Frankenstein, Dracula and Net Benefit Regression: What You Need to Know

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Disclaimers and Perspectives

Disclaimers

- My views represent my views, not views of:
    - St. Michael's Hospital
    - The Ministry of Health
    - Cancer Care Ontario
    - Canadian Cancer Society
    - University of Toronto

Perspective

- Academic
    - Teaching and research
- Have reviewed for
    - DQTC, CEDAC, CED / CCO subcommittee
- Occasionally interact with Industry

Plan

- More research on population therapeutics
- Cost-effectiveness using models and trials
- Net benefit regression

×More research demanded

×Cost-effectiveness

×Net benefit regression

Three key trends

1) Comparative effectiveness research
2) The liberation of administrative data
3) Increasing drug prices

×More research demanded

×Cost-effectiveness

×Net benefit regression

Comparative effectiveness research in CANADA

- **Comparative effectiveness is**
    - "the evaluation of the relative (clinical) effectiveness, safety, and <u>cost</u> of 2 or more medical services, drugs, devices, therapies, or procedures used to treat the same condition."

- **Who uses this Canada?**
    - Common Drug Review (CDR) at the Canadian Agency for Drugs and Technologies in Health (CADTH)
    - Committee to Evaluate Drugs (CED & CED/CCO)
        - Ontario Ministry of Health and Long Term Care
    - Your hospital's pharmacy?

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Comparative effectiveness research in the USA

- In February, the United States Congress appropriated (via the economic stimulus bill)
- $1,100,000,000 (1.1 Billion) to
  - DHHS, AHRQ, and NIH
- for Comparative Effective Research (CER).

- With $100's of millions available for CER, more will be done.

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The potential impact

? More interest in CER?

  ? Policy makers / decision makers

  ? Researchers

  ? Journals / journalists

? Will you feel an elephant turn over in bed?

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The liberation of administrative data

- In ONTARIO,
  - ICES to create more satellite sites
  - Special focus on liberating cancer data
- Direct effect (from this action)
  - More access to data
- Indirect effect (as others respond)
  - More access to data
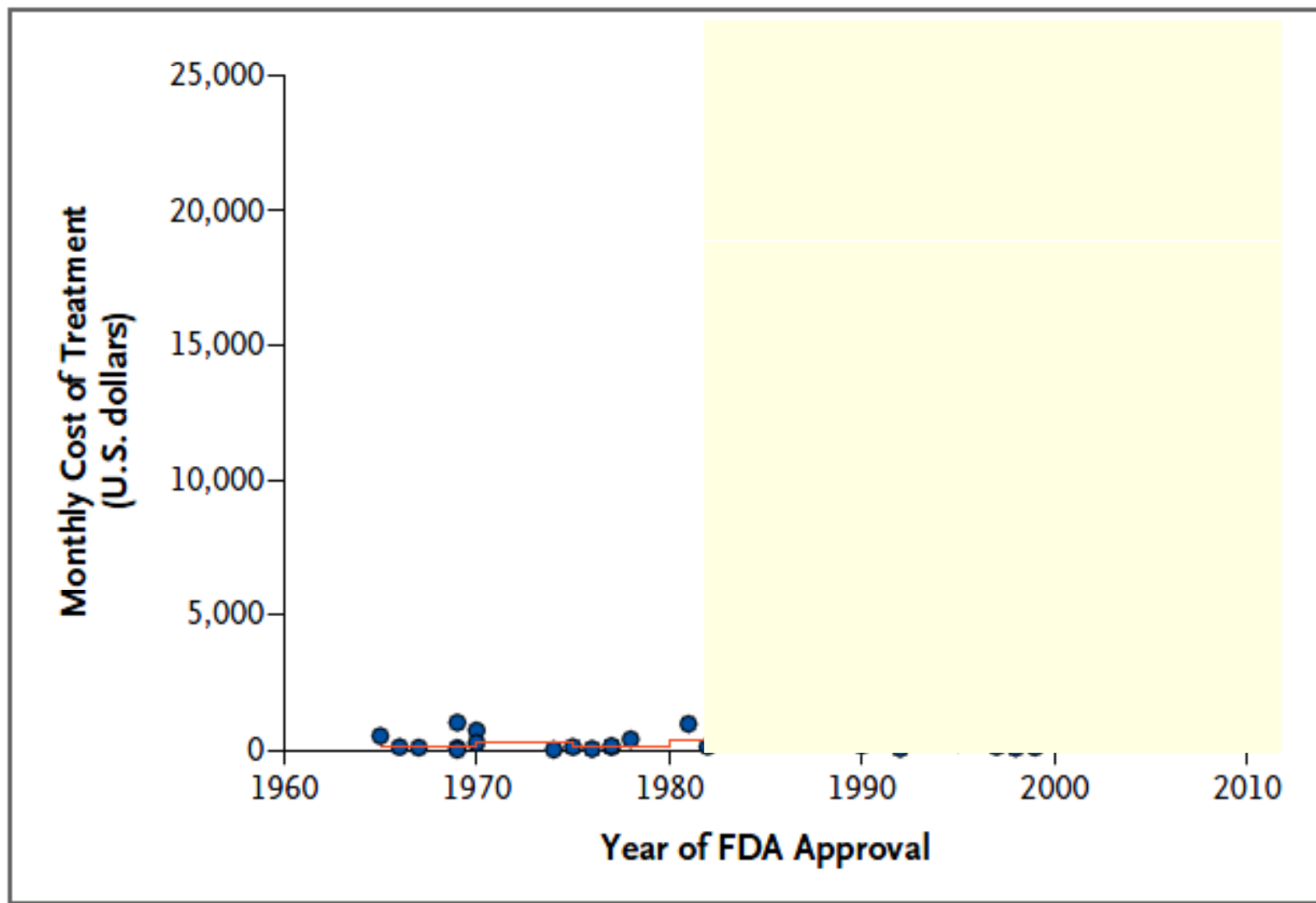 - More info about access to data
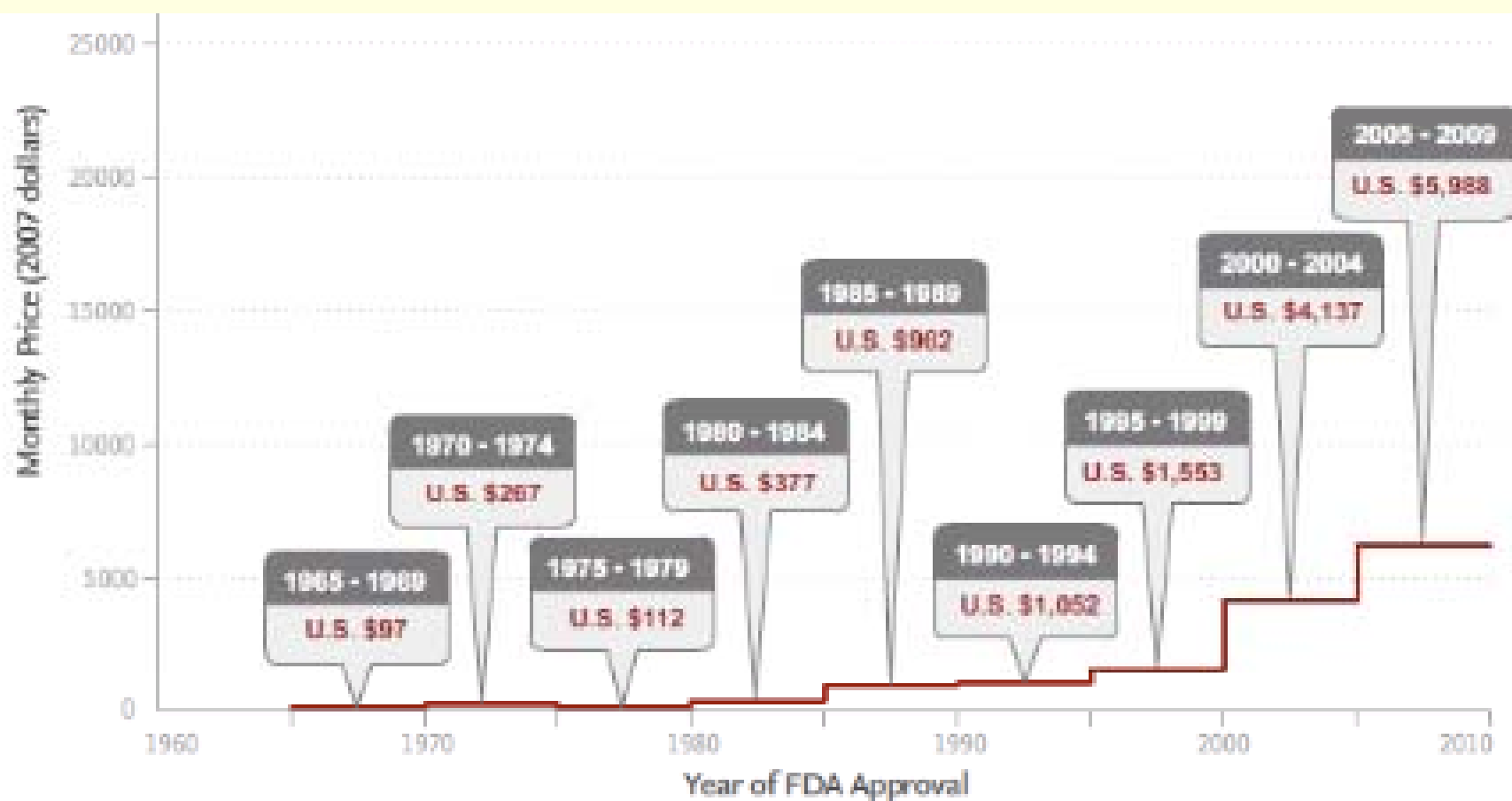
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Increasing drug prices: Bach (2009)

