Using the Net Benefit Regression Framework to Address Uncertainty and Heterogencity in Cost-Effectiveness Analysis Using Patient-Level Data.

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- I gratefully acknowledge financial support from a Career Scientist Award from the Ontario Ministry of Health and Long Term Care.

Learning objectives

- Understand how the net benefit regression framework works.
- Understand how putting economic evaluation in a regression framework allows the use of regression tools.

- Cost-effectiveness analysis (CEA) is a type of economic evaluation that tells you the price of an extra unit of effect.
  - Example #1: Methadone maintenance has a cost per life-year gained of $16,967
    - Masson CL, Barnett PG, et al. (2004)
  - Example #2: Drug V for ED is < $15,000 per QALY
    - Smith KJ, Roberts MS (2000)
  - UK Examples from NICE
    - national-level guidance on the effectiveness and cost-effectiveness of new health technologies in the NHS.

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Devlin and Parkin, (2004)

Guidance number	*Technology*	*ICER*
39	Smoking	£430
28	Topecetan Yes	£1000
5	**Cytology**	**£1100**
38	Asthma inhalers	£5000
3	Taxane Ovarian	£8271
12	Glycoprotein	£9250
26_a	Non-small cell lung (First line)	£9475
13	Methylphenidate	£12 500
25	Gemcitabine (First line)	£12 950
26_b	Non-small cell lung (other)	£14 000
19	Alzheimers	£15 000
30_a	Taxane Breast 2 (Second line)	£15 250
6	Taxane Breast	£15 500
30_b	**Taxane Breast 2 (First line)**	**£19 000**
34	Trastuzumub (monotherapy)	£19 000
15_a	Zanamavir At Risk	£20 400
14	Ribavarin	£20 500
33_a	Advanced colorectal 3	£22 500
31	Sibutramine	£22 500
35	Arthritis juvenile	£22 500
18_a	Laparascope hernia (recurrent)	£25 000
4	Stents	£25 000
11	ICDs	£28 500
33_b	**Advanced colorectal 1**	**£29 000**
36	Arthritis adult	£31 000
23	Temozolamide (Second line)	£35 000
34	Trastuzumub (combination)	£37 500
15_b	**Zanamavir All**	**£38 000**
20	Riluzole	£38 750
22	Orlistat	£46 000
18_b	**Laparascope hernia (primary)**	**£50 000**
27_b	**Cox II (Routine)**	**£150 000**
32	**Beta interferon**	**£187 000**

GREATER £ per QALY

Greeting Cards

- Decision makers think CEAs are useful
  - required internationally (UK, Canada, Australia)
  - becoming more popular in the US?
- Researchers think CEAs are publishable
  - everyone's doing it. (> 10,000 in last 5 yrs)

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  - A decision typically involves answering:
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    - Are the extra benefits worth more than the extra costs?

- $\Delta C / \Delta E < \lambda$? Or,
- $\Delta E \lambda < \Delta C$?
- $0 < \lambda \Delta E - \Delta C$?

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  - Data only give estimates of ΔE and ΔC
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- STEP 2: Calculate an estimate
  - OPTION A: $\Delta C / \Delta E$ (ICER = incremental cost-effectiveness ratio)
  - OPTION B: $\lambda \Delta E - \Delta C$ (INB = incremental net-benefit)
- STEP 3: Make a confidence interval for the estimate
- STEP 4: Wax poetic about the confidence interval
  - OPTION A: "it is $< \lambda$!"
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HEALTH ECONOMICS
Health Econ. 11: 415–430 (2002)
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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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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,

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CEA with 1 regression

- OLD: regression
- NEW: net benefit
- BORROWED: λ
- let $NB_i = \lambda\, e_i - c_i$

- $NB_i = \beta_0 + \beta_{TX} TX + \varepsilon$
- $\beta_{TX} = \lambda\, \Delta E - \Delta C$
- $\beta_{TX} = INB$

- If $\beta_{TX} > 0$ this means INB > 0 which means
  - $\lambda \Delta E - \Delta C > 0 \rightarrow \Delta C / \Delta E < \lambda$

- Because the economic analysis is in a regression format, $\exists$ "regression" concerns:
  - Are the assumptions for regression met?
  - Can I believe the results of this analysis?
  - My economic conclusions seem tied to λ!

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Laupacis A, et al. "How attractive does a new technology have to be to warrant adoption and utilization?" *CMAJ*. 1992

- What λ should be used?
- What if my data are:
  - probably different for different patients?
  - skewed?
  - not from an RCT (e.g., observational)
  - hierarchical?
  - to be added to prior info (e.g., Bayes)

Explanatory Variables	NB λ = $0 (2-sided p)	NB λ = $100 (2-sided p)	NB λ = $500 (2-sided p)	NB λ = $1000 (2-sided p)	Effect λ infinite (2-sided p)
Constant Term	-112200 (<0.001)	-99000 (0.003)	-45900 (0.292)	20400 (0.728)	100 (<0.001)
Treatment dummy:					
TX	62700 (0.053)	72600 (0.037)	111800 (0.015)	160800 (0.010)	100 (0.007)
R^2 (adjusted)	0.055	0.061	0.076	0.080	0.056
Prob > F **N = 145**	0.269	0.173	0.030	0.010	0.011

Table 1 from Hoch JS, Briggs A, Willan A. "Something old, something new, something borrowed, something **BLUE**: A framework for the marriage of health econometrics and cost-effectiveness analysis." *Health Econ* 2002;11(5):415-430.

