April 29, 2020

1. How cost-effectiveness analyses Are Used
2. Additional resources for cost-effectiveness analyses

## How CE Analyses Are Used

- At the bedside/In the office
- Health policy
  - –Public Health
  - –Clinical care

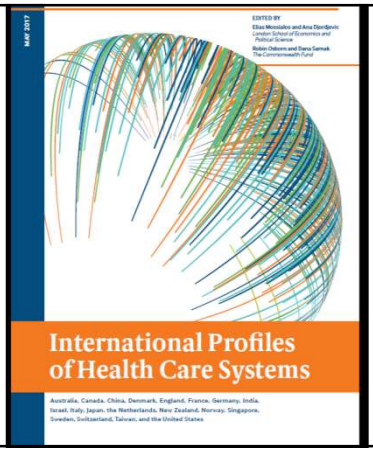
## Classic Examples

Annual Review of Public Health. Vol. 28: 365-91; 2007

- Childhood immunizations
- Screening for disease
- Tobacco control
- Preventing injury to motor vehicle occupants
- Blood product safety

# Cost-Effectiveness Analysis to Inform Health Policy outside the United States

Drug Pricing Is the Example




## Canada

The federal government cofinances provincial and territorial programs, which must adhere to the Canada Health Act (1985), . . . .

## Canada

The Canadian Agency for Drugs and Technologies in Health . . . . reviews the clinical effectiveness and cost-effectiveness of drugs and provides common, nonbinding formulary recommendations to the publicly funded provincial drug plans (except in Quebec) . . . .

## Australia

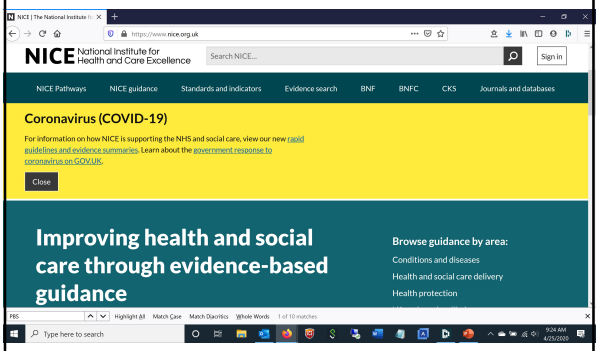
The Australian Government is a near-monopolist purchaser of patent medicines which, combined with tight prescribing requirements, allows it to control pharmaceutical pricing. . . . Pharmaceutical subsidies are provided through the PBS [Pharmaceutical Benefits Scheme]. To be listed, pharmaceuticals need to be approved for cost-effectiveness by the independent Pharmaceutical Benefits Advisory Committee (PBAC).

## England

. . . . the Secretary of State has a legal duty to promote a comprehensive health service that provides care free of charge . . . day-to-day responsibility for running the NHS rests with a separate public body, NHS England.

## England

- The National Institute for Health and Clinical Excellence (NICE) sets guidelines for clinically effective treatments and appraises new health technologies for their efficacy and cost-effectiveness.
- Started in 1999
- Problem was “Postcode Lottery”




## NICE

- Guidance based on cost-effectiveness analyses, modified by “other social values”
- NICE recommends against proposed drug coverage 10-15% of time
  - 30% of these recommendations are appealed
  - 10% of these appeals are successful

N ENGL J MED 364;14 NEJM.ORG APRIL 7, 2011

In general, NICE considers treatments cost-effective if their incremental cost-effectiveness ratio is £20,000 ($34,400) or less per QALY. This ratio, however, is not a rigid cutoff. On occasion, NICE accepts values between £20,000 and £30,000 ($51,600). On rare occasions, it accepts values beyond £30,000. This ap-

N ENGL J MED 359;19 WWW.NEJM.ORG NOVEMBER 6, 2008

Some of the more controversial NICE decisions have concerned drugs for the treatment of Alzheimer's disease (donepezil, galantamine, rivastigmine and memantine ) and for renal cell carcinoma (bevacizumab, sorafenib, sunitinib and temsirolimus). All are drugs with a high cost per treatment, and NICE has either rejected or restricted their use on the grounds that they are not cost-effective.