"Health economists are concerned... because the prices of cancer drugs appear to be rising faster than the health benefits associated with them... the increase in the cost of treatment exceeded the magnitude of improvement in efficacy... making each treatment advance less cost-effective than the one that preceded it."

The New York Times

January 27, 2009

Medicare Widens Drugs It Accepts for Cancer

By REED ABELSON and ANDREW POLLACK

Medicare, with little public debate, has expanded its coverage of drugs for cancer treatments not approved by the Food and Drug Administration.

Cancer doctors had clamored for the changes, saying that some of these treatments, known as off-label uses, were essential if patients were to receive the most up-to-date care. But for many such uses there is scant clinical evidence that the drugs are effective, despite costing as much as $10,000 a month. Because the drugs may represent a patient's last hope, though, doctors are often willing to try them.

The new Medicare rules are the latest twist in a protracted debate over federal spending on off-label drugs — drugs prescribed for uses other than those for which they have been specifically approved.

Proponents of the changes say such spending not only helps patients, but can also enhance medical understanding of which treatments work against various forms of cancer.

But opponents argue that the new approach may waste money and needlessly expose patients to the side effects of drugs that may not help them. They also raise the possibility of conflicts of interest, because the rules rely on reference guides that in some cases are linked to drug makers.

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Meaning and implication

- There are compelling reasons to believe that there will be a growing need for research on what we are getting for what we are paying.

- Cost effectiveness analysis (CEA) provides this information.

- Net benefit regression is a way to do CEA.

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ANALYSIS

The "number needed to treat" turns 20 — and continues to be used and misused

Finlay A. McAlister MD MSc

In the 20 years since the initial description of the number needed to treat,[1] this method of expressing the efficacy of an intervention has become widely used. Indeed, the Consolidated Standards of Reporting Trials statement recommends that the number needed to treat be reported in randomized trial publications,[2] and journals of secondary publication (e.g., *American College of Physicians Journal Club*) routinely calculate and report the number needed to treat for studies of therapy. As well, there have been increasing calls for health care policy makers to use numbers needed to treat to inform their recommendations;[3] and league tables comparing numbers needed to treat have appeared in the literature[4-7] and on the internet (See www.cebm.utoronto.ca/glossary/nnts .htm#table and www.jr2.ox.ac.uk/bandolier/band50/b50-8 .html for examples from different branches of medicine).

Having attended hundreds of journal clubs as well as departmental and divisional rounds over the past 2 decades, I am consistently impressed by the frequency with which audience members display skepticism about a therapy if its efficacy is presented only in relative terms such as odds ratios or relative risk reductions. Not infrequently, this skepticism is healthy — the dangers of misinterpreting the importance of a therapy when relying solely on relative effect estimates are well known.[1] However, I have also been struck by the extent to which discussions of a therapy's number needed to treat, and even comparisons between therapies on this basis, are accepted at face value. A review of the literature and their experiences in journal club and critical appraisal settings led Chong and colleagues to also express concern that many clinicians appear to hold "the impression that NNT
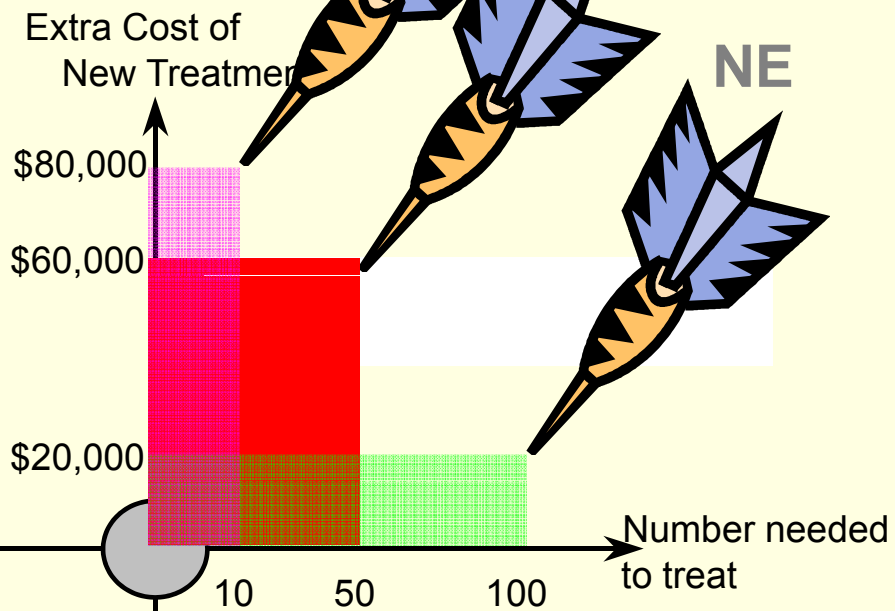
Key points