[a] All monetary measures in U.S. dollars. [b] When λ= $0, NMB = - Cost. [c] The coefficients from the Effect regression (and not the NMB regression with $\lambda \rightarrow \infty$) are reported since as $\lambda \rightarrow \infty$, the *p*-values for the NMB coefficient estimates are equivalent to those obtained when 'days stable housing' is the dependent variable.
[d] Huber-White robust standard errors and *p*-values corrected for heteroskedasticity.

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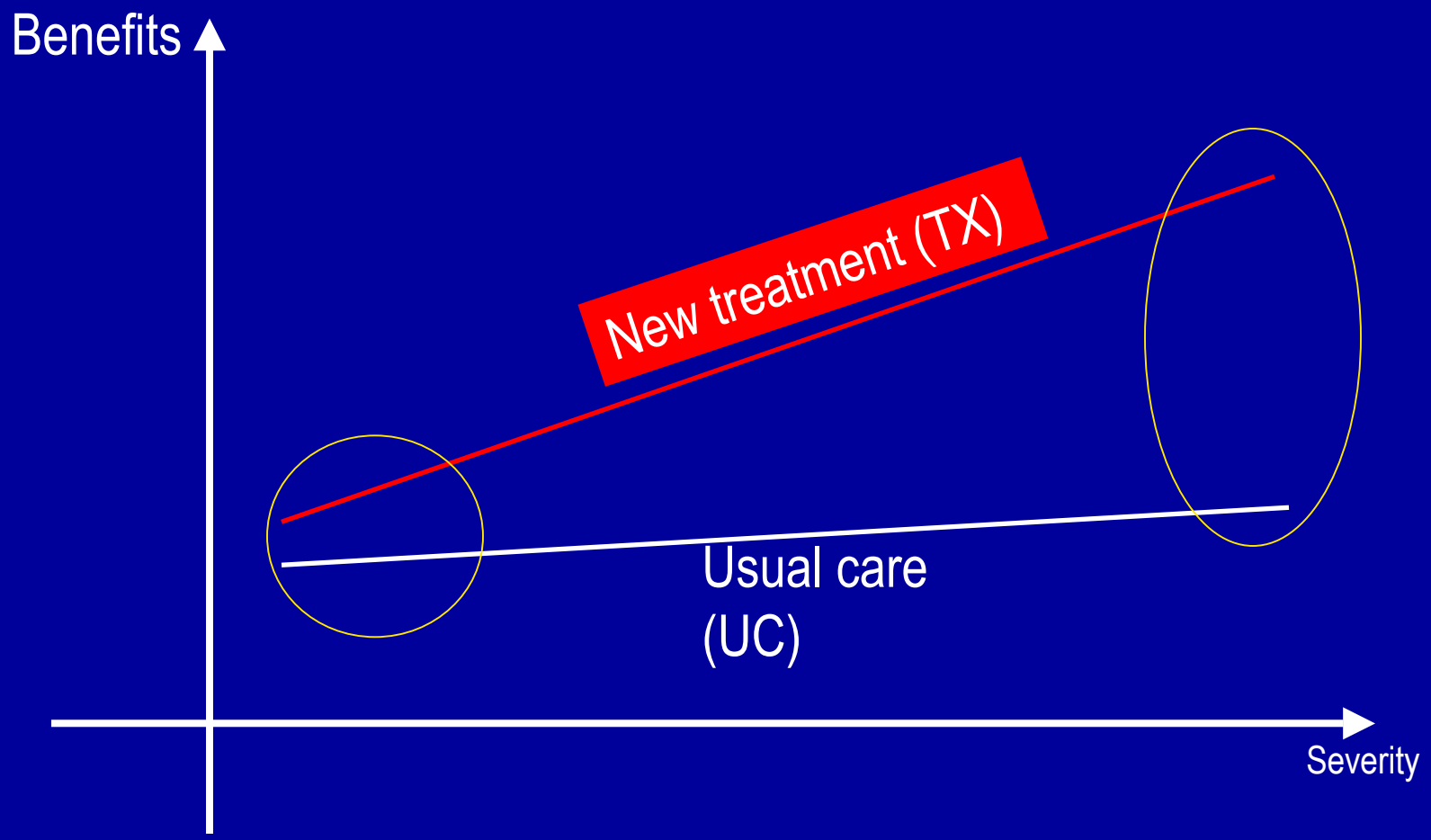
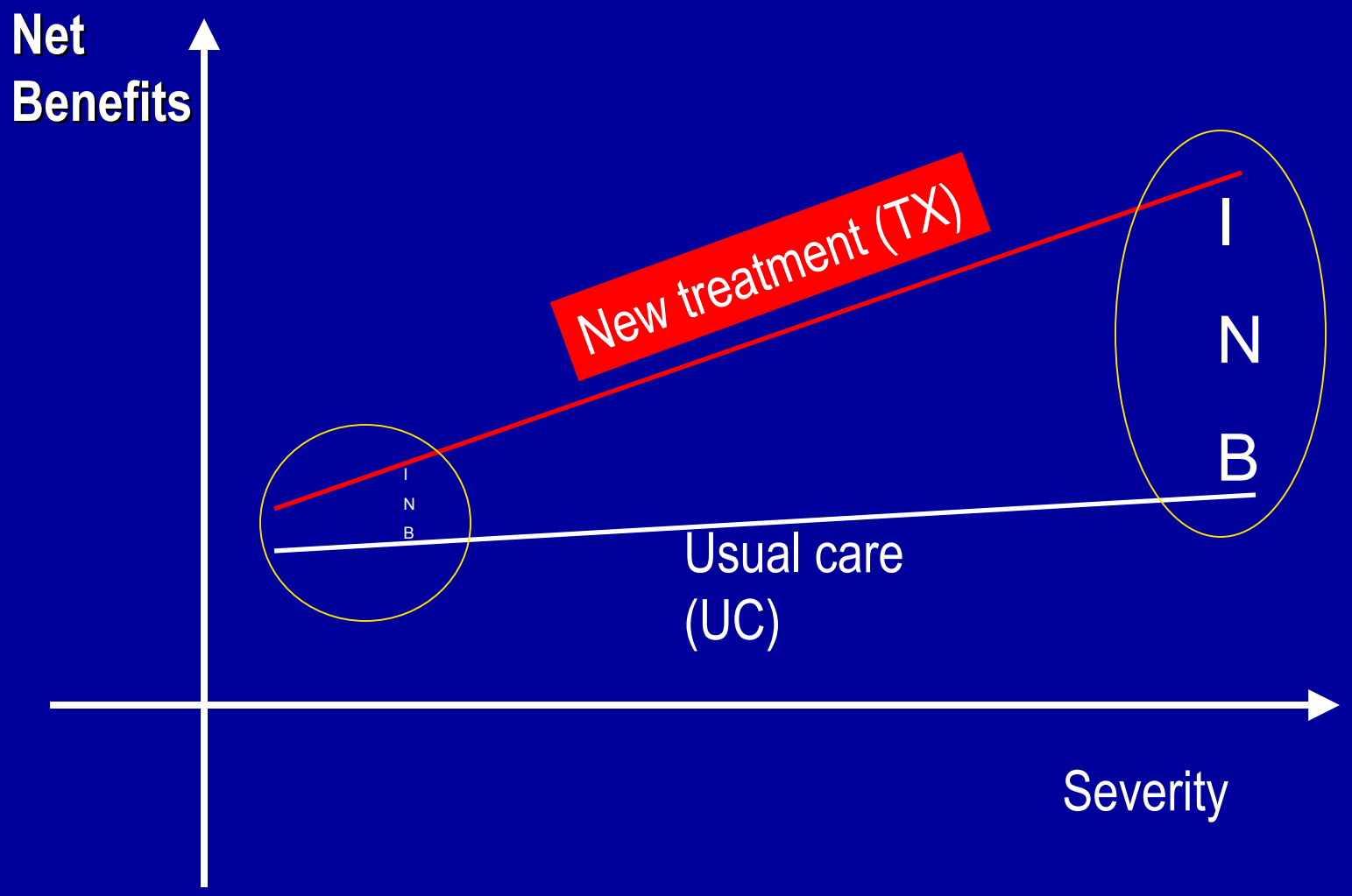
Health Benefits can differ by ____

