Economic Analyses in Clinical Trials

Natasha Leighl (and Nicole Mittmann)

Committee on Economic Analysis, NCIC CTG

Natasha.Leighl@uhn.on.ca; Nicole.Mittmann@sunnybrook.ca

Financial Disclosures

- Research Funding – Novartis

Learning Objectives

- Review concepts including:
  - Cost effectiveness
  - Cost utility
  - Cost minimization
  - Incremental cost effectiveness ratio (ICER)
- Review criteria for inclusion of economic analysis alongside clinical trial
- To understand the impact of molecular testing on design of economic analyses

Economics and Cancer

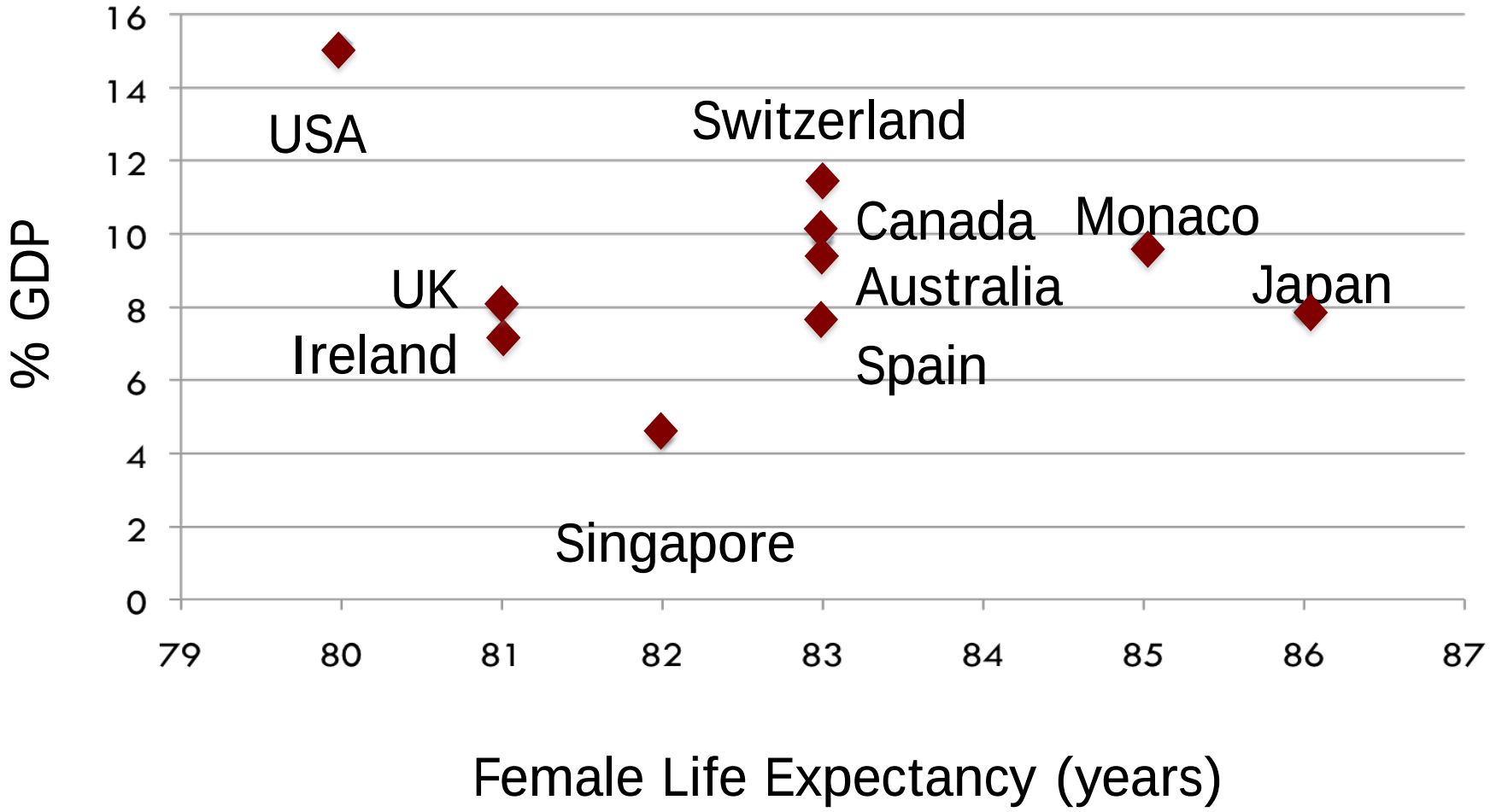
- Cancer is growing problem – estimated cost of cancer care in US >$210 billion USD Meropol & Schulman, J Clin Oncol 2007;25(2):180-186

- New treatments that improve outcome should be adopted
- But with limited resources, economic constraints factor into resource allocation, in order to maximize population health

- 3 pillars of FDA approval of novel interventions:
  - Safety; Mechanism of action; Clinical efficacy
- 4th pillar (pCODR): cost-effectiveness!

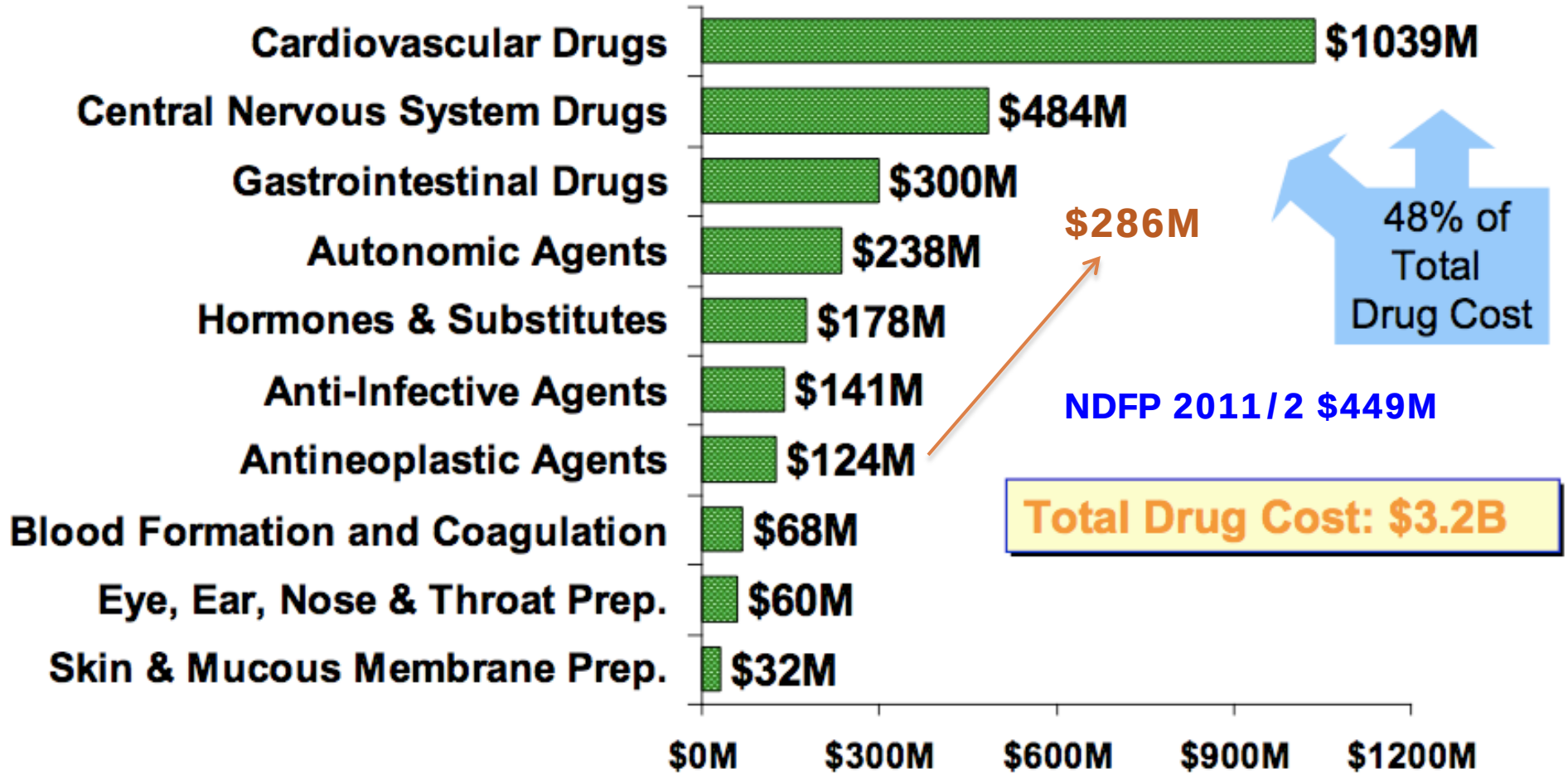
- Cost effectiveness – expression of an intervention's cost in relation to its benefit