## NICE and Multiple Sclerosis

- Beta interferon and glatiramer acetate
- Rejected
- Controversy over how to judge long-term results with only short-term trials
- Conditional acceptance
  - If the drugs don't deliver a long-term ICER less than $66,000 per QALY, the pharmaceutical companies will return the monies they received from the government

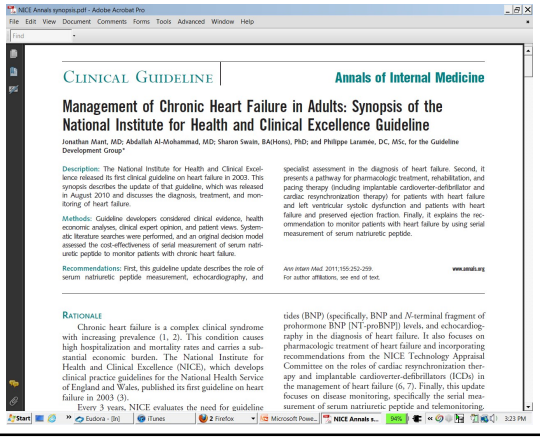
**NICE and Antibodies against Proprotein Convertase Subtilisin/Kexin type 9 (PCSK9) to Lower Cholesterol**

- In November 2015
  - NICE rejected Repatha (Amgen) for reasons of cost and effectiveness
- In February 2016
  - NICE approved Repatha for limited use in specific types of patients contingent on Amgen offering a discount
  - Rejected Praluent (Sanofi/Regeneron) and 3 months later approved it for limited use in specific types of patients contingent on a discount

http://www.adamwishart.info/the-price-of-life

https://evestrust.co.uk/eves-dreams/the-story-of-a-brave-man-and-his-dream/


The Price of Life: cancer patient Eric Rutherford Photo: BBC



CLINICAL GUIDELINE

Annals of Internal Medicine

Management of Chronic Heart Failure in Adults: Synopsis of the National Institute for Health and Clinical Excellence Guideline

Jonathan Mant, MD; Abdallah Al-Mohammad, MD; Sharon Swain, BA(Hons), PhD; and Philippe Laramée, DC, MSc, for the Guideline Development Group*

**Description:** The National Institute for Health and Clinical Excellence released its first clinical guideline on heart failure in 2003. This synopsis describes the update of that guideline, which was released in August 2010 and discusses the diagnosis, treatment, and monitoring of heart failure.

**Methods:** Guideline developers considered clinical evidence, health economic analyses, clinical expert opinion, and patient views. Systematic literature searches were performed, and an original decision model assessed the cost-effectiveness of serial measurement of serum natriuretic peptide to monitor patients with chronic heart failure.

**Recommendations:** First, this guideline update describes the role of serum natriuretic peptide measurement, echocardiography, and specialist assessment in the diagnosis of heart failure. Second, it presents a pathway for pharmacologic treatment, rehabilitation, and pacing therapy (including implantable cardioverter-defibrillator and cardiac resynchronization therapy) for patients with heart failure and left ventricular systolic dysfunction and patients with heart failure and preserved ejection fraction. Finally, it explains the recommendation to monitor patients with heart failure by using serial measurement of serum natriuretic peptide.

*Ann Intern Med.* 2011;155:252-259. www.annals.org
For author affiliations, see end of text.

RATIONALE

Chronic heart failure is a complex clinical syndrome with increasing prevalence (1, 2). This condition causes high hospitalization and mortality rates and carries a substantial economic burden. The National Institute for Health and Clinical Excellence (NICE), which develops clinical practice guidelines for the National Health Service of England and Wales, published its first guideline on heart failure in 2003 (3).

