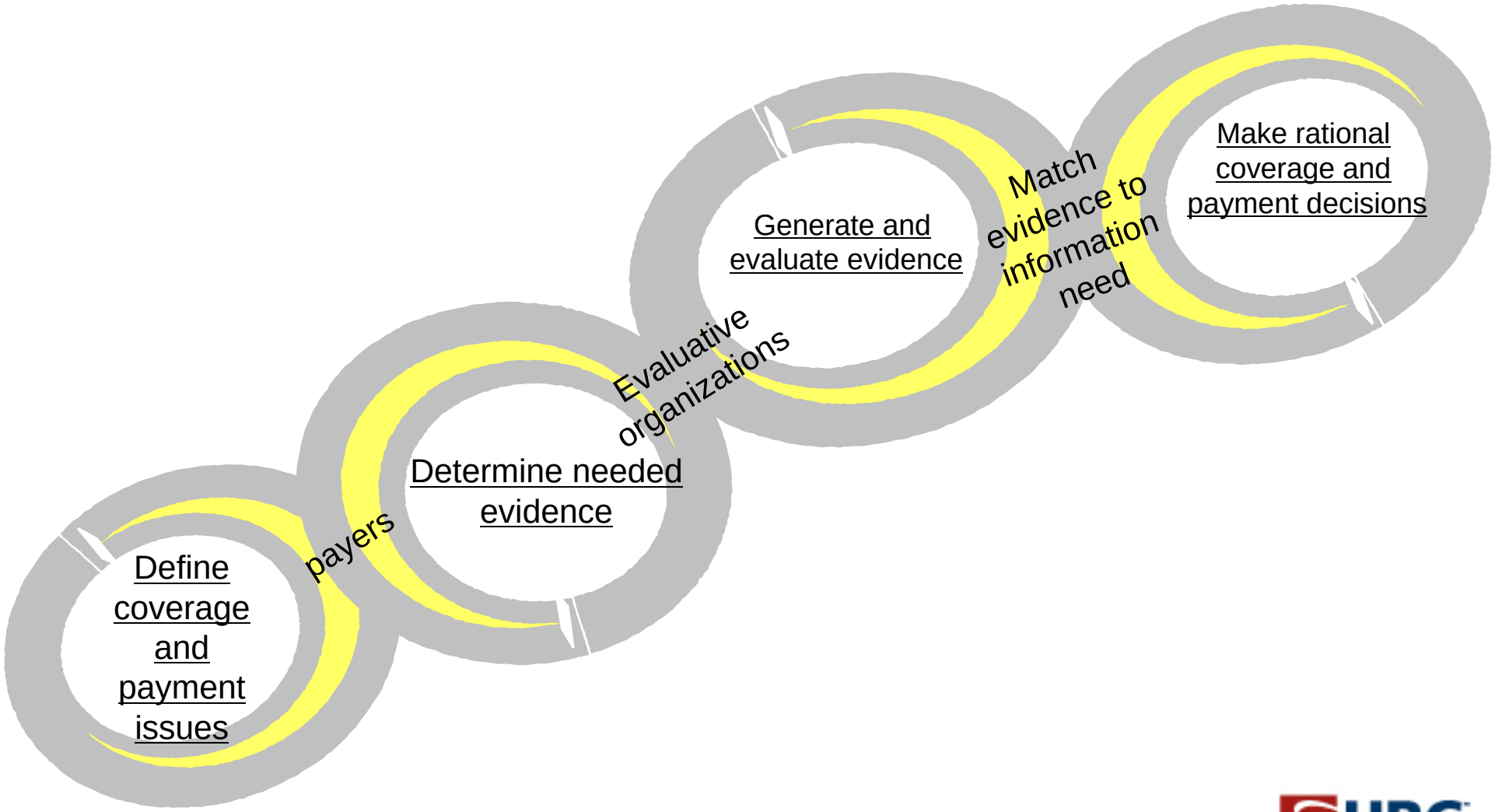
Who is Defining Value and What Is Their Perspective?