Cost of Health Care and Life Expectancy



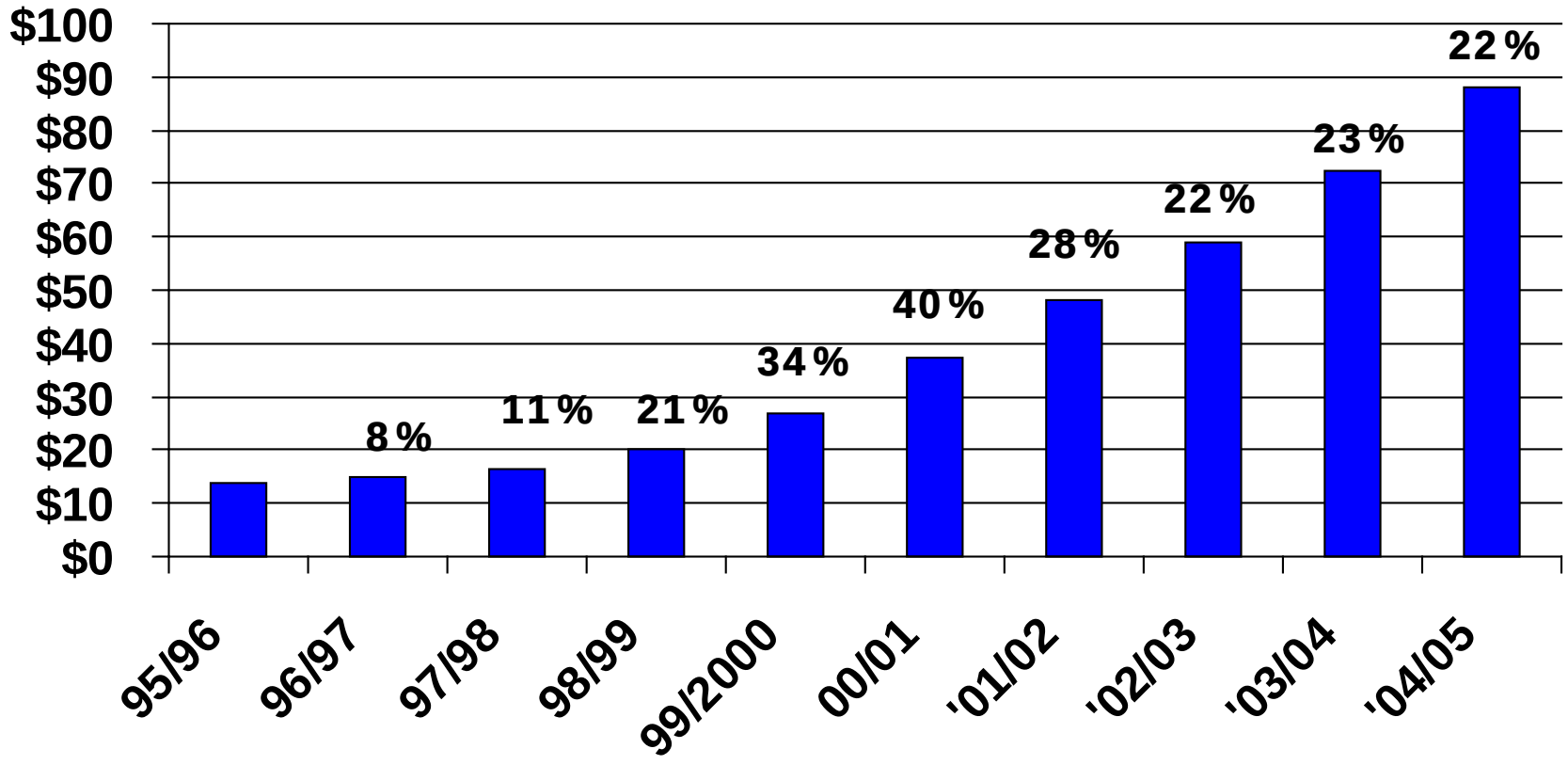
Meropol & Schulman J Clin Oncol 2007;25(2):180-186

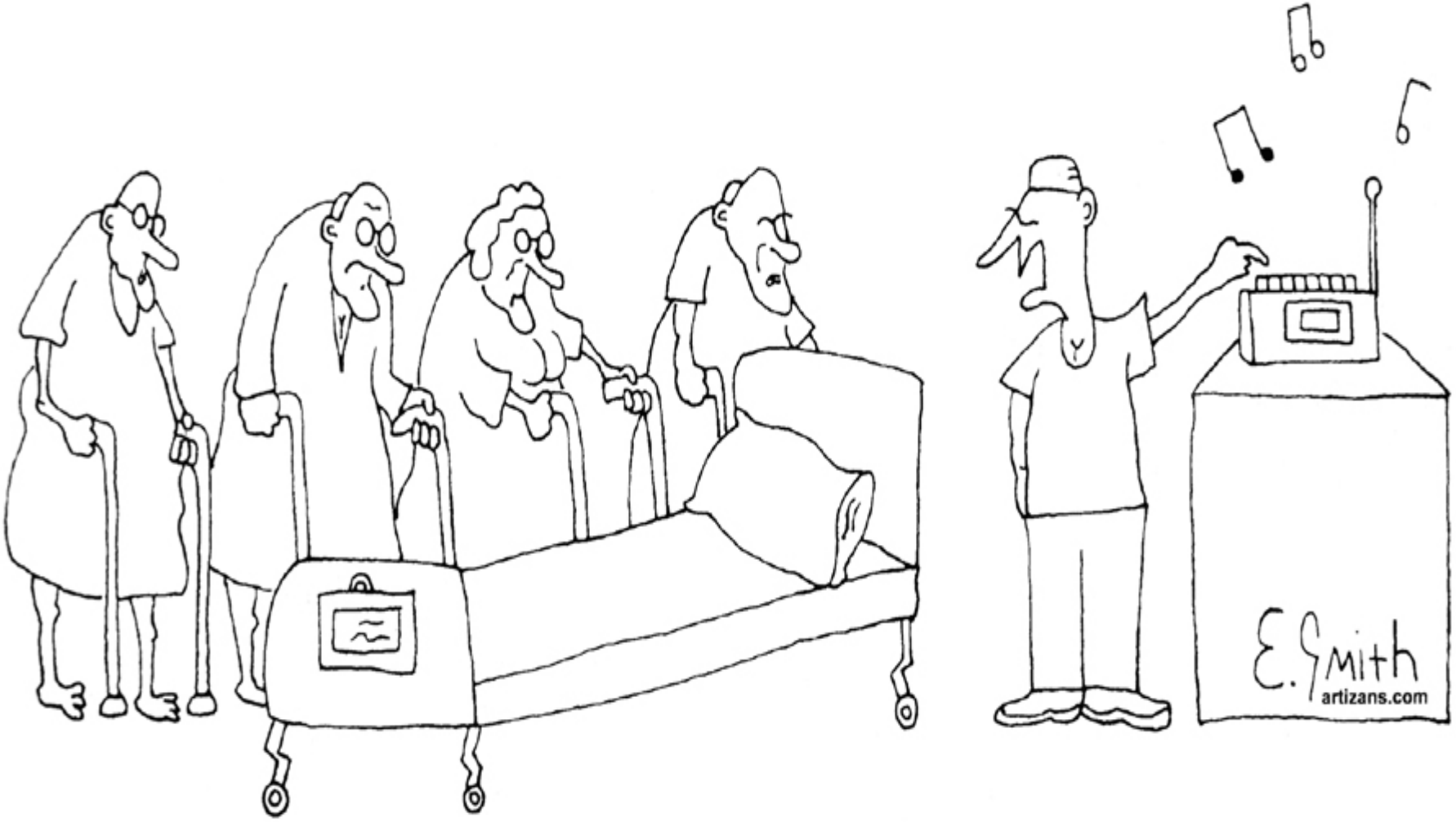
Top-10 Therapeutic Classes by Drug Cost, 2007/08