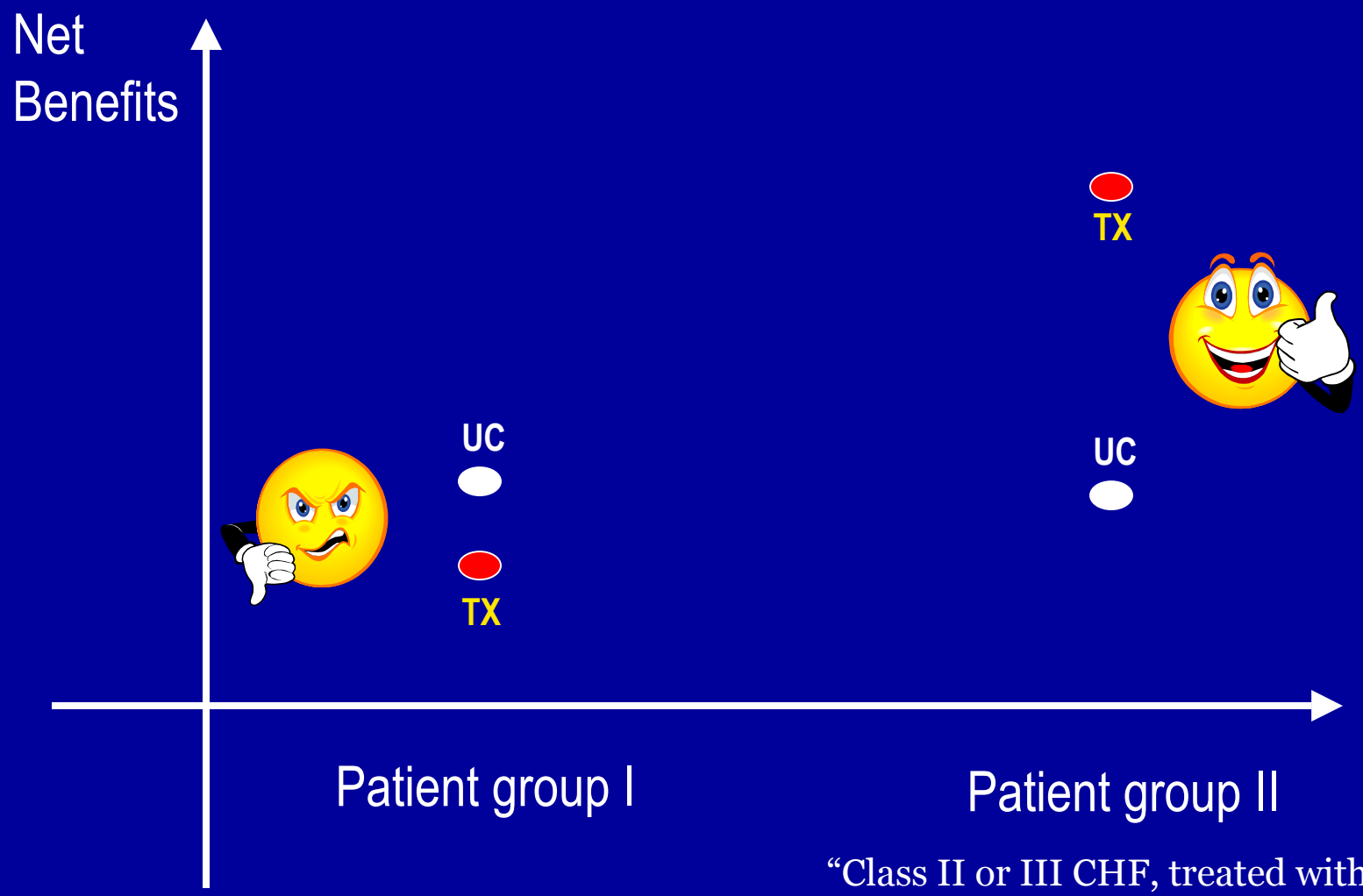


"High-severity patients treated in high-intensity programs had better alcohol, drug, and psychiatric outcomes at follow-up… than did those in low-intensity programs. For moderate-severity patients, high service intensity improved the effectiveness of treatment in only a single domain (drug abuse)…" -Chen S, Barnett PG, et al. (2006)

INB differ by severity



INB differ by patient type



"Class II or III CHF, treated with ACE inhibitor and EF $\leq$ 35%" for the drug to be covered in Ontario.

Subgroup analysis

- General case
  - For group 1:
    - $Outcome_i = a_0 + a_1TX$
  - For group 2:
    - $Outcome_i = b_0 + b_1TX$
  - Fancy (or continuous X):
    - $Outcome_i = c_0 + c_1TX + c_2X + c_3TX \cdot X$
      - X = Patient group indicator or continuous variable like severity
- Economic case
  - For group 1:
    - $NB_i = a_0 + a_1TX$
  - For group 2:
    - $NB_i = b_0 + b_1TX$
  - Fancy (or continuous X):
    - $NB_i = c_0 + c_1TX + c_2X$ $c_3TX \cdot X$

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Treatment dummy:					
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Covariate:					
PatType1	53800 (0.094)	57000 (0.097)	69800 (0.125)	85700 (0.164)	31.9 (0.337)
Treatment-covariate interaction:					
TX·PatType1	-57700 (0.099)	-63900 (0.088)	-88900 (0.076)	-120200 (0.082)	-62.5 (0.136)
R^2 (adjusted)	0.055	0.061	0.076	0.080	0.056
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What does one ordinarily do when the dependent variable is skewed?

- What λ should be use
- **What if my data are:**
  - probably different
  - **skewed?**
  - not from an RCT (
  - hierarchical?
  - to be added to pric

1) Hope it is not too bad (look at histogram)
2) Hope it will go away (different λ?)
3) Transform so the data are not skewed
   - Remember to transform back!
4) Use a method that does not depend on normality
5) Check the residuals, test for unequal variance (heteroskedasticity), outliers, leverage, influence, etc.