- The number needed to treat is a useful measure for counselling patients about their potential to benefit from a particular intervention.
- It is sometimes used as a basis for comparing 2 or more therapies; however, it is important to appreciate that this number is not therapy-specific, but rather it is specific to the results of a single comparison.
- If it is to be used to compare treatments, the therapies must have been tested in similar populations with the same condition at the same stage, using the same comparator, time period and outcomes.
- The factors that influence the number needed to treat beyond the efficacy of the treatment must be taken into account to avoid drawing erroneous conclusions when comparing numbers needed to treat for 2 or more interventions.

cussing treatment options with patients. A detailed discussion of how to personalize this number to each patient's situation, including means to incorporate potential harms as well as patient values and preferences, has been published.[8]
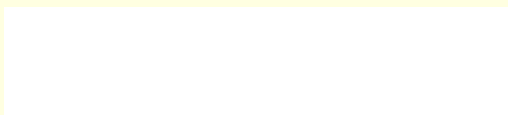
Given the many heuristics that guide medical decision-making, it is not surprising that the number needed to treat has also been embraced by those wishing to compare 2 or more therapies. Proponents use it as though it offers a single dimensionless metric. Although the number needed to treat may appear to be an absolute measure of clinical benefit, it is in fact specific to a single comparison in a single study because it is the reciprocal of the difference in event rates between 2 treatment options. Thus, this number should not be

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NNT and cost-effectiveness

NW

Extra Cost of
New Treatment

NE

$80,000
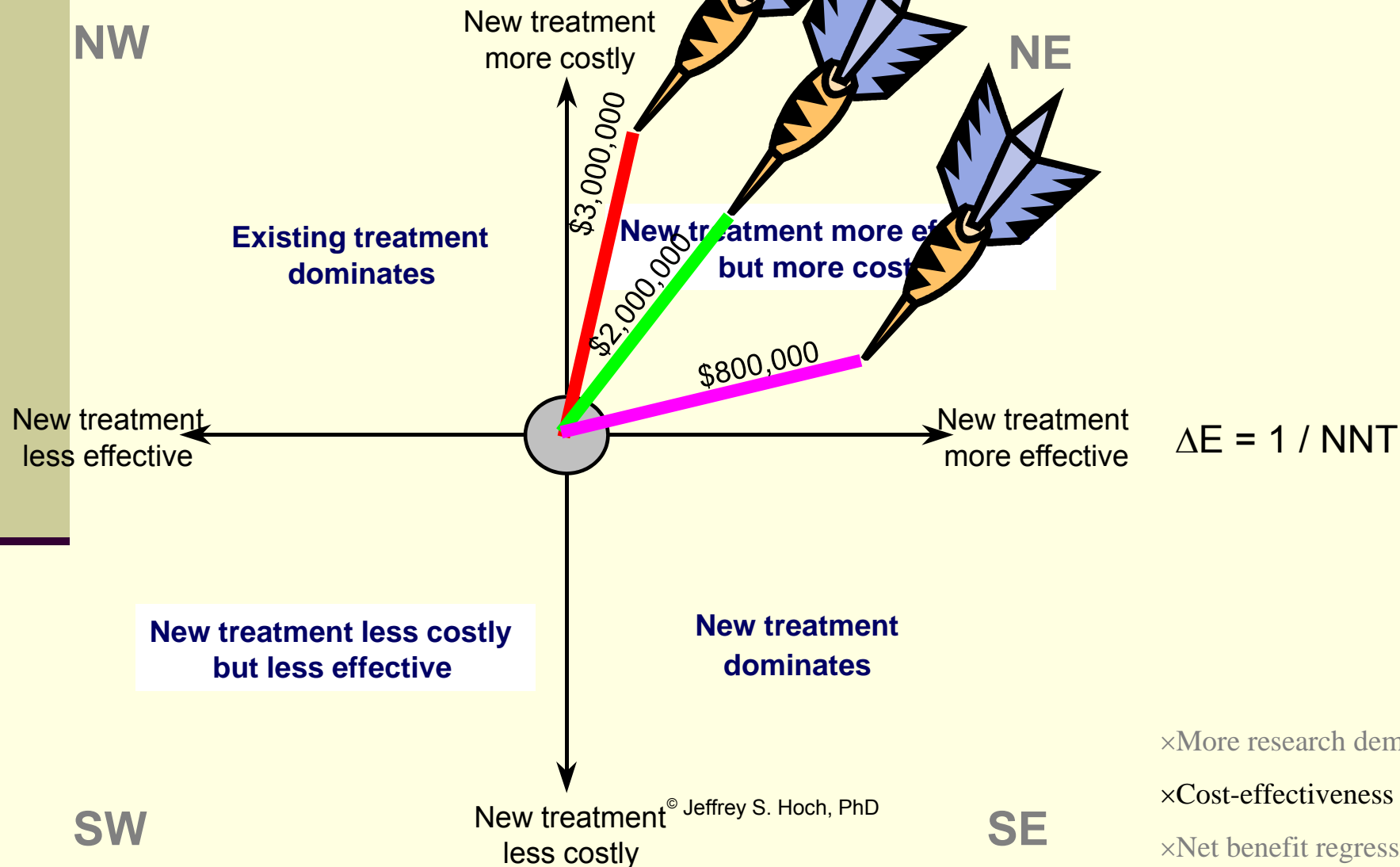
$60,000

$20,000

Number needed
to treat

10   50   100

New treatment
less costly

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SW

SE

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The cost-effectiveness plane

NW

New treatment
more costly

NE

**Existing treatment
dominates**

$3,000,000

**New treatment more effective
but more costly**

$2,000,000

$800,000

New treatment
less effective

New treatment
more effective

$\Delta E = 1 / NNT$

**New treatment less costly
but less effective**

**New treatment
dominates**

SW

New treatment
less costly

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SE

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Cost-effectiveness analysis (CEA)

- The goal of CEA is to compare the costs and effects of one treatment to a relevant alternative.
- CEA computes an incremental cost-effectiveness ratio (ICER).
- Researchers compute the ICER using data from
  - Individuals, based on their reported costs and effects
  - or
  - Various sources, cobbling together a prediction model

$$\hat{R} = \frac{\overline{C}_T - \overline{C}_C}{\overline{E}_T - \overline{E}_C} = \frac{\Delta C}{\Delta E}$$