Every 3 years, NICE evaluates the need for guideline updates (BNP) (specifically, BNP and *N*-terminal fragment of prohormone BNP [NT-proBNP]) levels, and echocardiography in the diagnosis of heart failure. It also focuses on pharmacologic treatment of heart failure and incorporating recommendations from the NICE Technology Appraisal Committee on the roles of cardiac resynchronization therapy and implantable cardioverter-defibrillators (ICDs) in the management of heart failure (6, 7). Finally, this update focuses on disease monitoring, specifically the serial measurement of serum natriuretic peptide and telemonitoring.

## Beginning in April 2013

- NICE became a public body independent of the government
- New name: National Institute for Health and Care Excellence (still NICE)
- New responsibilities included guidance for social services

## Additional Criteria for Drug Pricing

- Prices reflect factors that are not fully recognized by QALYs, for example, drugs for diseases with
  - A greater "burden of illness"
  - Unmet need
  - Particularly severe consequences
- And drugs with
  - Greater therapeutic innovation
  - Wider societal benefits

**NICE: Moving Onward**
Michael D. Rawlins, M.D.
n engl j med 369;1 nejm.org july 4, 2013

"If the United States is to meet the needs of all its citizens, especially in the face of an increasingly elderly population, it will someday have to take both clinical effectiveness and cost-effectiveness into account in determining the contents of its package of universal health care. Our experience in the United Kingdom shows that, though sometimes uncomfortable, it is possible."

## What about the United States?

## Medicare

- 1965 authorizing legislation prohibits payment for ". . . items and services that are not reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member."
- Reasonable and necessary means safe, effective, generally accepted ("customary")

## Medicare Exceptions

- Some adult vaccines
- Screening mammography
- Annual Medicare wellness exam
- Implantable cardiac defibrillators

"We don't use cost to decide the evidence issue, but we do use cost to decide if the issue is important enough to address."

## Medicare

- 1989 proposed regulations
  "We believe the requirement . . . that a covered service be 'reasonable' encompasses the authority to consider cost as a factor in making Medicare coverage decisions."
- Opposition ("rationing")
- 1998 Medicare Coverage Advisory Committee (MCAC)
  - Cost considered only when effects are equivalent

## National Center for Health Care Technology (NCHCT)

In 1978, Congress established the National Center for Health Care Technology (NCHCT) to conduct health technology assessment and advise the Health Care Financing Administration (HCFA [now HHS]) on Medicare coverage issues. . . . when Ronald Reagan became president, he eliminated funding for NCHCT.

## Oregon

- Expand Medicaid to cover more people
- Identify conditions paired with treatments
- Rank condition-treatment pairs
  - Use CE analyses
  - Telephone survey of utilities using rank-and-scale method
- Pay only for condition-treatment pairs above the budget line
  - 688 condition-treatment pairs were ranked, and only the first 568 were covered.

## Oregon

- 1990 list
  - Tooth capping ranked higher than surgery for ectopic pregnancy
  - Splints for TM joints ranked higher than appendectomies
- 1992 list
  - Expert judgment, not CE analyses

## Oregon's 1992 List

- Challenged by the federal government
- Violated Americans with Disabilities Act
  - Quality of life measures were based only on the preferences of healthy individuals
  - Treatments that restored people to their usual disabled state were undervalued relative to treatments that restored people to their usual normal state

The Upshot
THE NEW HEALTH CARE

**Forbidden Topic in Health Policy Debate: Cost Effectiveness**

DEC. 15, 2014
**Aaron E. Carroll**

"But the plan hit a snag in 2008 when a woman with recurrent lung cancer was denied a drug that cost $4,000 a month because the proven benefits were not enough to warrant the costs. . . . The Oregon health plan made things worse in this case, however, by offering to cover drugs for the woman's physician-assisted suicide, if she wanted it. Even supporters of the plan found the optics of this decision difficult to accept."

## What Happened in Oregon?

"The most fundamental lesson . . . was that the use of CE analysis was unlikely to produce a socially or politically acceptable definition of necessary care" in the United States.