Residuals

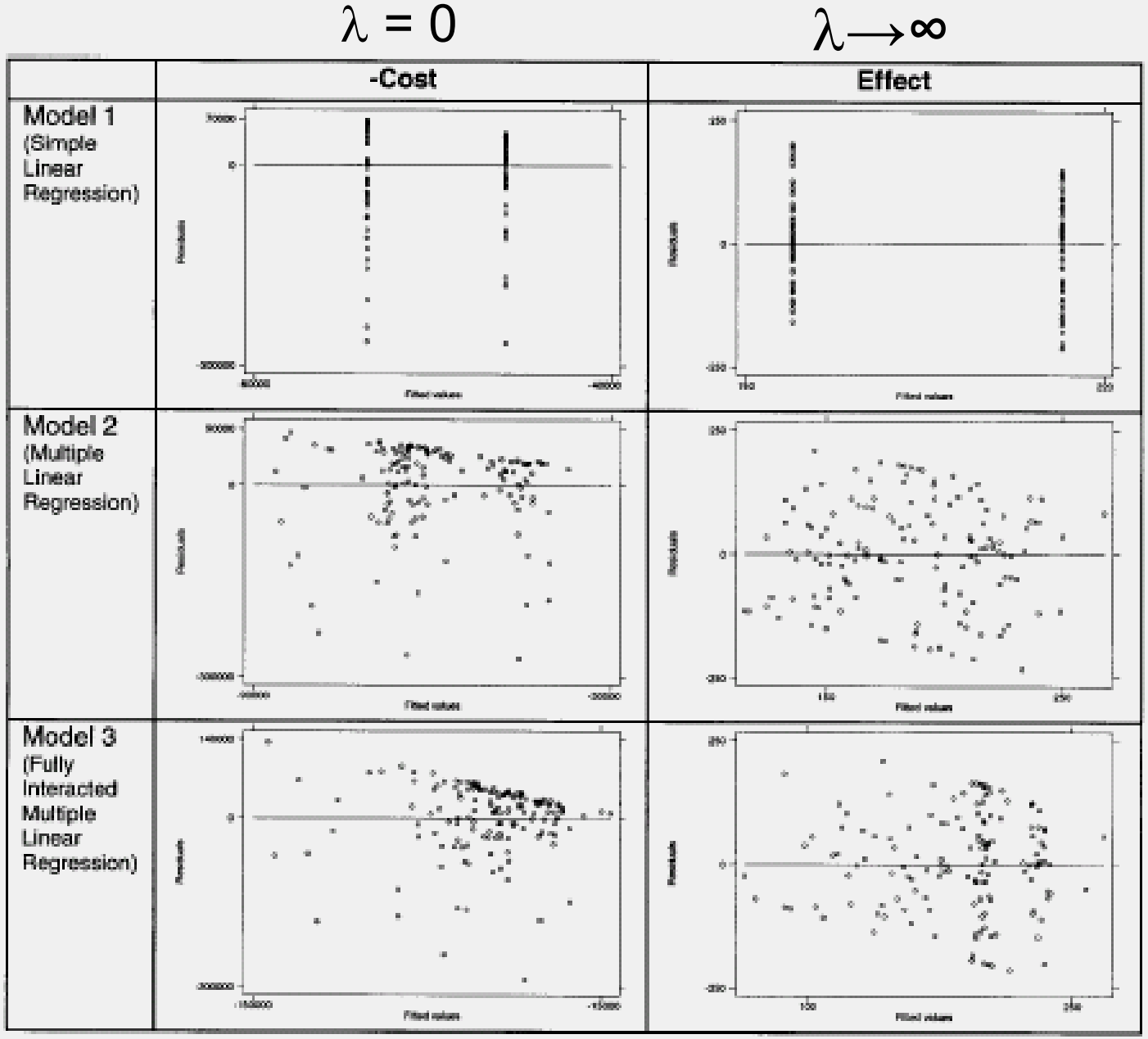

Figure 6. Residual plots for the regressions on -cost (equivalent to NMB when $\lambda = 0$) and effect (equivalent to NMB when $\lambda \to \infty$) for each of the three models

Figure 6 from Hoch et al. (2002).

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Handling selection bias

- Use IV or <u>propensity scores</u>
  - STEP 1: Run a regression to obtain a propensity score (PS)
  - STEP 2: Use the NBRF & PS