- Societal vs. individual goals
  - Resource allocation
  - Risk/benefit weighting by individuals
  - Willingness to pay
- "Individuals with dementia and their families constitute an integral unit."
  U.S. Congress Office of Technology Assessment (1992)



- Missing from the patient/society dichotomy:
  - families and small social aggregates key to AD

From Evidence to Payer: The Chain of Evidence

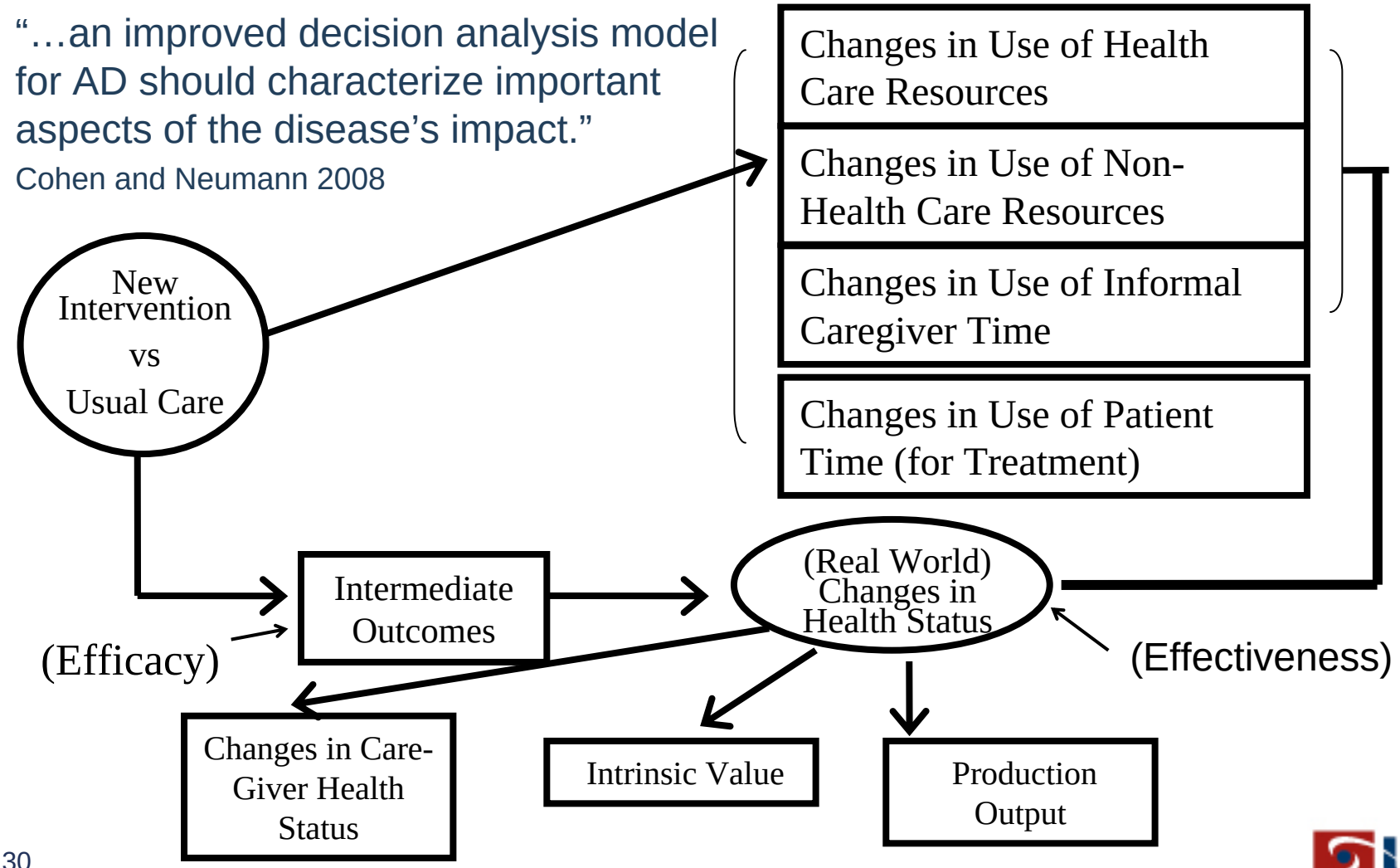


The Rest of the Evidence

Gold et al. Cost-effectiveness in Health and Medicine. By M.R. Gold, J.E Siegel, L.B. Russell, and M.C. Weinstein (eds). New York: Oxford University Press, 1996.

"…an improved decision analysis model for AD should characterize important aspects of the disease's impact."