--Peter J. Neumann, ScD

## Agency for Health Care Policy and Research, now AHRQ

In 1995, the Agency for Health Care Policy and Research was nearly eliminated by . . . opponents, in part because of the agency's use of CEA.

Health Aff (Millwood). 2003 Jan-Jun;Suppl Web Exclusives:W3-283-307.
DOI: 10.1377/hlthaff.w3.283

## Other Organizations that Use Cost-Effectiveness Analyses

- Department of Veterans Affairs
- Department of Defense
- Centers for Disease Control (CDC)
- Agency for Healthcare Research and Quality (AHRQ)
- Health system and hospital drug formularies
- Some state Medicaid programs
- Blue Cross Technology Evaluation Center and other insurers

## Comparative Effectiveness Research

- 2008 IOM recommended national program of comparative effectiveness research
- 2009 American Recovery and Reinvestment Act (ARRA)

## American Recovery and Reinvestment Act (ARRA) of 2009 (P.L. 111-5)

- Comparative-effectiveness research (CER) covers “research that compares the clinical outcomes, effectiveness, and appropriateness of items, services, and procedures that are used to prevent, diagnose, or treat diseases, disorders, and other health conditions.”

## JAMA. 303(10):951-8, 2010 Mar 10

- Analyzed 328 medication studies recently published in 6 top medical journals
- Just 32% were aimed at determining which available treatment was best
- The rest compared a medication with a placebo
- 87% of the comparative effectiveness studies were funded entirely or in part by nonprofit foundations or government institutions

## Patient Protection and Affordable Care Act , March 2010 Obamacare

- The bill establishes an independent, not-for-profit corporation, the Patient-Centered Outcomes Research Institute (PCORI)
- "to assist patients, clinicians, purchasers, and policy-makers in making informed health decisions . . . with respect to the relative health outcomes, clinical effectiveness, and appropriateness of medical treatments, services, . . . . "

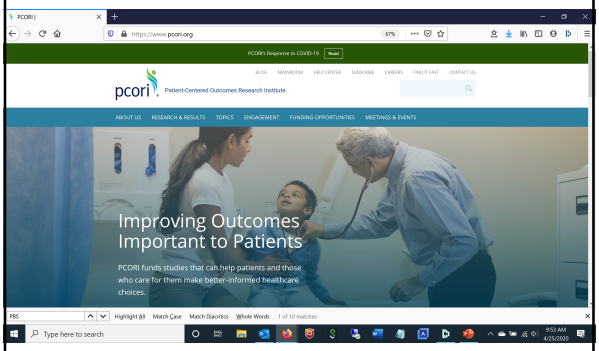
## Patient Protection and Affordable Care Act , March 2010

- Research priorities based on the prevalence and burden of diseases and patient care
- Primary research and systematic reviews of existing studies
- Contracts with NIH, AHRQ, and non-government researchers

## Funding

Patient-Centered Outcomes Research Trust Fund (~$500 m/yr)

The PCOR Trust Fund receives income each year from three funding streams: appropriations from the general fund of the Treasury, transfers from the Centers for Medicare and Medicaid trust funds, and a fee assessed on private insurance and self-insured health plans (the PCOR fee).




## Legislating against Use of Cost-Effectiveness Information

Peter J. Neumann, Sc.D., and Milton C. Weinstein, Ph.D.

N ENGL J MED 363;16 NEJM.ORG OCTOBER 14, 2010

> The Patient-Centered Outcomes Research Institute . . . shall not develop or employ a dollars per quality adjusted life year (or similar measure that discounts the value of a life because of an individual's disability) as a threshold to establish what type of health care is cost effective or recommended. The Secretary shall not utilize such an adjusted life year (or such a similar measure) as a threshold to determine coverage, reimbursement, or incentive programs under title XVIII.
>
> — The Patient Protection and Affordable Care Act[1]

The Incidental Economist
Who says PCORI can't do cost effectiveness?
Posted: 14 Oct 2013 03:00 AM PDT
*The following is a guest post by Nicholas Bagley, University of Michigan Assistant Professor of Law.*

- The first thing to notice is that this isn't a flat prohibition on folding cost into PCORI research. . . . it means that PCORI can't say that a treatment costs "too much" just because its costs exceed, say, $50,000 for every QALY saved. That $50,000-per-QALY line would be a threshold.
- But does the statute prohibit PCORI from considering costs altogether? Nope. .. .The institute could, for example, compile cost information about the treatments that it studies. No thresholds there. Alternatively, it could rank the cost-effectiveness of alternative treatments. Again, no thresholds.