  - E.g., $NB_i = \beta_0 + \beta_{TX}TX + \beta_{PS}PS + \varepsilon$
- For a study of other methods:
  - Austin PC, Mamdani MM. "A comparison of propensity score methods" *Stat Med*. [Epub]
- <u>Empirical example</u>

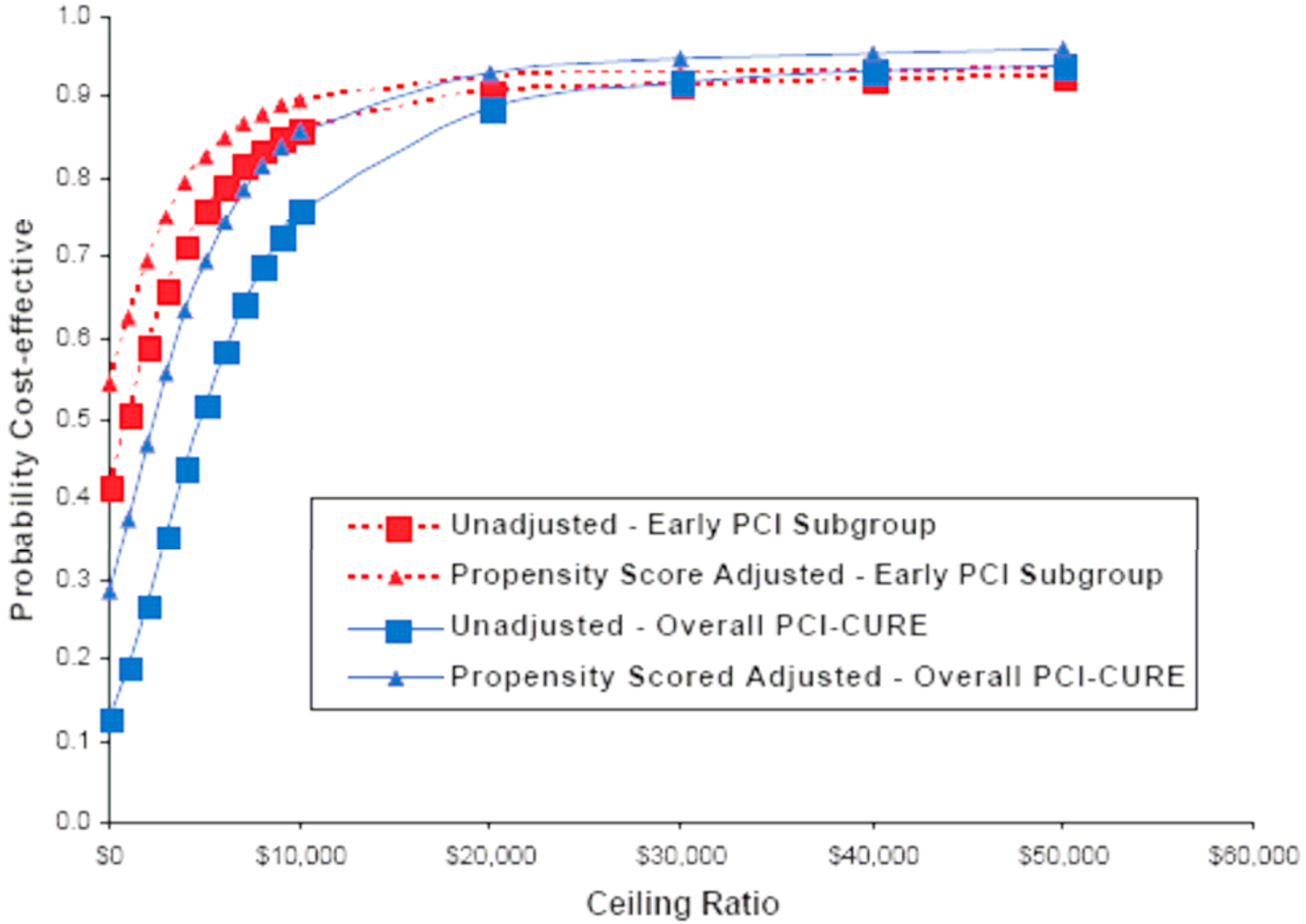
Mahoney EM et al., "Long-term cost-effectiveness of early and sustained clopidogrel therapy for up to 1 year in patients undergoing percutaneous coronary intervention after presenting with acute coronary syndromes without ST-segment elevation." *Am Heart J*. 2006.