Cohen and Neumann 2008



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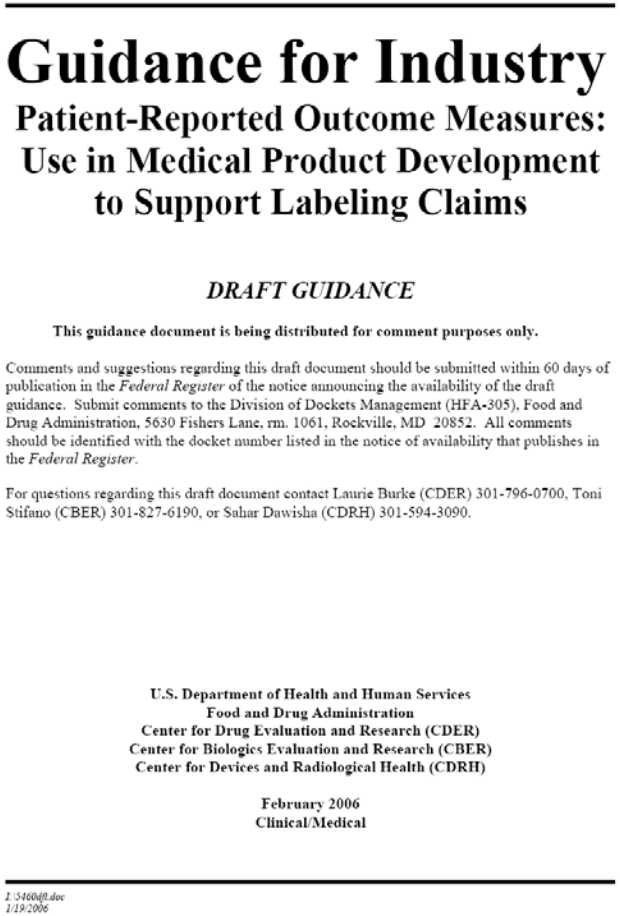

Guidance for Industry

Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact Laurie Burke (CDER) 301-796-0700, Toni Stifano (CBER) 301-827-6190, or Sahar Dawisha (CDRH) 301-594-3090.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

February 2006
Clinical/Medical

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Interpreting Outcomes

MID: The smallest change that patients perceive as beneficial and/or which would require a change in clinical management (Jaeschke et al., 1989)

- No single clearly accepted approach for determining MID
- What is the 'M' in MID?
  - Patient perspective; sensitivity of global ratings
  - Other biases in rating changes over time (recall, reliability)
  - Definitions vary

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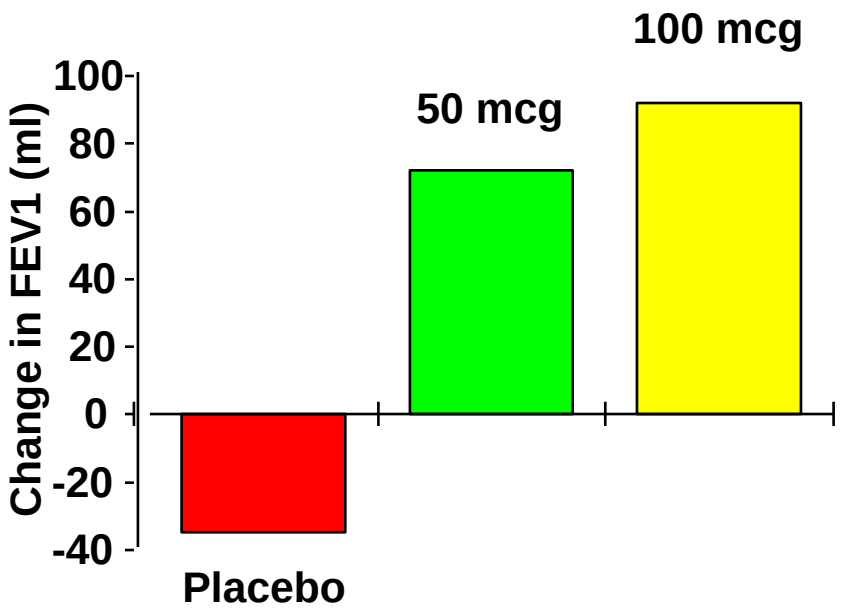
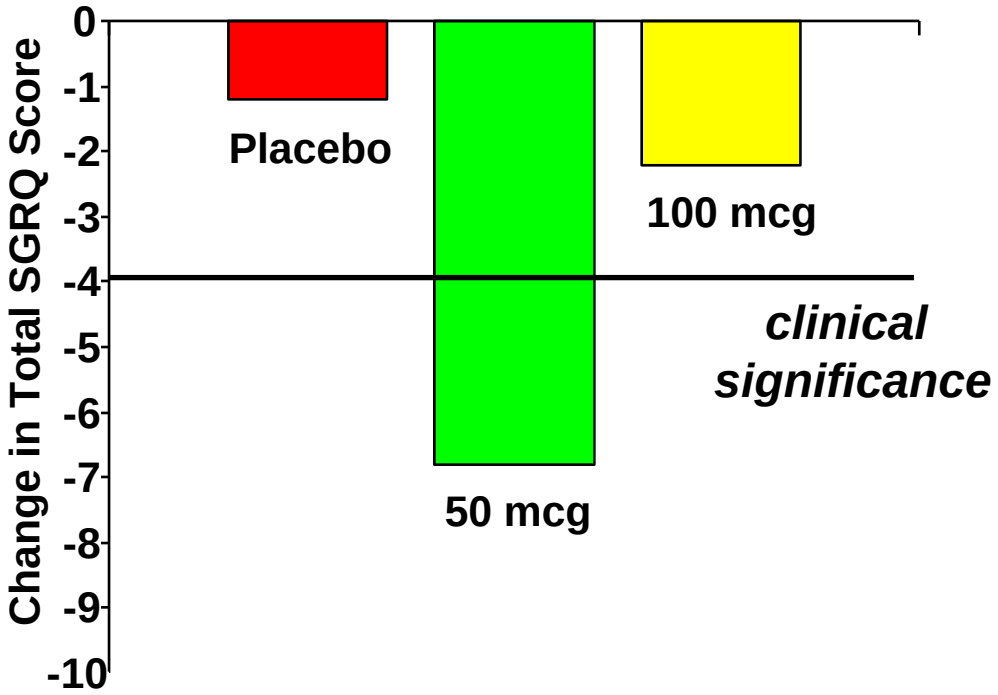
Two Approaches to Evaluating Effectiveness of Bronchodilator Therapy in COPD