Joe V. Selby, MD, MPH, Executive Director


**Will PCORI fund cost-effectiveness research?**

No. We're very clear in our funding announcements that we do not fund—in fact, we don't even review—proposals that have cost-effectiveness analyses in them or projects that propose to compare the cost of care for two different treatments. It has to do with the intent of the legislation, both as written and as described to us by people who were there [in Congress]. We feel that we have our plates full with the comparative clinical-effectiveness research, and, in many ways, if you're going to do a cost-effectiveness analysis, you need good comparative clinical-outcomes data first. That's our business.

VOLUME 18 | NUMBER 8 | AUGUST 2012 NATURE MEDICINE

## 2019 Reauthorization of PCORI Changes the Rules

Consideration of the "full range of outcomes data" to include the "potential burdens and economic impacts of the utilization of medical treatments. . . . These potential burdens and economic impacts include medical out-of-pocket costs, . . ., non-medical costs to the patient and family, . . . and healthcare utilization."

Nakela Cook, M.D., M.P.H., F.A.C.C. became PCORI's Executive Director on April 15, 2020. Dr. Cook comes to PCORI from the National Institutes of Health's National Heart, Lung, and Blood Institute (NHLBI), where she served as Senior Scientific Officer and Chief of Staff.

## Why the Public Aversion to CEA?

- People don't trust government involvement in health care
  - CEA = cost-saving or rationing
- People don't trust CEAs
  - Pharmaceutical sponsorship
  - NEJM editorial

EDITORIAL

**The Journal's Policy on Cost-Effectiveness Analyses**

Jerome P. Kassirer, M.D., and Marcia Angell, M.D.

N Engl J Med 1994; 331:669-670

The following conditions must be met: First,. . . . We will not review such studies if any of the authors is receiving a direct salary from the sponsoring company or a competing company or if any author has an equity interest in, an ongoing consultancy with, or membership on the scientific advisory board of such a company, or a related patent pending. Second, we must receive written assurance that the agreement between the authors and the funding company ensures the authors' independence. . . . Third, . . . the manuscript must include all the data used in the analysis, all assumptions on which the data are based, and any model used in the analysis.

## Organized Opposition

- Ideological opposition to government interference in the private market
- CEA is viewed as a potential threat to technologies that produce a lot of income for those who manufacture and use them

## Why Are Decision Maker Averse to CEA?

- CEAs are not relevant
  - Budget constraints
- Fear of lawsuits about coverage decision
- Decision makers' short-term outlook vs CEA's long-term outlook

## Legal Issues

- Some state regulations require insurance coverage "unhindered by a plan's fiscal concerns"
- Courts have overturned coverage decisions based less on scientific evidence and more on "usual, customary, and reasonable"

## Conflict in Ethical Principles

- This course has emphasized the utilitarian principle – maximize total health
- Other principles
  - Equity -- equal access
  - Prioritarian principle – include the least advantaged
  - Principle of urgent need – favor urgent need over non urgent need
  - Rule of rescue – favor highly visible people over invisible people

## Methodological Issues

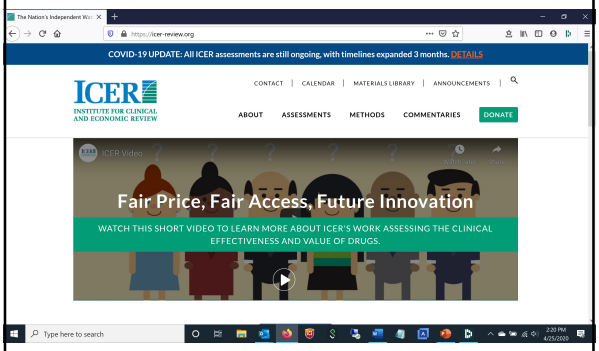
- Cost effectiveness reviews are particularly controversial for older patients, those with disabilities, cancer patients, and patients with rare diseases.
- Restoring a patient to good health can bring economic benefits not captured in the CEA model such as economic productivity, return to caregiver status, and better performance in school.