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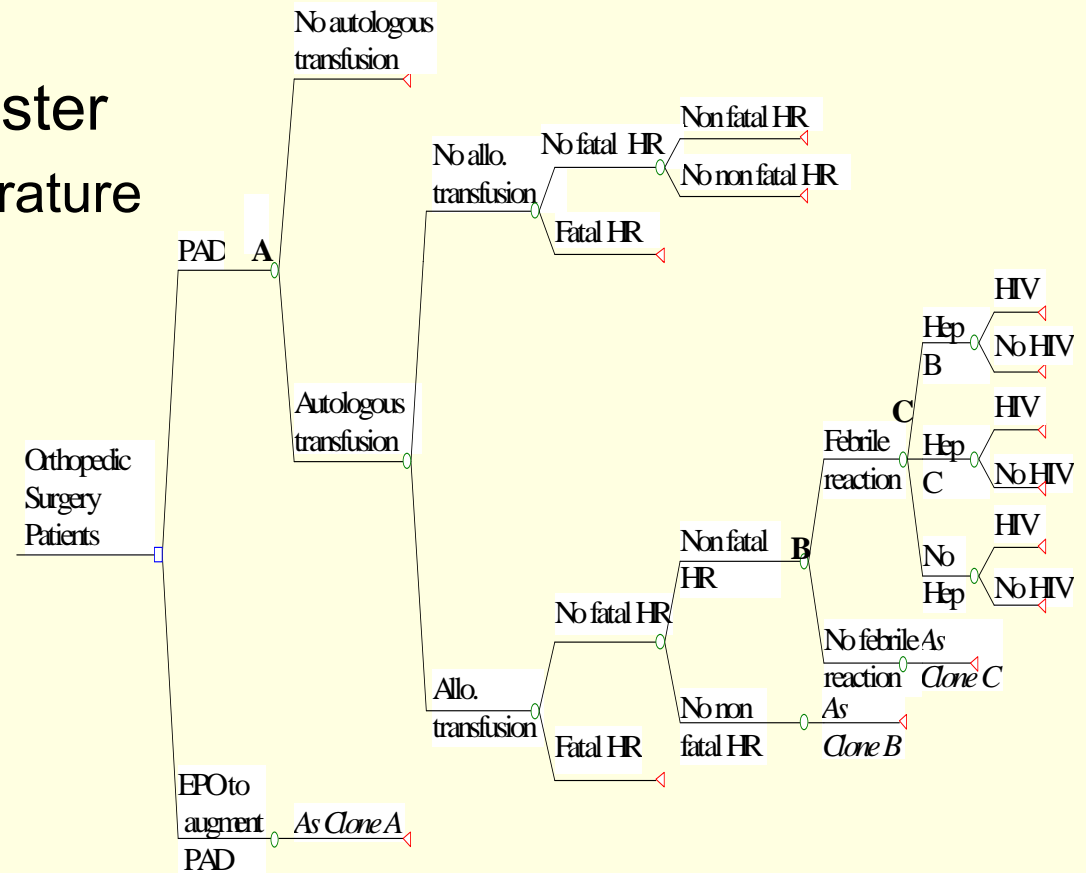
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Decision modeling: piecing together Frankenstein

- Decision model = Frankenstein's monster
  - Admin data, literature

No autologous transfusion

No allo. transfusion

No fatal HR

Non fatal HR

No non fatal HR

Fatal HR

PAD **A**

HIV

Hep B

No HIV

C

HIV

Febrile reaction

Hep C

No HIV

Autologous transfusion

Orthopedic Surgery Patients

Non fatal HR **B**

HIV

No Hep

No HIV

No fatal HR

No febrile reaction

As Clone C

Allo. transfusion

No non fatal HR

As Clone B

EPO to augment PAD

As Clone A

Fatal HR

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Trial based CEA: Dracula!!!

- Based on trial data,
- C_{TX} and C_{UC}
- E_{TX} and E_{UC}

- Trial based CEA = Vampire
  - i.e., the analysis feeds off the clinical trial data

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O'Brien's nightmare

- Decision model = Frankenstein's monster
  - Admin data, literature

- Trial based CEA = Vampire
  - E.g., clinical trial data

Both are scary!

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Economic Evaluation of Pharmaceuticals
Frankenstein's Monster or Vampire of Trials?

BERNIE O'BRIEN, PhD

[...]
[...]c
evaluat[...] as cost-effectiveness analy-
sis are used to d[...]l cost
at which a new[...]addi-
tional health b[...]re re-
quired formally by governme[...] for phar-
maceutical reimbursement na[...]onally in
A[...] the Province of Ontario in
[...] Canadian guidelines also
h[...]ped.[3] The foundation of
such econom[...] appraisal is good quality evi-
dence on the epidemiology of the new inter-

dence for effectiveness of pharmaceutical
products is provided by well designed ran-
domized controlled trials...".[2] But the same
guidelines go on to recognize that data from
premarketing phase III randomized control
trials (RCTs), designed to test safety and *ef-
ficacy* hypotheses, may not be the most suit-
able for reliably answering questions about
the *effectiveness* of a new drug. This latter
phenomenon is how the drug will perform
outside the RCT in routine clinical practice
where the environment of the experiment
no longer holds.

Challenges with RCT data and models

- Choice of comparison
- Outcome
  - Right one?
  - Intermediate vs. final
- Follow up length
- Not real treatment
- Wrong treatment patterns
- Wrong patients or MDs

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Additional challenges with models

- "The overall validity of the economic study… depends… the… relations between intermediate and final outcomes. Ideally… modeling [projects]… intermediate into final outcomes, but this is seldom achieved without problems arising…

- Expert advisory boards are composed largely of people more familiar with RCTs not models.

- What to do if people don't believe your model but no more studies will be done?

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Challenges, cont.

- "For example, in an early cost-effectiveness model of tissue plasminogen activator versus streptokinase in acute MI, mortality predictions… [were used]; subsequent trials with mortality as the measured outcome have yielded more conservative estimates of the mortality benefits of [the] drug"

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Problem

- How to get <u>real data</u> for the <u>right question</u>?

- A modest proposal:
  - Post-marketing monitoring to determine whether the estimated cost-effectiveness matches the real cost-effectiveness

- HOW?
  - Formal Phase IV trials
  - Coverage with evidence development
  - Informal analysis of administrative data

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Analytical challenges

- How to analyze non-randomized, non-controlled person-level cost and outcome data?
  - What if cost-effectiveness varies by patient subgroup?
  - How do you make a 95% CI for a ratio with no known distribution? What if it is negative?
  - How to tell if the model fits the data well?
  - How to use other regression tools?
  - Is the extra cost per extra effect a good deal?

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CEA w/ incremental net benefit (INB)

■ CEA:

- Is the extra benefit > than the extra cost?

■ Is $\Delta E \cdot \$ > \Delta C$?

■ Is $\Delta E \cdot \$ - \Delta C > 0$?

■ Is   INB   > 0 ?

■ Why not estimate INB with regression?

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Something old, something new, something borrowed, something blue: a framework for the marriage of health econometrics and cost-effectiveness analysis

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[b] *Health Economics Research Centre, University of Oxford, UK*
[c] *Department of Clinical Epidemiology and Biostatistics, McMaster University, Canada*

Summary

Economic evaluation is often seen as a branch of health economics divorced from mainstream econometric techniques. Instead, it is perceived as relying on statistical methods for clinical trials. Furthermore, the statistic of interest in cost-effectiveness analysis, the incremental cost-effectiveness ratio is not amenable to regression-based methods, hence the traditional reliance on comparing aggregate measures across the arms of a clinical trial. In this paper, we explore the potential for health economists undertaking cost-effectiveness analysis to exploit the plethora of established econometric techniques through the use of the net-benefit framework – a recently suggested reformulation of the cost-effectiveness problem that avoids the reliance on cost-effectiveness ratios and their associated statistical problems. This allows the formulation of the cost-effectiveness problem within a standard regression type framework. We provide an example with empirical data to illustrate how a regression type framework can enhance the net-benefit method. We go on to suggest that practical advantages of the net-benefit regression approach include being able to use established econometric techniques, adjust for imperfect randomisation, and identify important subgroups in order to estimate the marginal cost-effectiveness of an intervention. Copyright © 2002 John Wiley & Sons, Ltd.