- "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"

CEAC based on a propensity score–adjusted CEA using the NBRF

Figure 4

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.



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The EVALUATE trial compared laparoscopic-assisted hysterectomy and standard hysterectomy. Manca and colleagues (2005) analyzed CE data from 25 English hospitals.

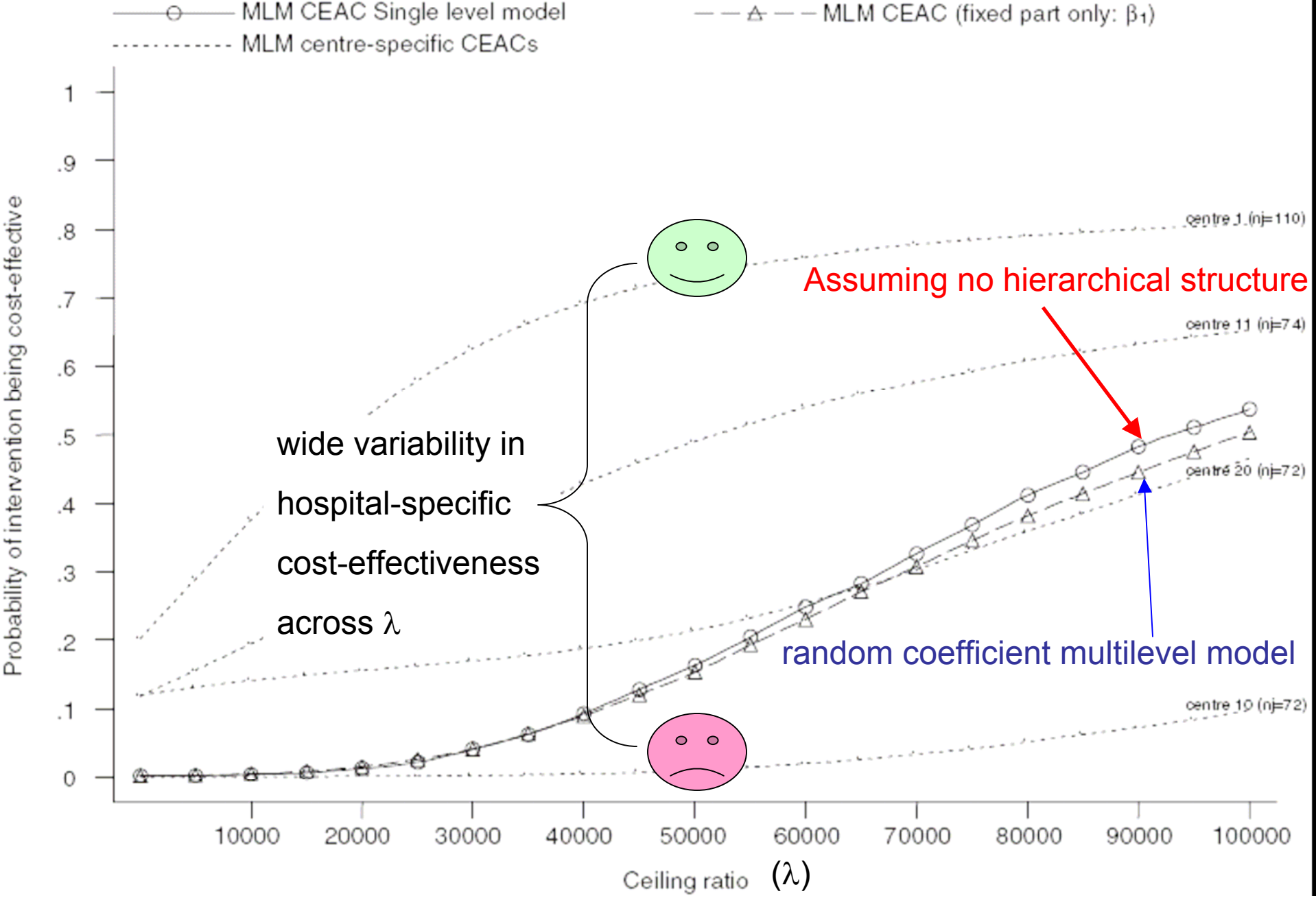

Figure 3 from Manca A et al. "Assessing generalisability by location in trial-based cost-effectiveness analysis: the use of multilevel models." *Health Econ*. 2005.