* Does not include New Drug Funding Program (NDFP) expenditures, administered on behalf of the MOHLTC by Cancer Care Ontario (CCO). For 2007/2008 NDFP expenditures =$162.5million

BCCA: Projected Growth in Provincial Drug Costs ($ Millions)





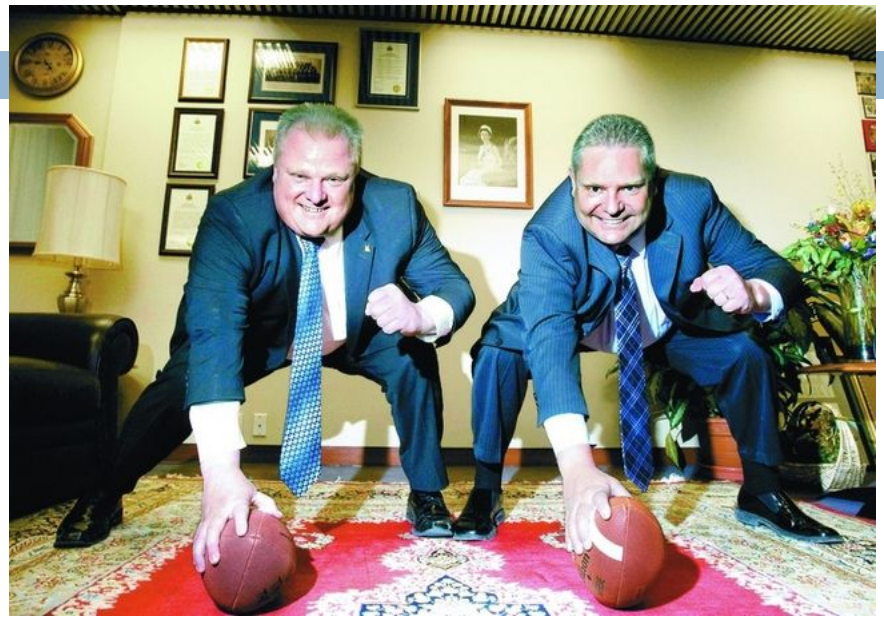
"First one on when the music stops gets today's hip operation."

Types of Economic Evaluation

- **Cost-effectiveness analysis (CEA)** – outcome measured units, e.g. life-years gained or clinical event avoided; sometimes used to refer to all economic evaluations
- **Cost-utility analysis (CUA)** – outcome measured in terms of health-related preference or value, e.g. quality-adjusted life-years (QALYs)
- **Cost-benefit analysis (CBA)** – values net benefits and opportunity costs in monetary terms
- **Cost-minimization analysis (CMA)** – Outcomes of intervention & alternatives are considered equivalent; alternative with lowest cost is selected
- **Cost-consequence analysis (CCA)** – costs and outcomes are listed separately in a disaggregated format, (no ICER)

Incremental Cost Effectiveness Ratio (ICER)

Option A



Option B

- Δ cost between option A and option B/ Δ benefit
- Treatment A costs $10,000 - B $8,000/A improves survival by 1 year, quality-adjusted survival by 0.8 yrs
- ICER – $2,000/LYG; $2,500/QALY

Components of EA

- Select type of analysis (CUA, CEA, CMA)
- Perspective – Societal; Payer (government), Patient
- Prospective or Retrospective Data Collection
- Costs – direct and indirect medical, lost productivity
- Time Horizon – lifetime; duration of clinical trial
  - What about after trial? Adjuvant – late effects, relapse and treatment
- Outcomes – OS in Phase III trial; (what about PFS in phase II?)
  - How do you value OS with cancer vs. cancer-free? Utilities, QALY
  - What about value of PFS, RR? Time with toxicity?
  - What comparator(s) should be used?
- Discounting – used for valuation of future costs, benefits
- Uncertainty – 95% confidence intervals, sensitivity analyses

Quality Adjusted Life Year (QALY)

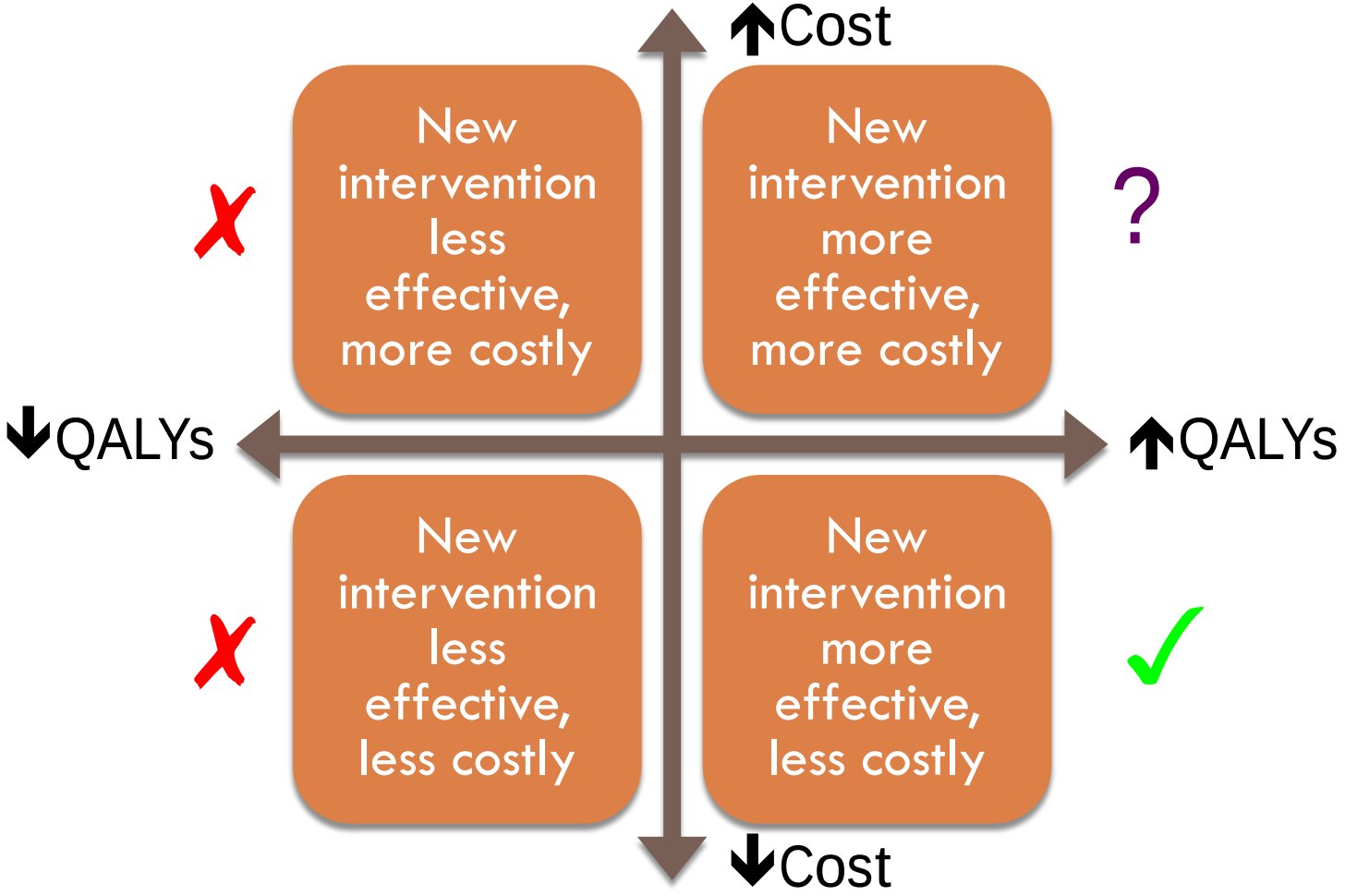
- Integrates mortality and morbidity
- QALY= duration of health state * utility score during that health state
- 1 year with disease = fraction of a healthy year
- Considers impact on quality of life
- Considers impact of toxicity