Keywords   cost-effectiveness analysis using regression; net-benefit framework; cost-effectiveness acceptability curve; economic evaluation; econometrics

Introduction

The development of applied health economics has progressed along two broad paths. The traditional path sees applied health economics undertaken in economics departments, employing applied econometrics methods. The second way in which health economics has developed has been in the economic evaluation of health care technologies. In these cases, health economists have undertaken such evaluations as members of multidisciplinary teams composed of clinicians, statisticians, epidemiologists and trialists. They assist in facilitating the team's goals of producing information about the cost-effectiveness of interventions. It is perhaps of little surprise, therefore, that the development of economic evaluation alongside clinical trials owes more to medical statistics than to econometrics,

*Correspondence to: Department of Epidemiology and Biostatistics, The University of Western Ontario, London, Ontario, Canada N6A 5C1. Tel: 519-661-2162; fax: 519-661-3766; e-mail: jeffhoch@biostats.uwo.ca

CEA w/ 1 regression

- $e_i \cdot \$ - c_i \equiv NB_i$

- $NB_i = \beta_0 + \beta_{TX} TX$

- $\beta_{TX} = \Delta E \cdot \$ - \Delta C$
- $\beta_{TX} = INB$
- If $\beta_{TX} > 0$ ➜
  - TX is CE

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Net benefit regression: Regression based CEA

- **Simple Analysis**
  - $NB = \beta_0 + \beta_1\, TX + \nu$
- **More precise estimates of β_1**
  - $NB = \beta_0 + \boxed{\beta_1}\, TX + \beta_2\, \mathbf{X} + \nu$ $\longrightarrow$ β_1 = the INB. I.e., $\lambda\Delta E - \Delta C$
- **Cost-effectiveness varies by sub-group?**
  - $NB = \beta_0 + \beta_1\, TX + \beta_2\, \mathbf{X} + \boxed{\beta_3}\, \mathbf{X} \cdot TX + \nu$

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Example 1: Handling selection bias with net benefit regression

- STEP 1: Run a regression to obtain a propensity score (PS)
- STEP 2: Use NBR & PS

- E.g.,
- $NB_i = \beta_0 + \beta_{TX}TX + \beta_{PS}PS + \varepsilon$

- Mahoney EM et al., "Long-term cost-effectiveness of early and sustained clopidogrel therapy for up to 1 year in patients undergoing percutaneous coronary intervention after presenting with acute coronary syndromes without ST-segment elevation." *Am Heart J.* 2006.

- "Because the… study did not directly randomize patients to clopidogrel versus placebo, there is the possibility of selection bias… The analysis of the clinical results… adjusted for this possibility through the use of a propensity score covariate obtained from a logistic regression analysis. A similar propensity score–adjusted cost-effectiveness analysis was carried out in the current study using a net benefit regression model"

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CEA results using a propensity score–adjusted CEA using the Net benefit regression framework

Figure 4

Figure showing Probability Cost-effective (y-axis, 0.0 to 1.0) versus WTP or $ (x-axis, $0 to $60,000) with four curves:
- Unadjusted - Early PCI Subgroup (red dashed, squares)
- Propensity Score Adjusted - Early PCI Subgroup (red dashed, triangles)
- Unadjusted - Overall PCI-CURE (blue solid, squares)
- Propensity Scored Adjusted - Overall PCI-CURE (blue solid, triangles)
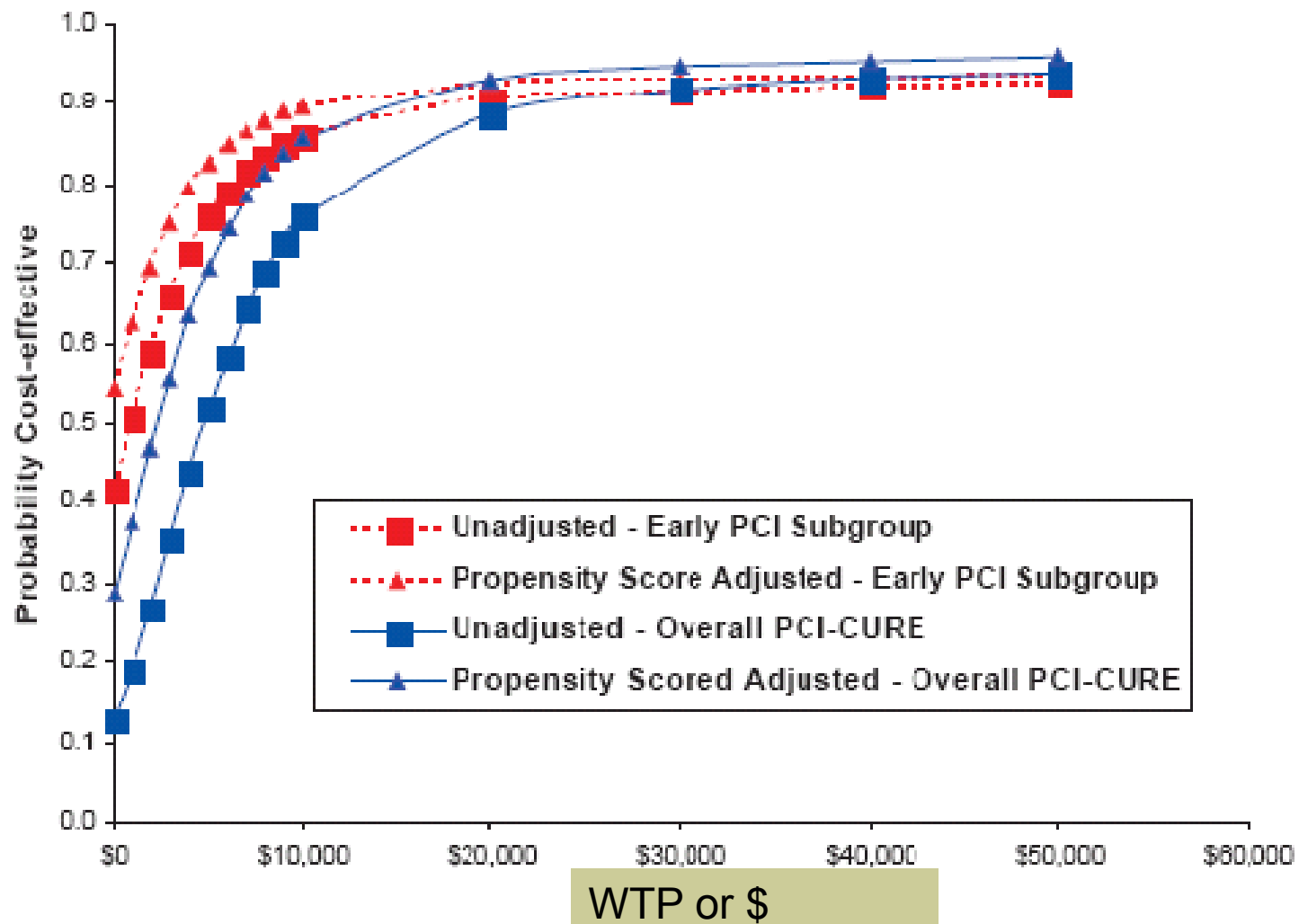
Example 2:
Adjusting for X can affect CE
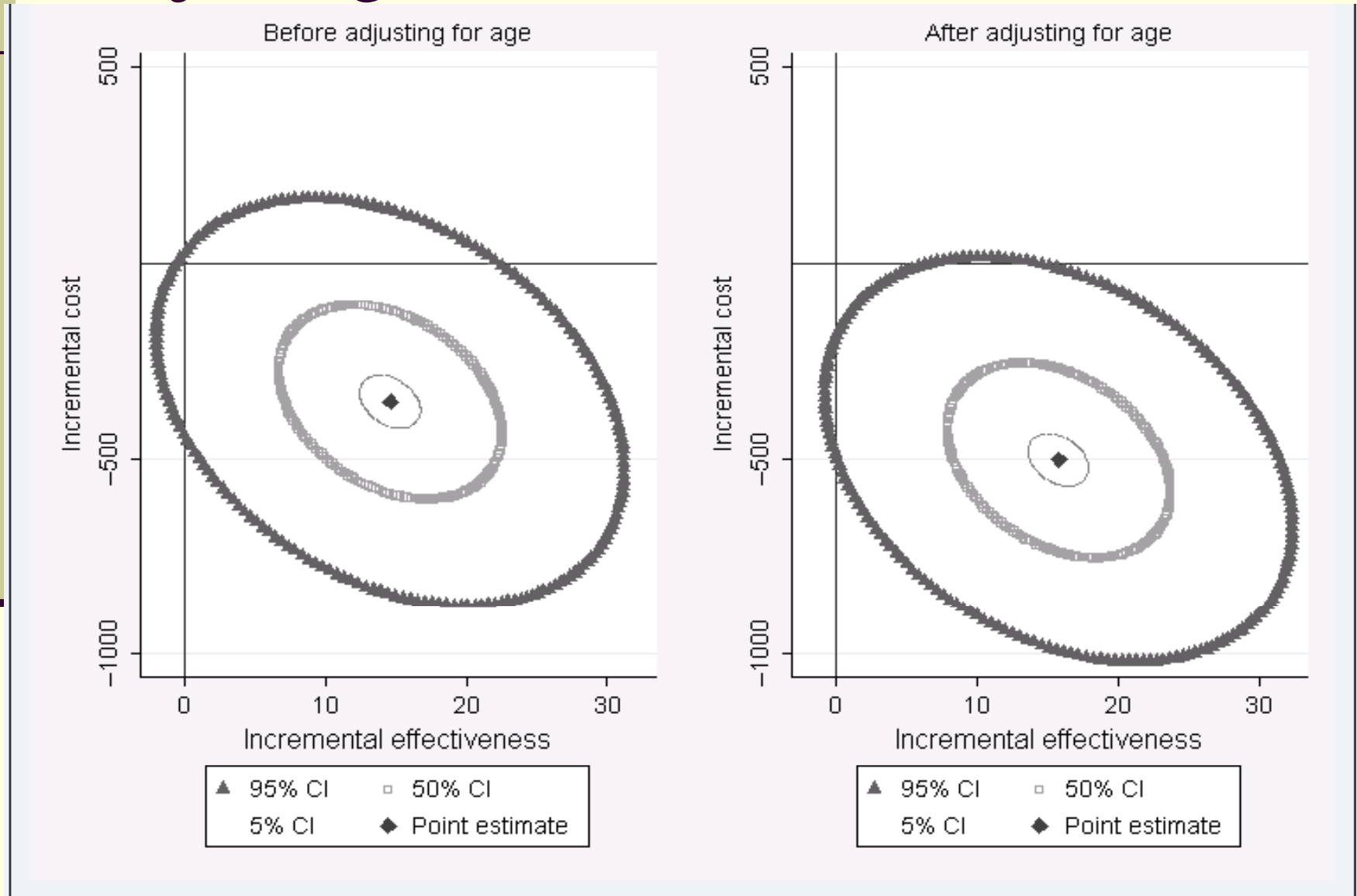
Example 3: Bayesian methods