Boyd G *Eur Respir J* 1997; 10:815-821

Jones *Am J Resp Crit Care Med* 1997;155:1283

What Is Persuasive to Whom?

"The magnitude of a clinically relevant change may vary depending on whether importance is defined by the patient, caregiver, or clinician."

Raina P et al. Effectiveness of cholinesterase inhibitors and memantine for treating dementia: Evidence review for a clinical practice guideline. *Ann Int Med* 2008; 148:379-397.

The Patient-Reported Outcomes Measurement Information System (PROMIS) Initiative

- The broad objectives of the PROMIS network are to:
  - Develop and test a large bank of items measuring patient-reported outcomes.
  - Create a computerized adaptive testing system that allows for efficient, psychometrically robust assessment of patient-reported outcomes in clinical research involving a wide range of chronic diseases.
  - Create a publicly available system that can be added to and modified periodically and that allows clinical researchers to access a common repository of items and computerized adaptive tests.

http://www.nihpromis.org

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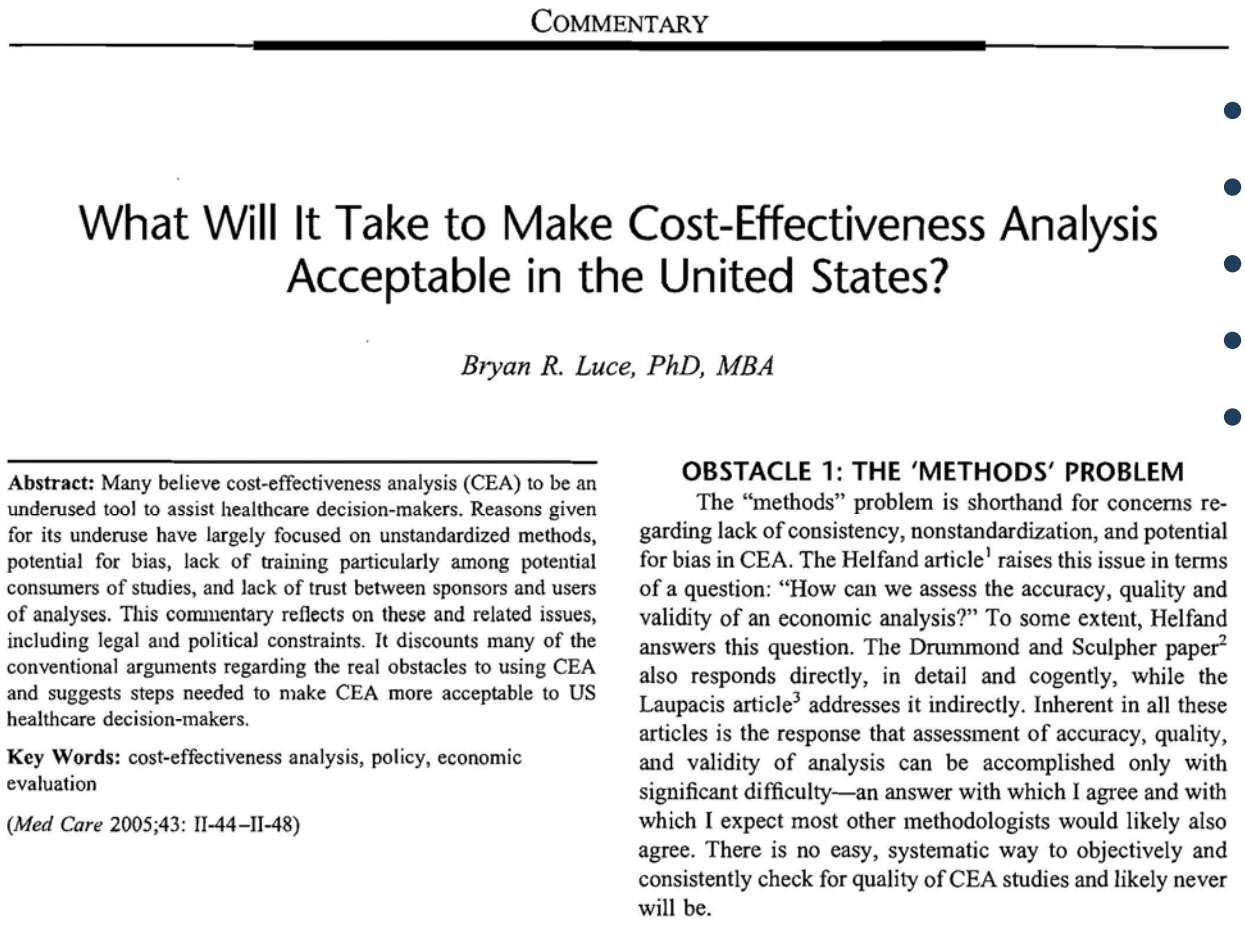
Barriers to Acceptance of the Rest of the Evidence



COMMENTARY

What Will It Take to Make Cost-Effectiveness Analysis Acceptable in the United States?

Bryan R. Luce, PhD, MBA

Abstract: Many believe cost-effectiveness analysis (CEA) to be an underused tool to assist healthcare decision-makers. Reasons given for its underuse have largely focused on unstandardized methods, potential for bias, lack of training particularly among potential consumers of studies, and lack of trust between sponsors and users of analyses. This commentary reflects on these and related issues, including legal and political constraints. It discounts many of the conventional arguments regarding the real obstacles to using CEA and suggests steps needed to make CEA more acceptable to US healthcare decision-makers.