## Institute for Clinical and Economic Review (ICER)

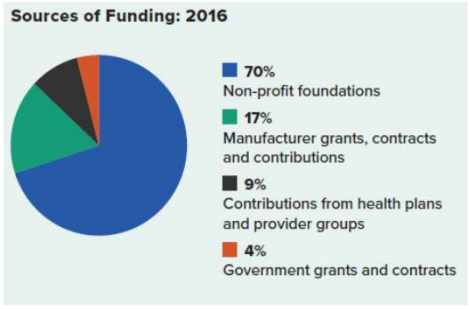
- Conducts cost-effectiveness analyses on drugs and medical devices for the US market
- Some refer to it as “America’s NICE”

## Institute for Clinical and Economic Review (ICER)

- Founded in 2006 as an academic research project at Harvard Medical School
- Became a private, non-profit, independent organization in 2013
- Has no regulatory or reimbursement authority




## ICER



## Why is ICER successful?

- It has filled a vacuum created by the absence of US Government entities
- It contracts with academic groups to produce its cost-effectiveness analyses
- Its process is open with two public comment periods for input from patients, drug manufacturers, clinicians, clinical researchers, and others

## Organizations That Use ICER

- Insurance Companies
- Pharmaceutical Companies
- Pharmaceutical Benefits Managers (PBMs)

## What are PBMs?

PBMs manage the pharmaceutical part of the business for insurance companies. They decide which drugs to include in the formularies, administer drug claims, and negotiate with drug manufacturers and pharmacies on behalf of insurers.

## PBMs that Use ICER

- Express Scripts Holding Co.
- CVS
- Optum (United Health)
- Prime Therapeutics LLC
- Together, they have more than 180 million customers and control approximately 80% of the market

## Insurers that Use ICER

- Care Inc.
- Aetna Inc.
- Anthem Inc.
- Harvard Pilgrim Health

## Why would a pharmaceutical company work with ICER?

- When faced with an expensive, new drug, insurance companies and PBMs can deny coverage for the drug, restrict coverage to only some patients, and require that patients pay high deductibles and copayments for the drug
- These restrictions limit sales of the new drug and decrease profits

## Pharmaceutical Companies that Use ICER

Only one so far:

Sanofi and Regeneron Pharmaceuticals Inc.

- Dupixent (dupilumab) for atopic dermatitis, before the drug was launched and before the price was announced
- Praluent (alirocumab), a PCSK9 inhibitor for treating hypercholesterolemia, after the drug was launched and after the price was announced

## The Story of Alirocumab

- In 2015 FDA approved alirocumab for lowering cholesterol after existing drugs fail
- Alirocumab entered the market with a list price of about $14,000 per year
- In 2016, global net sales of alirocumab were $116 million, far short of expectations
- In the US only 47% of prescriptions received payer approval, and 31% of approved prescriptions were not filled by patients, most because of high out-of-pocket costs

## The Story of Alirocumab

- The company shared with ICER prepublication data from the first trial that examines all-cause mortality and cardiovascular mortality
- In November 2018, ICER concluded that the list price would have to be reduced by 86% to meet a willingness-to-pay threshold of $100,000 per QALY

## The Story of Alirocumab

In March 2019 the company offered to reduce the price of alirocumab by approximately 60% to $5,850 annually for a subgroup of patients who derive the greatest mortality benefit if payers remove barriers to access