Health Preference (Utility)

- Measure of health preference
  - 1-perfect health
  - 0-death
  - Average Canadian 0.92-0.96
  - Changes according to disease state

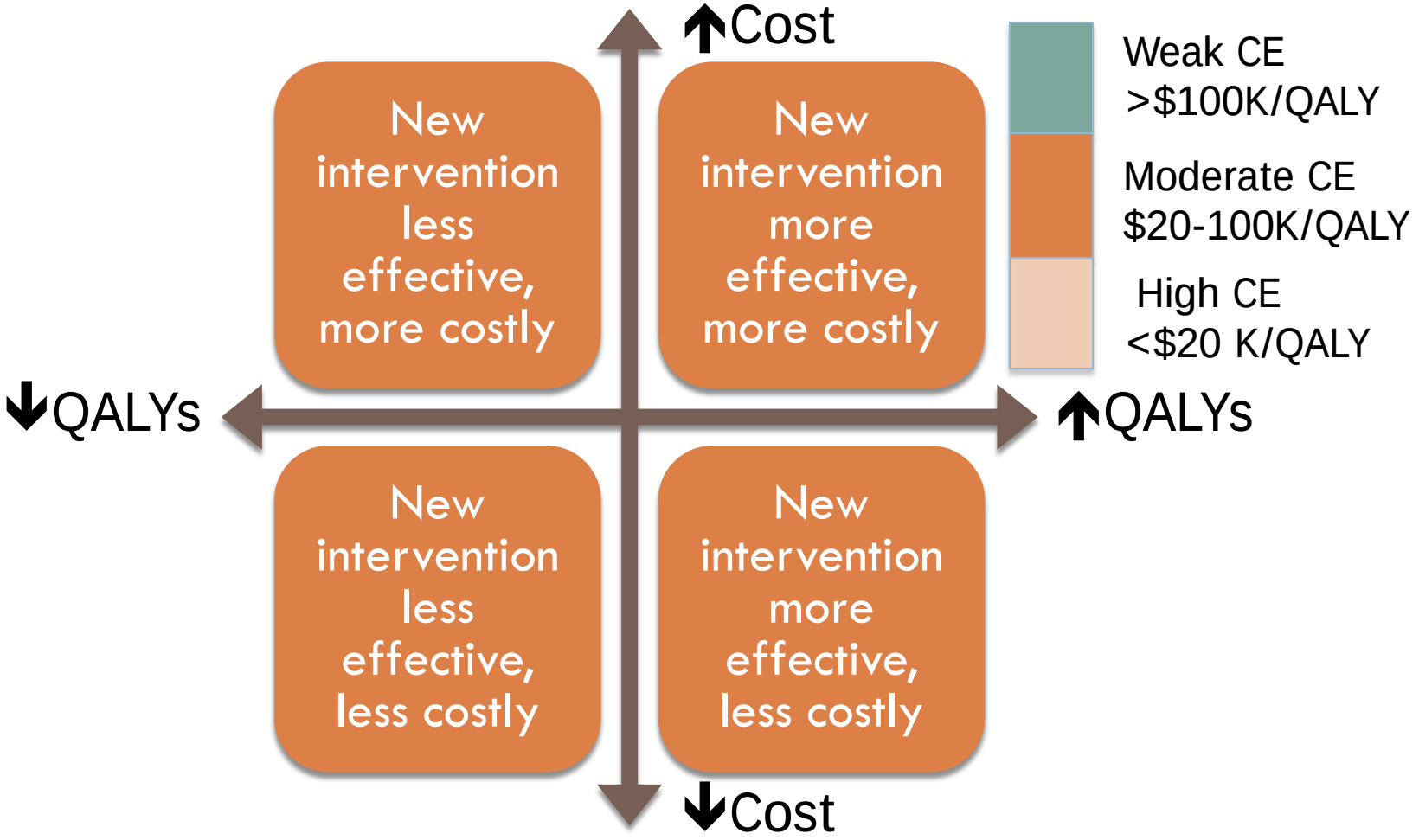
- Standardized tools available to measure
  - Direct-Time Trade Off, Standard Gamble
  - Indirect-HUI, EQ5D, VAS