Key Words: cost-effectiveness analysis, policy, economic evaluation

(*Med Care* 2005;43: II-44–II-48)

OBSTACLE 1: THE 'METHODS' PROBLEM

The "methods" problem is shorthand for concerns regarding lack of consistency, nonstandardization, and potential for bias in CEA. The Helfand article[1] raises this issue in terms of a question: "How can we assess the accuracy, quality and validity of an economic analysis?" To some extent, Helfand answers this question. The Drummond and Sculpher paper[2] also responds directly, in detail and cogently, while the Laupacis article[3] addresses it indirectly. Inherent in all these articles is the response that assessment of accuracy, quality, and validity of analysis can be accomplished only with significant difficulty—an answer with which I agree and with which I expect most other methodologists would likely also agree. There is no easy, systematic way to objectively and consistently check for quality of CEA studies and likely never will be.

- "methods" problem
- "training" problem
- "legal" problem
- "trust" problem
- "political" problem

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Meeting the Evidence Needs of Payers

- Improves behavior, delays onset of behavioral symptoms, and slows both functional and cognitive decline in clinical trials[1-4]
- Excellent safety and tolerability with low risk of unpleasant gastrointestinal side effects may improve therapy persistence[5-7]
- Proven to reduce caregiving time, cost, and caregiver distress[1,5,8]
- Reduced care dependence* in 26% more patients with NAMENDA vs placebo in a nursing home study[8]

Preferred status on the majority of health plan and Medicare Part D formularies[7]

Namenda®
memantine HCl
Extending memory and function

NAMENDA® (memantine HCl) is indicated for the treatment of moderate to severe Alzheimer's disease.