## Recent ICER Change

. . . the Equal Value of Life Years Gained (evLYG), . . . evenly measures any gains in length of life, regardless of the treatment's ability to improve patients' quality of life. . . . whether treating individuals with cancer, multiple sclerosis, diabetes, epilepsy, or a severe lifelong disability

**Future Directions for Cost-effectiveness Analyses in Health and Medicine**

**Peter J. Neumann, et al. Medical Decision Making 2018, Vol. 38(7) 767–777. DOI: 10.1177/0272989X18798833**

We highlight 7 key areas:

1. CEA and perspectives (determining, valuing, and summarizing elements for the analysis)
2. Modeling (comparative modeling and model transparency)
3. Health outcomes (valuing temporary health and path states, as well as health effects on caregivers)

**Future Directions for Cost-effectiveness Analyses in Health and Medicine**

4. Costing (a cost catalogue, valuing household production, and productivity effects)
5. Evidence synthesis (developing theory on learning across studies and combining data from clinical trials and observational studies)
6. Estimating and using cost-effectiveness thresholds (empirically representing 2 broad concepts: opportunity costs and public willingness to pay)
7. Reporting and communicating CEAs (written protocols and a quality scoring system).

## What are models good for?

"A model isn't a crystal ball to make predictions," he said. "It's more like a pensieve* — you take what you already have in your brain, you pull it out, and you swirl it around, so that you can better understand the ramifications of your assumptions. That's all these models are for — to get our head around what's already going on and what we can do about it."

*The *Pensieve* in Harry Potter's Hogwarts school is a magical instrument used by the Headteachers to view memories.

## What are models good for?

Robert Ross, an infectious disease researcher, said over 100 years ago: "Such calculations…are useful, not so much for the numerical estimates yielded by them, but because they give us more precision to our ideas, and a guide for future investigations."

A model is only an argument. It gives provisional answers to different kinds of what-if scenarios, which we can then examine and debate. Most of the time it's an argument with ourselves.

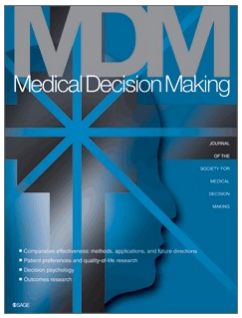
--Michael Z. Levy, PhD, Associate Professor of Epidemiology, Perelman School of Medicine
https://www.pennmedicine.org/news/news-blog/2020/april/coronavirus-models-arent-crystal-balls-so-what-are-they-good-for

## Let's Switch Direction
Resources for CEAs

- Journals
- Professional Societies and Their Meetings

## Journals That Are Resources for CEAs

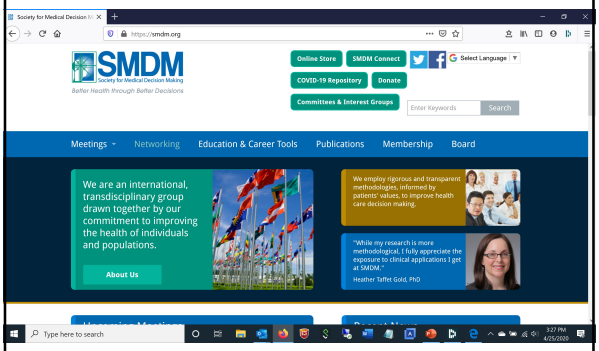
- **Methodology and CE Analyses**
  - *Medical Decision Making*
  - *Health Economics*
- **CE Analyses**
  - *Value in Health*
  - *Pharmacoeconomics*






## Societies and Meetings That Are Resources for CEAs

- Society for Medical Decision Making
  - http://www.smdm.org/
- International Society for Pharmacoeconomics and Outcome Research (ISPOR)
  - http://www.ispor.org/



# 42nd Annual North American Meeting

Relationships in Medical Decision Making

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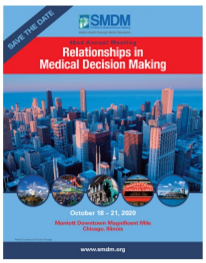
October 18 - October 21, 2020
Chicago, IL

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