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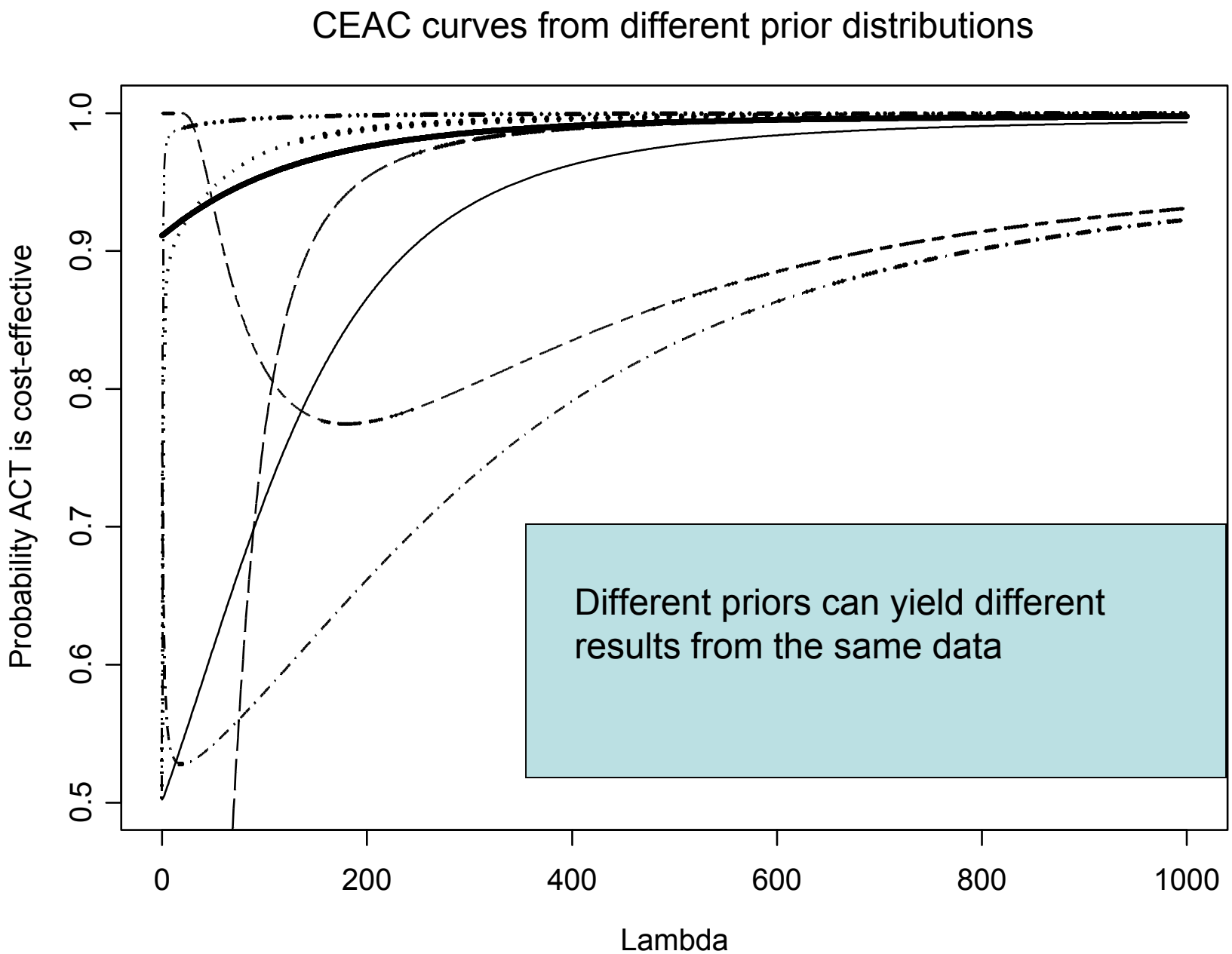
Prob(TX is cost-effective) =

Prob(INB > 0) =

$p(\beta_{TX} > 0)$



Hoch and Blume, “Measuring and illustrating statistical evidence in a cost-effectiveness analysis” (2006).

- Use regression tools for person-level CEA
  - NBRF facilitates answers to:

- What if my data are:
  - probably different for different patients?
  - skewed?
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  - hierarchical?
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Using the net benefit regression framework to address uncertainty and heterogeneity in cost-effectiveness analysis

☑ Uncertainty

* fewer challenges making a 95% CI for $\lambda\Delta E - \Delta C$ than $\Delta C / \Delta E$

(especially if the regression program is making the 95% CI)

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☑ Heterogeneity

* the NBRF allows subgroup analysis via regression as well as methods to adjust for selection bias, hierarchical structure, skewness of the data, residual diagnostics, etc.

- Questions?