Use of Bayesian Net Benefit Regression Model to Examine the Impact of Generic Drug Entry on the Cost Effectiveness of Selective Serotonin Reuptake Inhibitors in Elderly Depressed Patients

Yu-Chen Tina Shih, Nebiyou B. Bekele and Ying Xu

Department of Biostatistics, Division of Quantitative Sciences, The University of Texas M.D. Anderson Cancer Center, Houston, Texas, USA

Abstract

Introduction: Since their invention in the late 1980s and early 1990s, selective serotonin reuptake inhibitors (SSRIs) have become the primary form of pharmaceutical treatment for depression. As the patents of several top-selling SSRIs have expired or are soon to be expired, the SSRI market is expected to witness an increasing share of generic SSRIs. We explored the impact of generic drug entry on the cost effectiveness of SSRIs.

Method: Using Medicare MarketScan claims data, we compared the cost effectiveness of sertraline, citalopram, escitalopram and fluoxetine with paroxetine in elderly depressed patients, before and after the entry of generic paroxetine. We followed users of SSRIs for 6 months, starting from the date of their first prescription of an SSRI. For each patient, we measured costs (C_i) as total medical costs and quantified effectiveness (E_i) as the avoidance of treatment failure, which was defined as having a break exceeding 45 days in the use of antidepressants. We then calculated individual net benefit as $\lambda \times E_i - C_i$ and employed both net benefit and Bayesian net benefit regression models to examine the impact of generic

- Using administrative data, the authors studied the cost-effectiveness of SSRIs in elderly depressed patients
  - Bayesian methods
  - Adjust for patient vars
  - Adjust for selection bias
  - Regression model
    - Tools and diagnostics

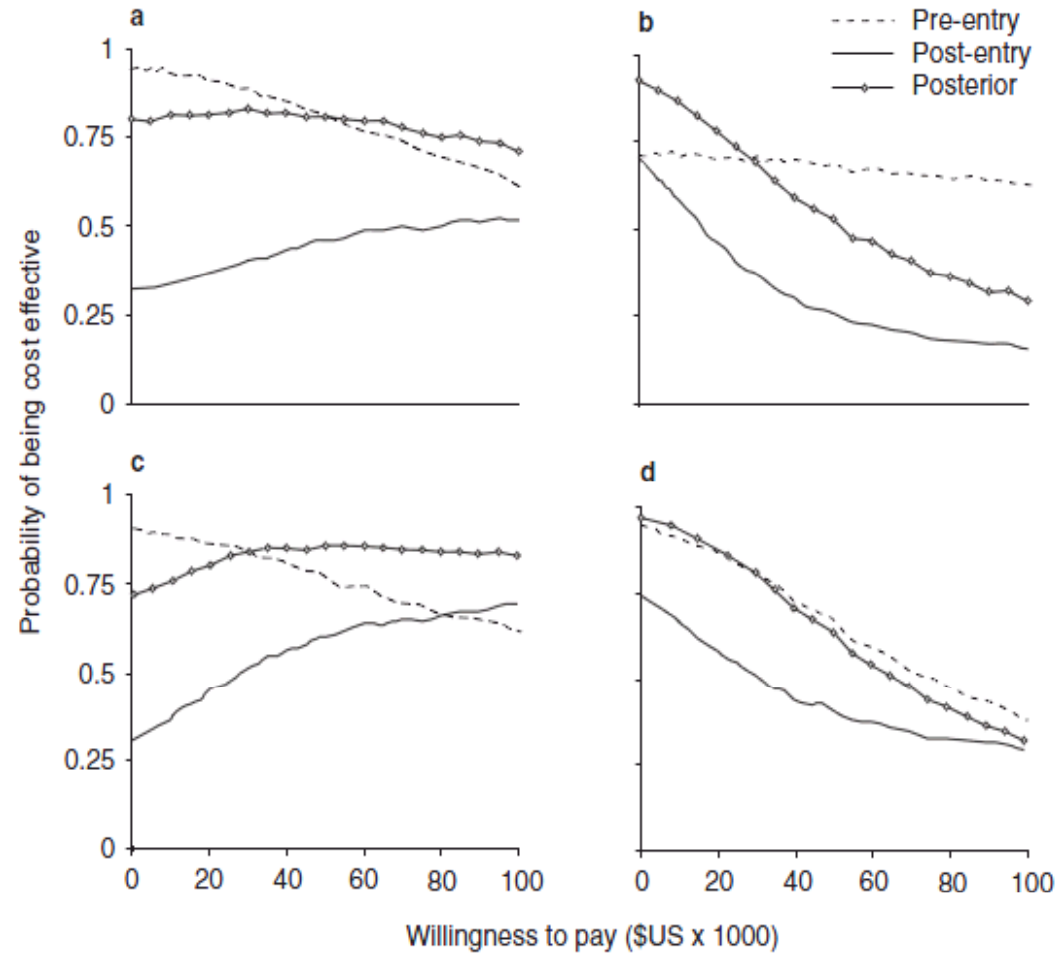# Results from Shih et al. (2007)

Fig. 3. Results of Bayesian net benefit regression analysis using pre-entry data to update post-entry data: cost effectiveness of (a) sertraline vs paroxetine; (b) citalopram vs paroxetine; (c) escitalopram vs paroxetine; (d) fluoxetine vs paroxetine.