Adopting a New Technology



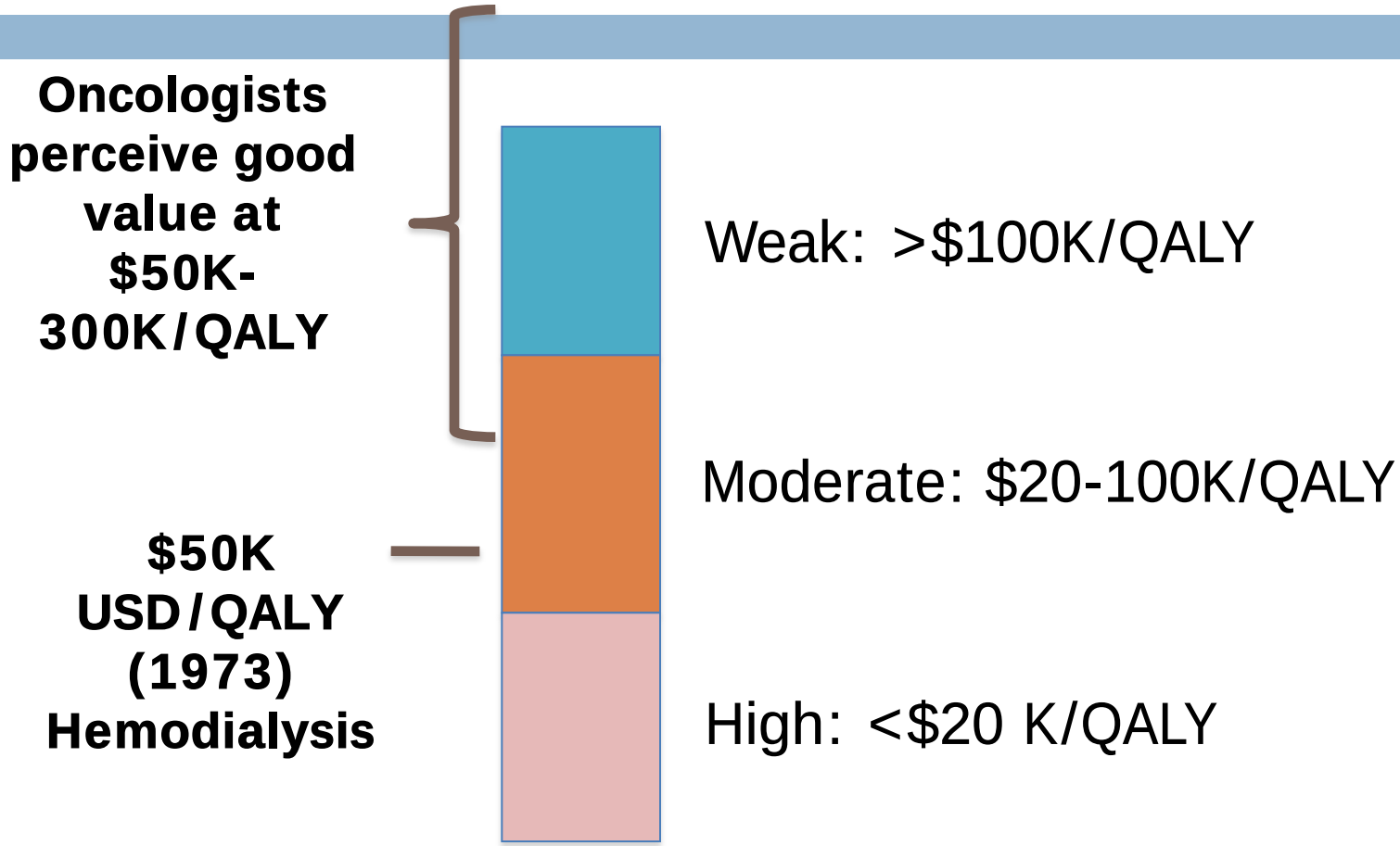
Laupacis et al. CMAJ 1992;146(4):473-81

Thresholds for Adopting Technology



Laupacis et al. CMAJ 1992;146(4):473-81

Thresholds for Adopting Technology



Laupacis *et al*. CMAJ 1992;146(4):473-81
Earle *et al.* J Clin Oncol 2000;18:3302-17
Nadler et al. Oncologist 2006; 11(2):90-5
Berry et al. J Clin Oncol 2010; 28:4149-53
Ubel et al. Health Aff 2012; 31:709-717

League Table

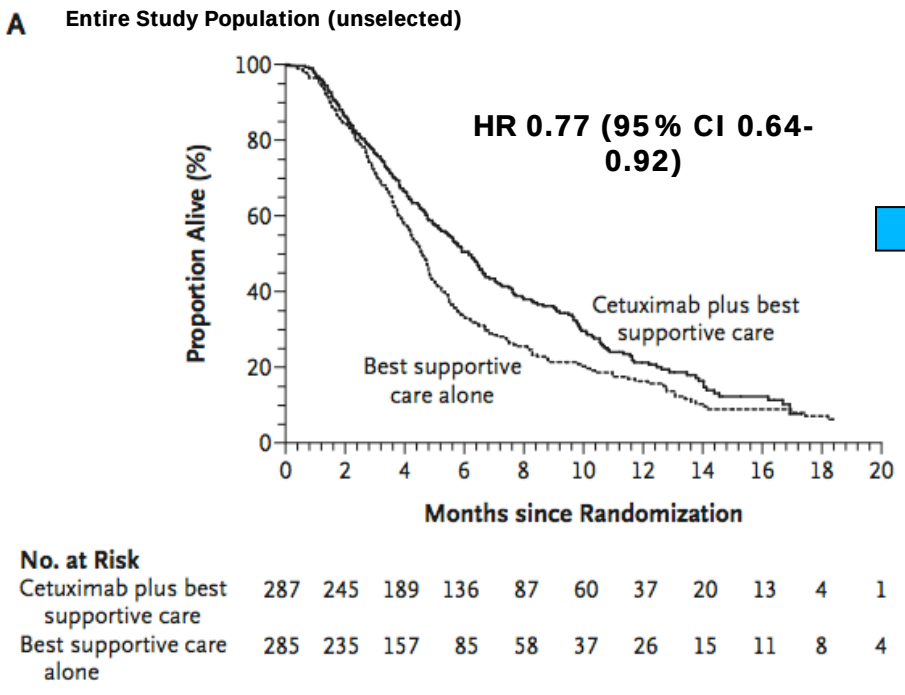
INTERVENTION	COST/life-yr gained
Bone marrow transplant	$220,000
Inpatient hemodialysis	$ 54,000
Neonatal ICU	$ 30,900
Automoblie airbags	$ 20,000
Treatment of mild hypertension	$ 19,100
Treatment of severe hypertension	$ 9,400
Bypass surgery (left main)	$ 4,200
Mandatory smoke detectors	$ 1,300
Smoking cessation counselling in men	$ 705

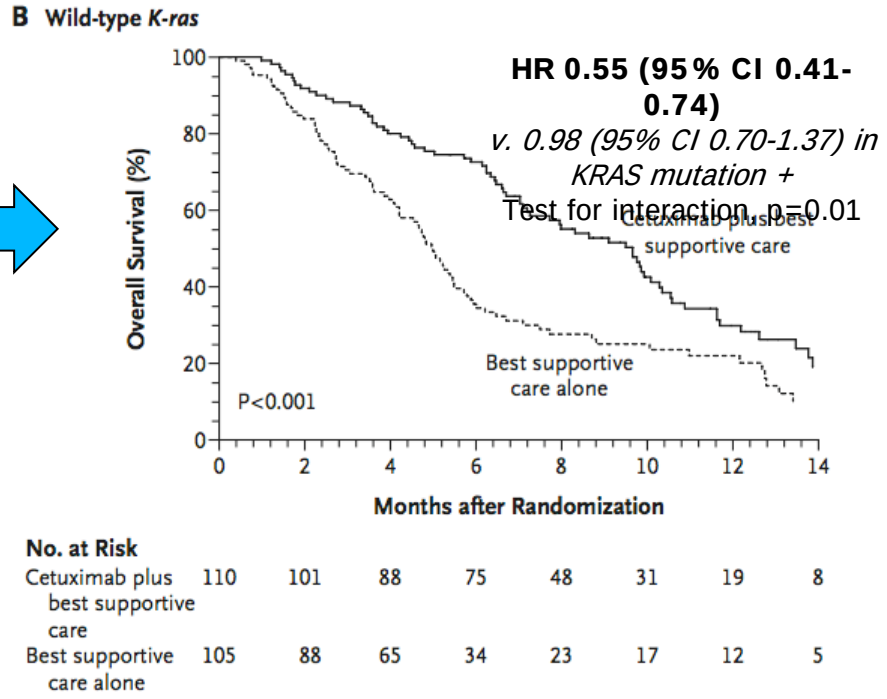
CEA Criteria for Determining if a Clinical Trial is Appropriate for an Economic Evaluation

- New intervention anticipated to have only a modest therapeutic benefit in a potentially large patient population
- Therapy potentially very costly
- High degree of uncertainty about economic impact of treatment
- Economic evaluation may yield important information in determining routine practice (e.g. equivalence trial)
- Economic data will assist future economic evaluations
- For intergroup trials, suitable number of Canadian patients (100)

Evans et al Chronic Dis Prev 2003

NCIC CTG CO.17: Cetuximab improves survival and quality of life in end-stage advanced colorectal cancer; greatest benefit in KRAS wild type (not KRAS mutant)



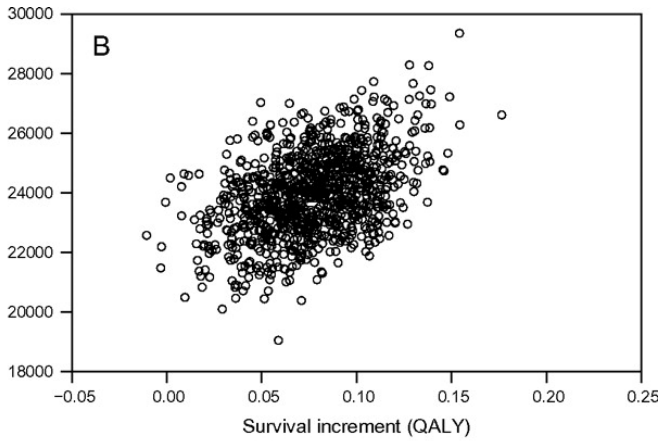


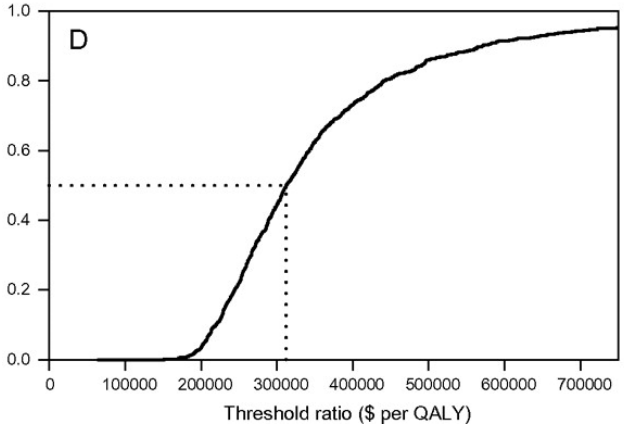
- 69% tumour samples (394/572), similar characteristics to overall population
- 58% KRAS wild type of those tested (230/394), 40% of entire study population