NAMENDA is contraindicated in patients with known hypersensitivity to memantine HCl or any excipients used in the formulation. The most common adverse events reported with NAMENDA vs placebo (≥5% and higher than placebo) were dizziness, confusion, headache, and constipation. In patients with severe renal impairment, the dosage should be reduced.

* Patients experienced ≥15% reduction in care dependence.

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Conclusion

- Who is defining value?
  - Payers and consumers but not regulatory, each with different goals: coverage, payment, use
- What are their evidence standards and how are they using the evidence?
  - RCT efficacy data and cost prevail, leaving value out
- What should U.S. payers know about AD products?
  - Identify relevant outcomes to measure: What is meaningful to clinicians, patients, caregivers?
  - Get outcomes measurement right
  - Generate comprehensive evidence – include observational studies, caregiver outcomes, AD impact, cost effectiveness models
  - Value value
- USE ALL OF THE EVIDENCE WISELY

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With Thanks to My Colleagues

- Bryan Luce
- Greg de Lissovoy
- Craig Hunter
- Rachael Fleurence
- Louisa Hefty
- William Lenderking
- Clark Paramore
- Denis Getsios
- Anne Samit
- Carrie Lancos

References

Benson K, Hartz AJ. A comparison of observational studies and randomized, controlled trials. *N Engl J Med.* 2000;342(25):1878-1886.

Bodenheimer T et al. Improving primary care for patients with chronic illness. *JAMA.* 2002; 288:1775-9.

Cohen JT and Neumann PJ. Decision analytic models for Alzheimer's disease: state of the art and future directions. *Alz & Dement*. 2008 May;4(3):212-22.

De Lissovoy G. How to collect data for FDA and CMS in the same study. *Medical Device & Diagnostic Industry*. April 2007.

Emanuel EJ, Fuchs VR, Garber AM. Essential elements of a technology and outcomes assessment initiative. *JAMA.* 2007;298(11):1323-1325

Feinstein AR. An additional basic science for clinical medicine: II.The limitations of randomized trials. *Ann Intern Med.* 1983;99(4):544-550.

Gold MR, Siegel JE, Russell LB, Weinstein MC (eds). Cost-effectiveness in Health and Medicine. NY: Oxford University Press, 1996

Laupacis A, Mamdani M. Observational studies of treatment effectiveness: Some cautions. *Ann Intern Med*. 2004;140:923–924.

Luce B. FMCP's Forum Paying for Pharmaceuticals: Performance Based Pricing & Outcomes; 4 08, San Francisco.

Luce B. "Cost, Evidence and Value". Presented to the "Cost-Over-Care Health Care Delivery Project"; June 26, 2007; Washington, DC.

Luce B. Critical Analysis of the 2008 National Landscape of Evidence-Based Medicine, Comparative Effectiveness and Health Technology Assessment Policies. Presented at: National Pharmaceutical Council Town meeting sponsored by JnJ, Evidence-based Medicine (EBM) and Comparative Effectiveness: Implications for the United States and the Pharmaceutical Industry; July 9, 2008; New Brunswick, New Jersey.

Luce B. FMCP's Forum Paying for Pharmaceuticals: Performance Based Pricing & Outcomes; 4 08, San Francisco.

Qaseem A et al. Current pharmacologic treatment of dementia: A clinical practice guideline from the American College of Physicians and the American Academy of Family Physicians. *Ann Intern Med* 2008; 148:370-378.

Raina P et al. Effectiveness of cholinesterase inhibitors and memantine for treating dementia: Evidence review for a clinical practice guideline. *Ann Intern Med* 2008; 148:379-397.

Revicki DA and Cella DF. Health status assessment for the twenty-first century: item response theory, item banking and computer adaptive testing. *Qual Life Res.* 1997; 6:595-600.

Revicki DA, Frank L. Pharmacoeconomic evaluation in the real world. Effectiveness versus efficacy studies. *Pharmacoeconomics.* 1999;15(5):423-434.

Rosenbaum PR. Discussing hidden bias in observational studies. *Ann Intern Med.* 1991;115(11):901-905.

Sackett DL, Gent M. Controversy in counting and attributing events in clinical trials. *N Engl J Med.* 1979;301(26):1410-1412.

Schwartz D, Lellouch J. Explanatory and pragmatic attitudes in therapeutic trials. *J Chronic Dis* 1967;20(8):637-648.

Wilson IB and Cleary PD. Linking clinical variables with health-related quality of life. A conceptual model of patient outcomes. *JAMA* 1995 Jan 4;273(1):59-65.

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