Summary

- Analysis of what we are getting for what we are paying will become more popular.

- Administrative databases offer a good source of "real world" data.

- Net benefit regression can be used to analyze these data

Implications

- Researchers have a role to play in helping decision makers both make and re-evaluate their decisions.

- Judgment and opinion must be supplemented with evidence from the "real world".

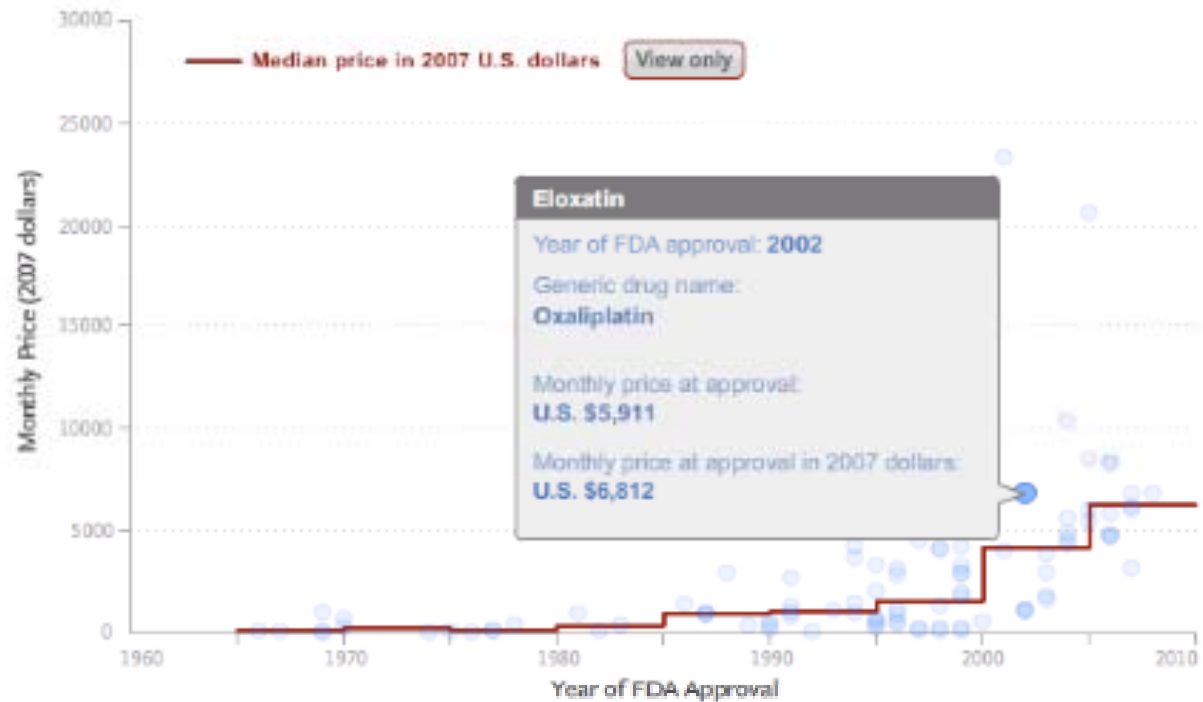- Economics and Statistics should constitute a part of the decision making cycle.
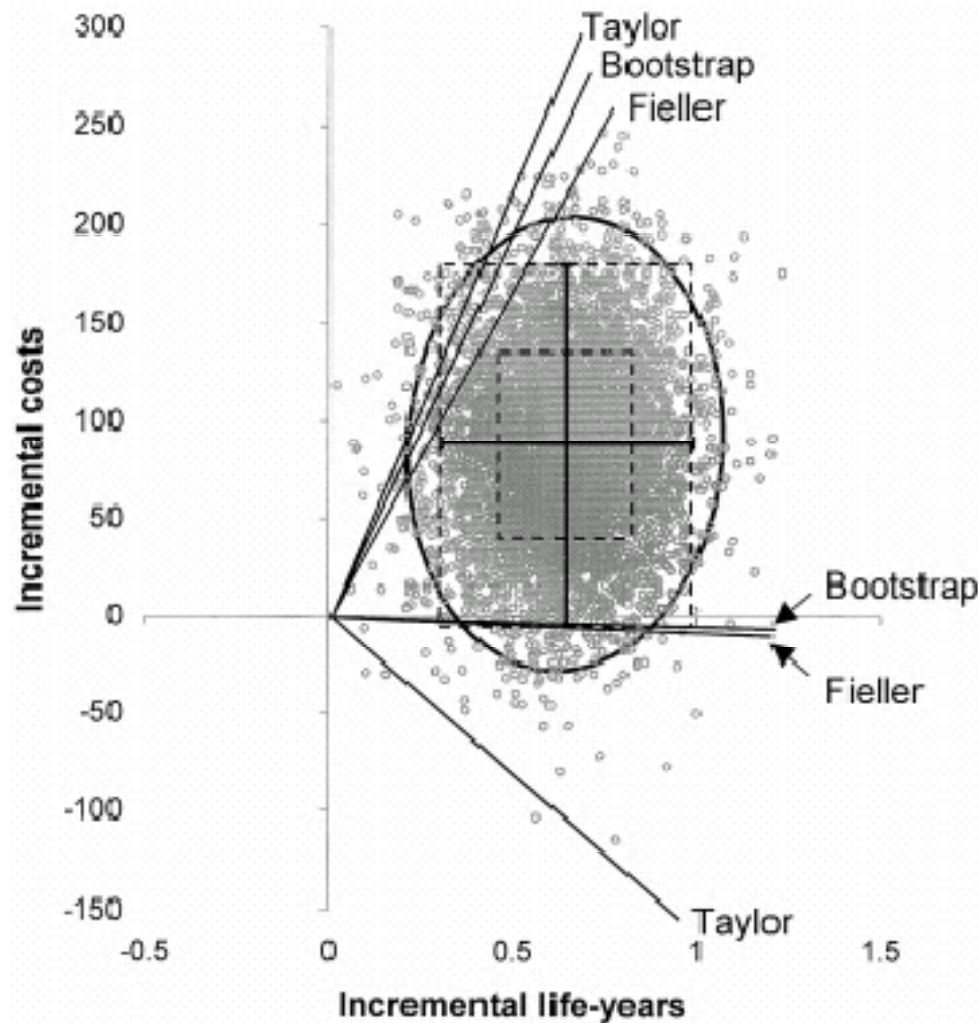
Extra slides