Jonker DJ et al. N Engl J Med 2007; 347:2040-8; Karapetis CS et al. N Engl J Med 2008; 359(17):1757-65

Prospective Economic Evaluation (resource utilization, HUI3) of Cetuximab Therapy in the entire study population and KRAS wild type subgroup

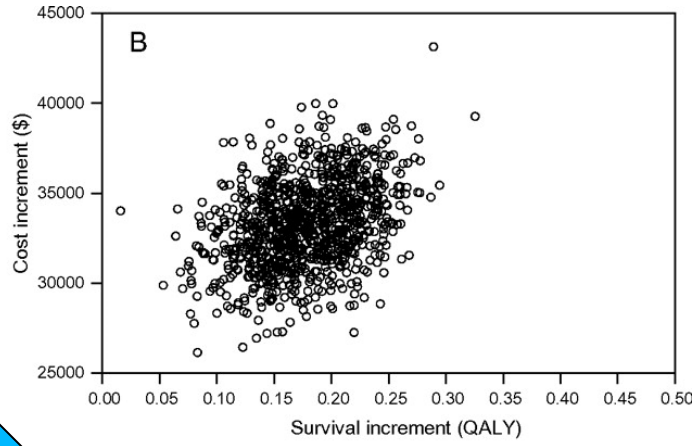
ICUR $300,000/QALY

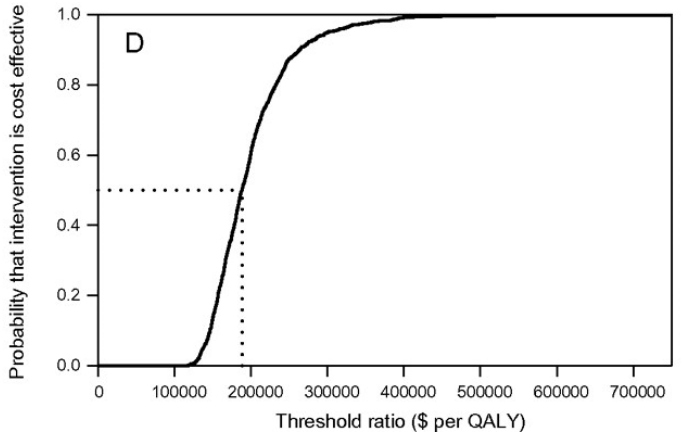




Entire study population (n=572)

ICUR $187,000/QALY





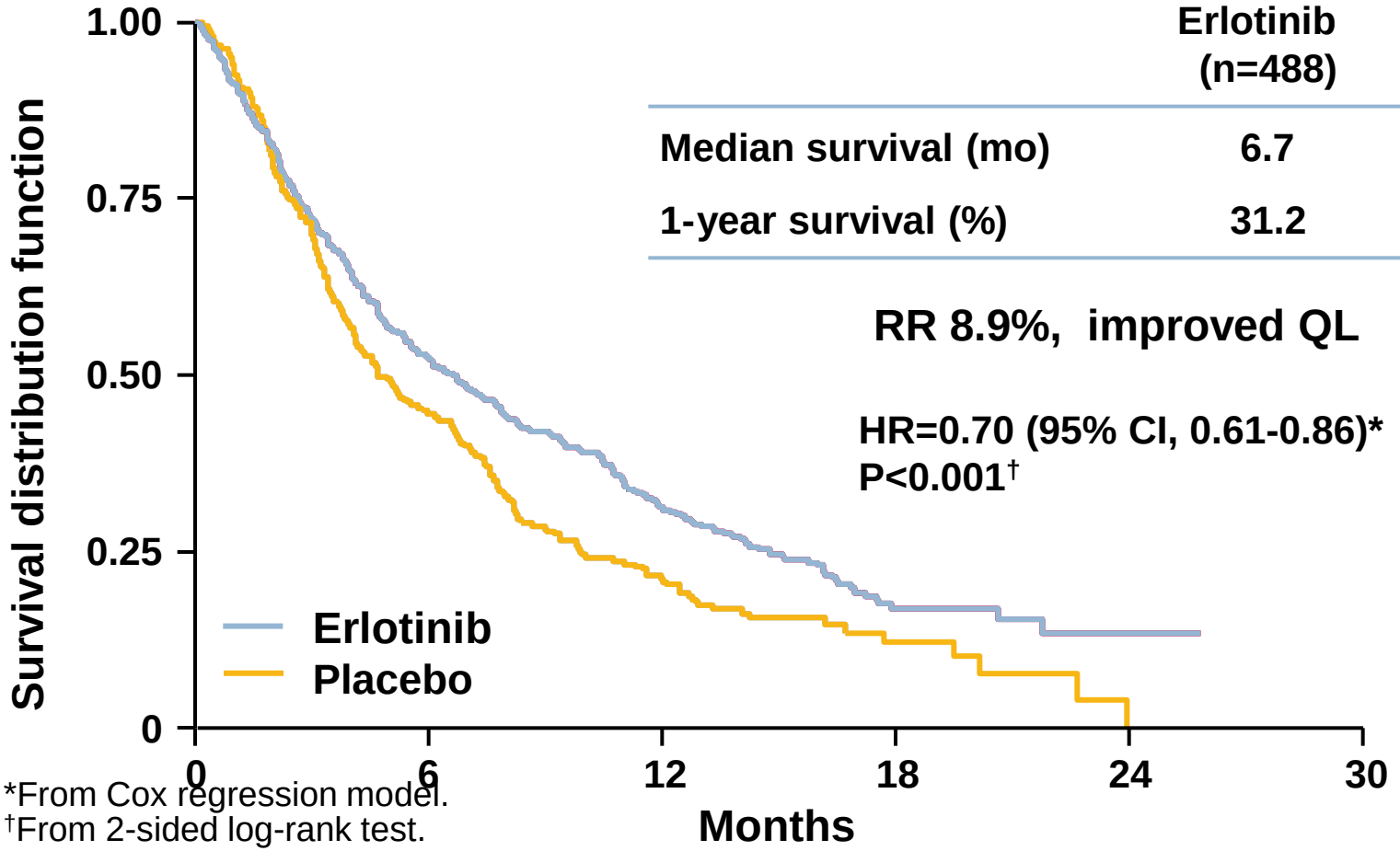
KRAS wild type (n=230)

Mittmann N et al. J. Natl. Cancer Inst. 2009; 101:1182-1192

How not to get your drug funded in Canada

"Tests on rats show that if you pay for these drugs through the nose, the effect increases dramatically."