Empirical Example

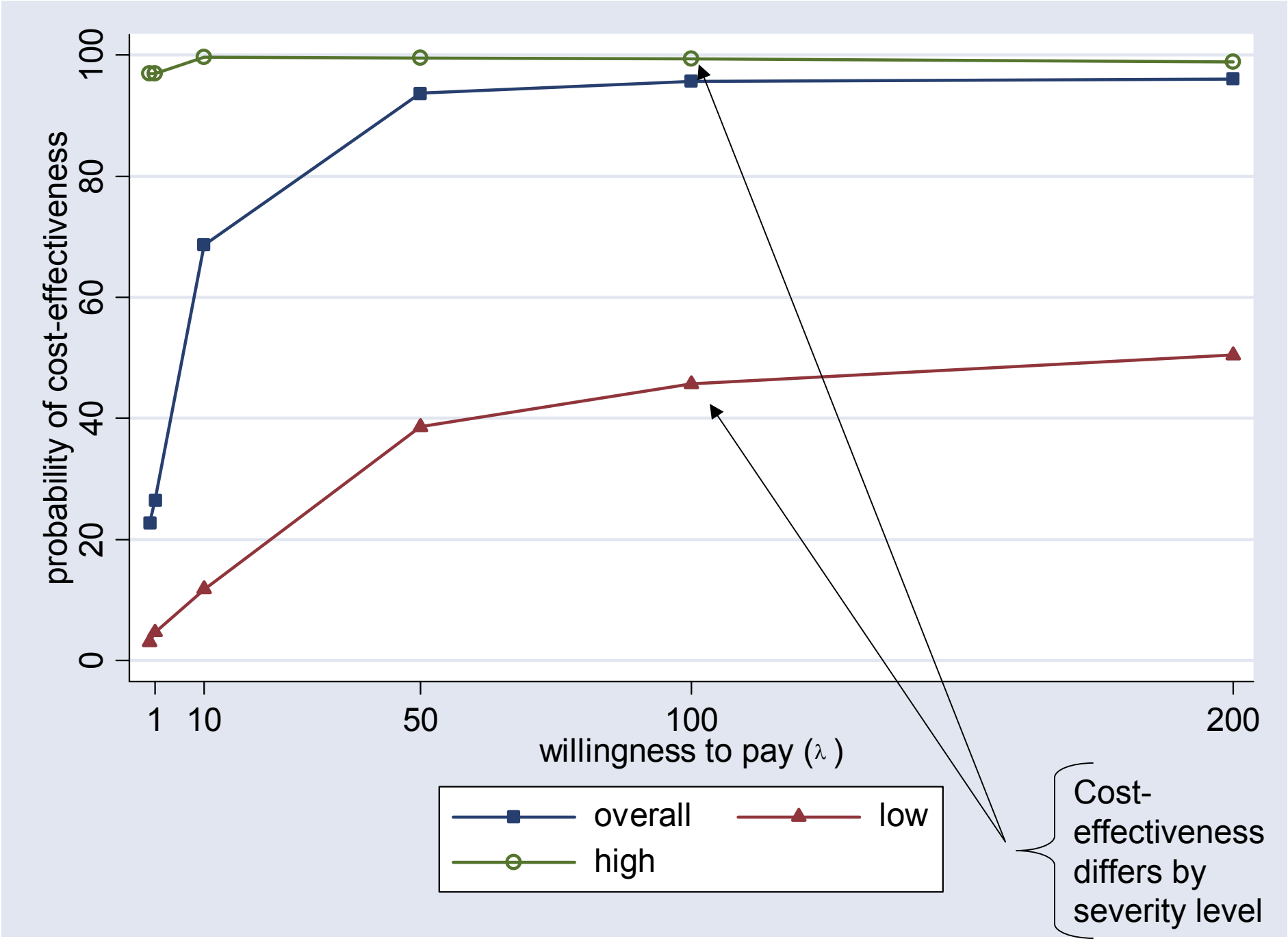
Table 3 (**this** page) and Table 4 (*next* page) from Hoch and Smith (2006).

Treatment Group	Effect measured in symptom free days	Cost measured in US $	Severity**
	Mean (SD)	Mean (SD)	Mean (SD)
Psychotherapy (n=45)	205 (117)	$2200 (1,207)	61 (9)
Medication (n=60)	165 (101)	$2000 (1,357)	58 (8)
Difference	$\Delta E = 40$	$\Delta C = \$200$	-3
p-value	$p = 0.064$	$p = 0.435$	$p = 0.084$
Incremental monetary value when willingness to pay = $10	$\$10 \times \Delta E = \$400$	$200	—
Incremental net benefit (INB) when willingness to pay = $10	$\$10 \times \Delta E - \Delta C = INB$ $\$400 - (\$200) = \$200$		—
Incremental cost-effectiveness ratio (ICER)	$\Delta C / \Delta E = ICER$ $\$200 / 40 = \$5$ ($5 per extra symptom-free day)		—

*Figures have been rounded to nearest whole number.
** The Severity variable represents hypothetical Clinician-Administered PTSD Scale (CAPS) scores.

Variables	Regressions Results					
	Effect Regressions (p-value)		**Cost Regressions (p-value)**		**Net Benefit Regressions with λ = \$10 (p-value)**	
	Simple regression	*Multiple regression*	*Simple regression*	*Multiple regression*	*Simple regression*	*Multiple regression*
Constant Term	165 (<0.001)	170 (<0.001)	2000 (<0.001)	1947 (<0.001)	-350 (0.165)	-244 (0.317)
Psych	40 (0.064)	37 (0.083)	200 (0.435)	206 (0.420)	200 (0.120)	164 (0.661)
Severity^{C}**	—	-4 (0.007)	—	42 (0.024)	—	-83 (0.002)
Psych x Severity^{C}**	—	5 (0.029)	—	-69 (0.022)	—	124 (0.005)
R^2 (adjusted)	0.024	0.077	-0.004	0.039	-0.007	0.074
F-statistic	3.51	3.89	0.61	2.42	0.27	3.79
Prob > F	0.064	0.0112	0.4352	0.0704	0.6021	0.0127
Psychotherapy overall statistical significance		F(2,101) = 3.74 Prob > F =0.027		F(2,101) = 3.20 Prob > F =0.045		F(2,101) = 4.08 Prob > F =0.020

*Figures have been rounded to nearest whole number.
**The CAPS severity variable has been centered at its mean of 60 and renamed *Severity^{C}*.
For a patient with a CAPS severity score of 60, both the *Severity^{C}* and the *psych x Severity^{C}* variables are equal to zero.


probability of cost-effectiveness
0
20
40
60
80
100
1
10
50
100
200
willingness to pay (λ)
overall
low
high
Cost-effectiveness differs by severity level