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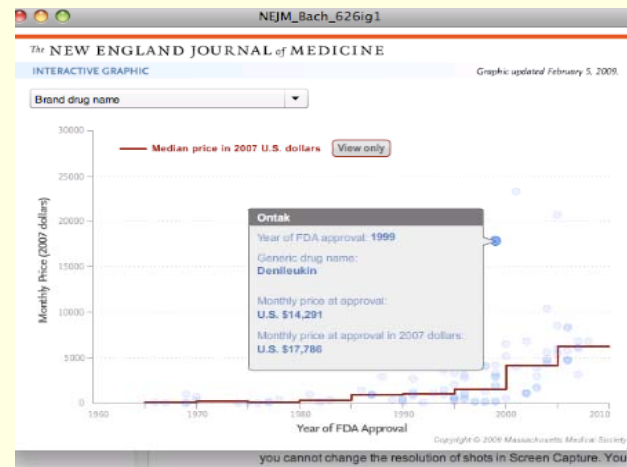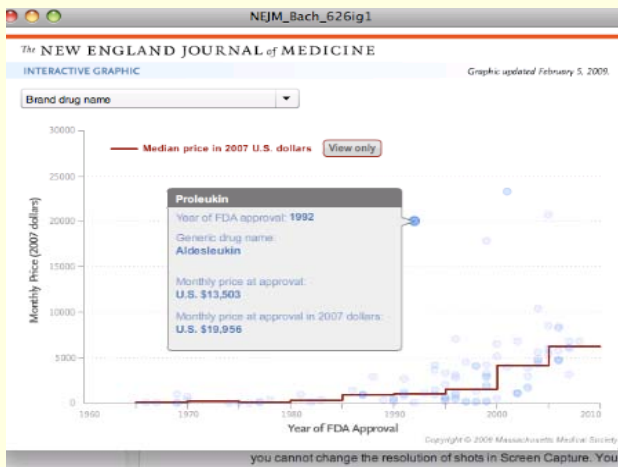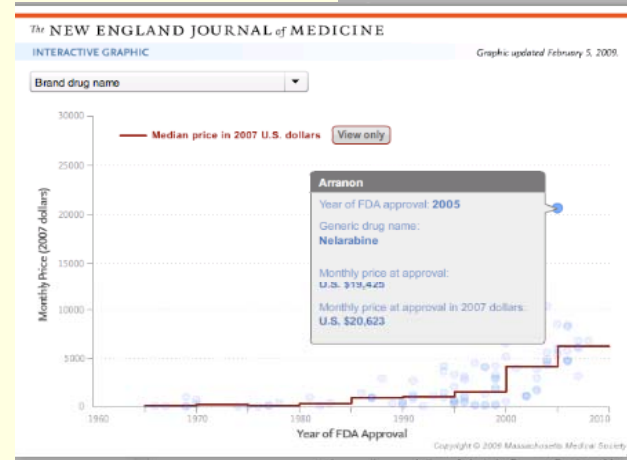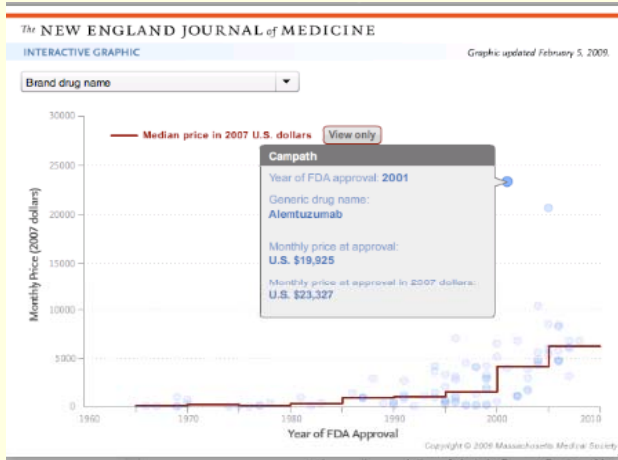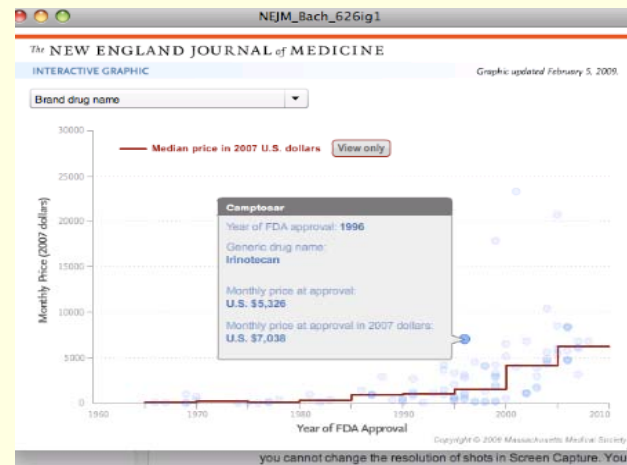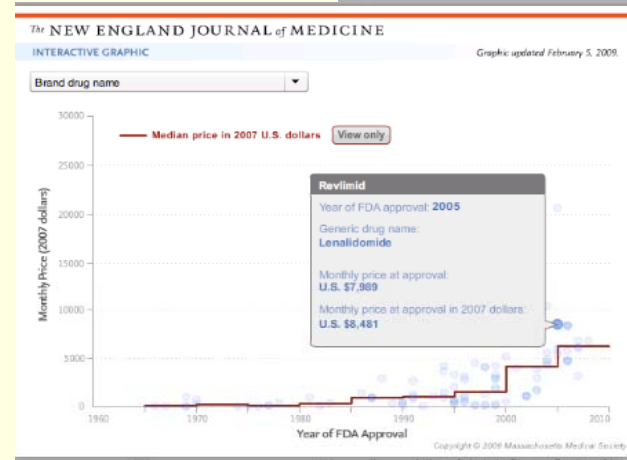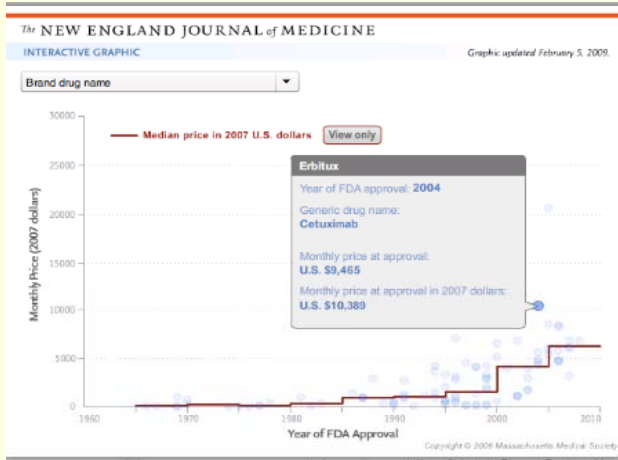
The confidence intervals challenge

- Different methods give different intervals
- All have challenges
- Key issues include:
  - ICERs < 0
    - No transitivity
  - ICERs with the same numerical value but different meanings

Why is CEA done?

- CEA is done to help decision makers understand the rate at which they must spend to get an additional patient outcome:
    - Cancer Drug A vs. Cancer Drug B: $160,000 for an additional year of life vs.
    - Exercise and CBT vs. Depression Drug Z: $25,000 for an additional year of life
- Do the advantages of the new medication / test / procedure justify the higher price?