BR.21: Erlotinib v. Placebo in pretreated advanced NSCLC
Overall Survival



	Erlotinib (n=488)	Placebo (n=243)
Median survival (mo)	6.7	4.7
1-year survival (%)	31.2	21.5

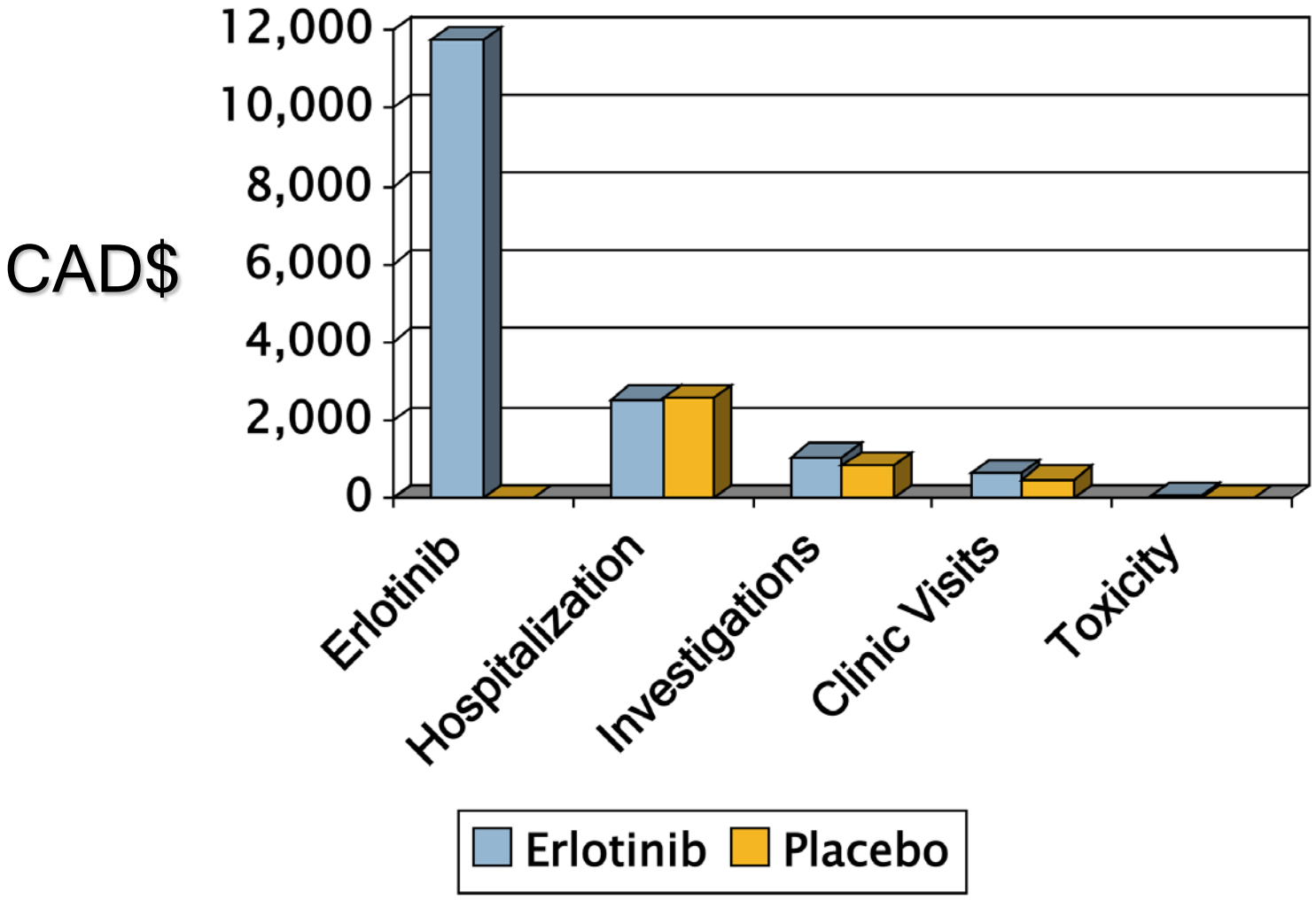
RR 8.9%, improved QL

HR=0.70 (95% CI, 0.61-0.86)*
P<0.001†

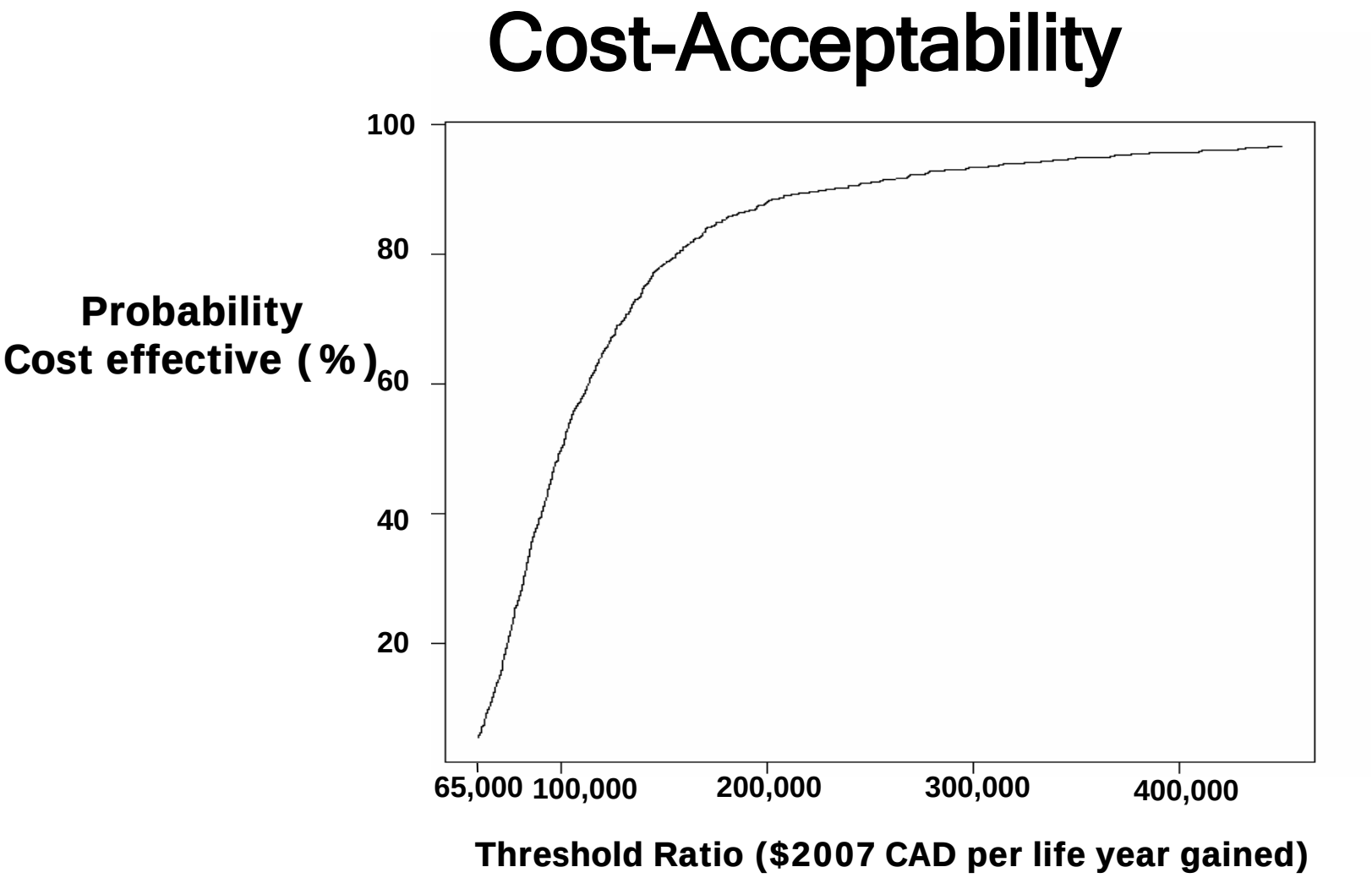
*From Cox regression model.
†From 2-sided log-rank test.
HR = hazard ratio.

Shepherd et al, Erlotinib in Previously Treated Non-small –Cell Lung Cancer, NEJM, 353;2; 123-132

Mean Costs per Treatment Arm

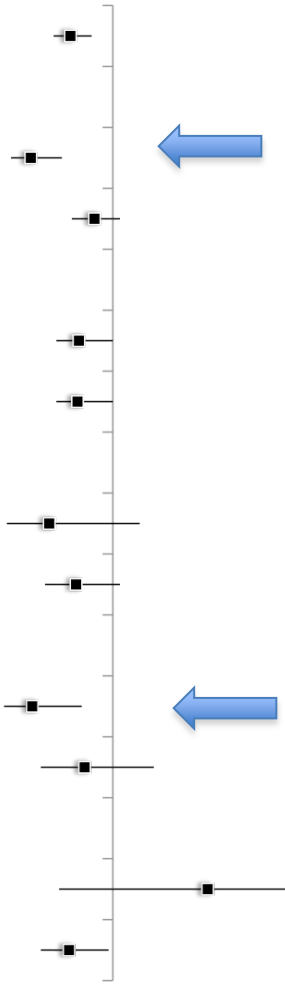


ICER $94,638 CAD/LYG (95% CI: $52,359 - $429,148/LYG)

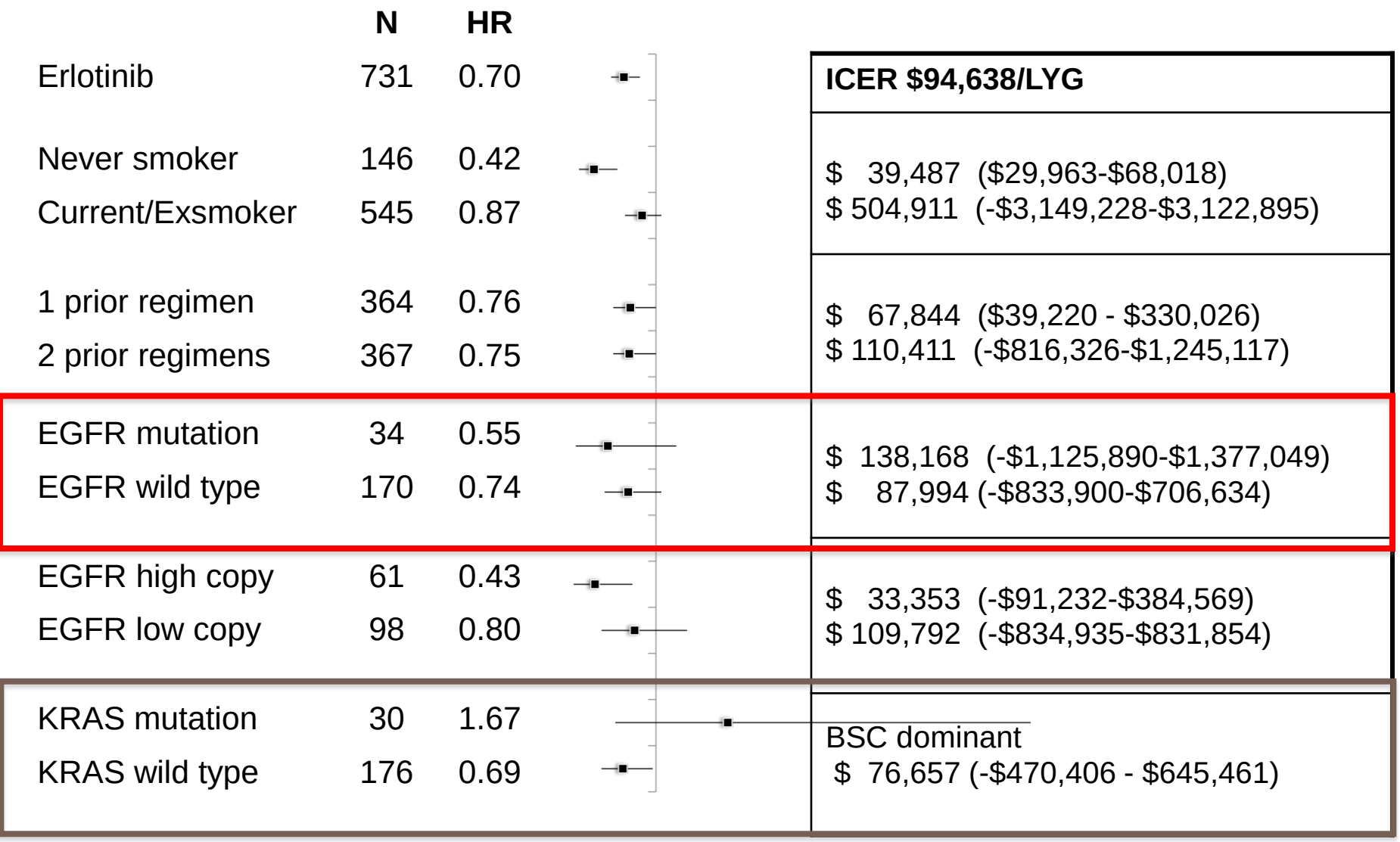


Forest Plot: Survival in BR.21 by Selected Clinical and Molecular Subgroups

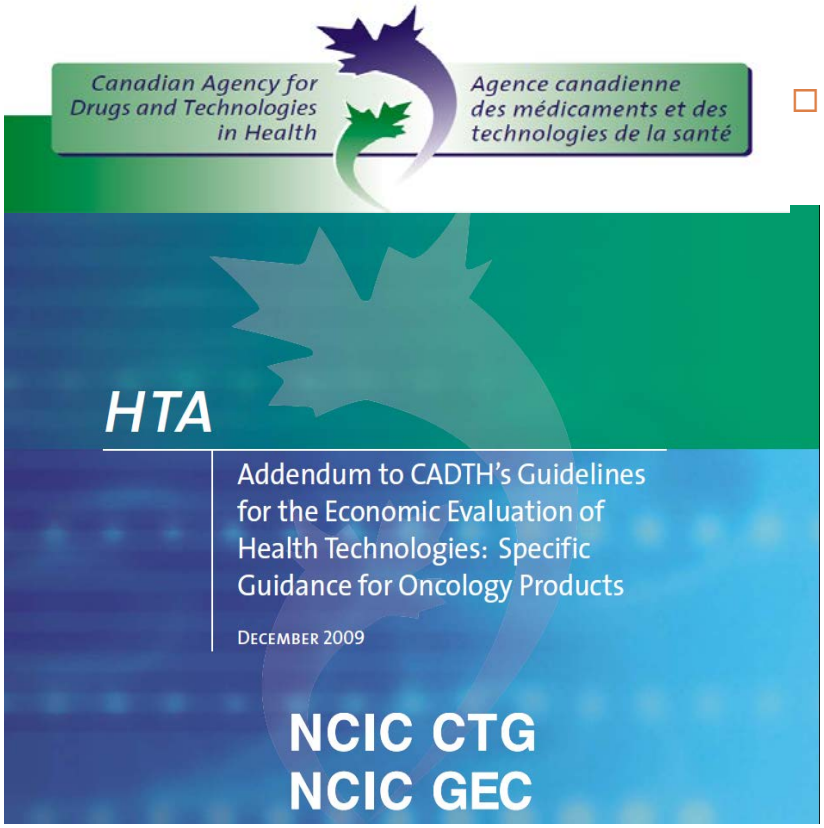
	N	HR	ICER $94,638/LYG
Erlotinib	731	0.70	
Never smoker	146	0.42	$ 39,487 ($29,963-$68,018)
Current/Exsmoker	545	0.87	$ 504,911 (-$3,149,228-$3,122,895)
1 prior regimen	364	0.76	$ 67,844 ($39,220 - $330,026)
2 prior regimens	367	0.75	$ 110,411 (-$816,326-$1,245,117)
EGFR mutation	34	0.55	$ 138,168 (-$1,125,890-$1,377,049)
EGFR wild type	170	0.74	$ 87,994 (-$833,900-$706,634)
EGFR high copy	61	0.43	$ 33,353 (-$91,232-$384,569)
EGFR low copy	98	0.80	$ 109,792 (-$834,935-$831,854)
KRAS mutation	30	1.67	BSC dominant
KRAS wild type	176	0.69	$ 76,657 (-$470,406 - $645,461)



Forest Plot: Survival in BR.21 by Selected Clinical and Molecular Subgroups



CEA Initiative to Consider Cancer as a "Special Case" in Health Technology Assessment



Cite as: Mittmann N., Evans W.K., Rocchi A., Longo C. J., Au H.-J., Husereau D., Leighl N., Isogai P., Krahn M., Peacock S., Marshall D., Coyle D., Malfair Taylor S.C., Jacobs P., Oh P.I. *Addendum to CADTH's Guidelines for the Economic Evaluation of Health Technologies: Specific Guidance for Oncology Products.* Ottawa: Canadian Agency for Drugs and Technologies in Health; 2009.

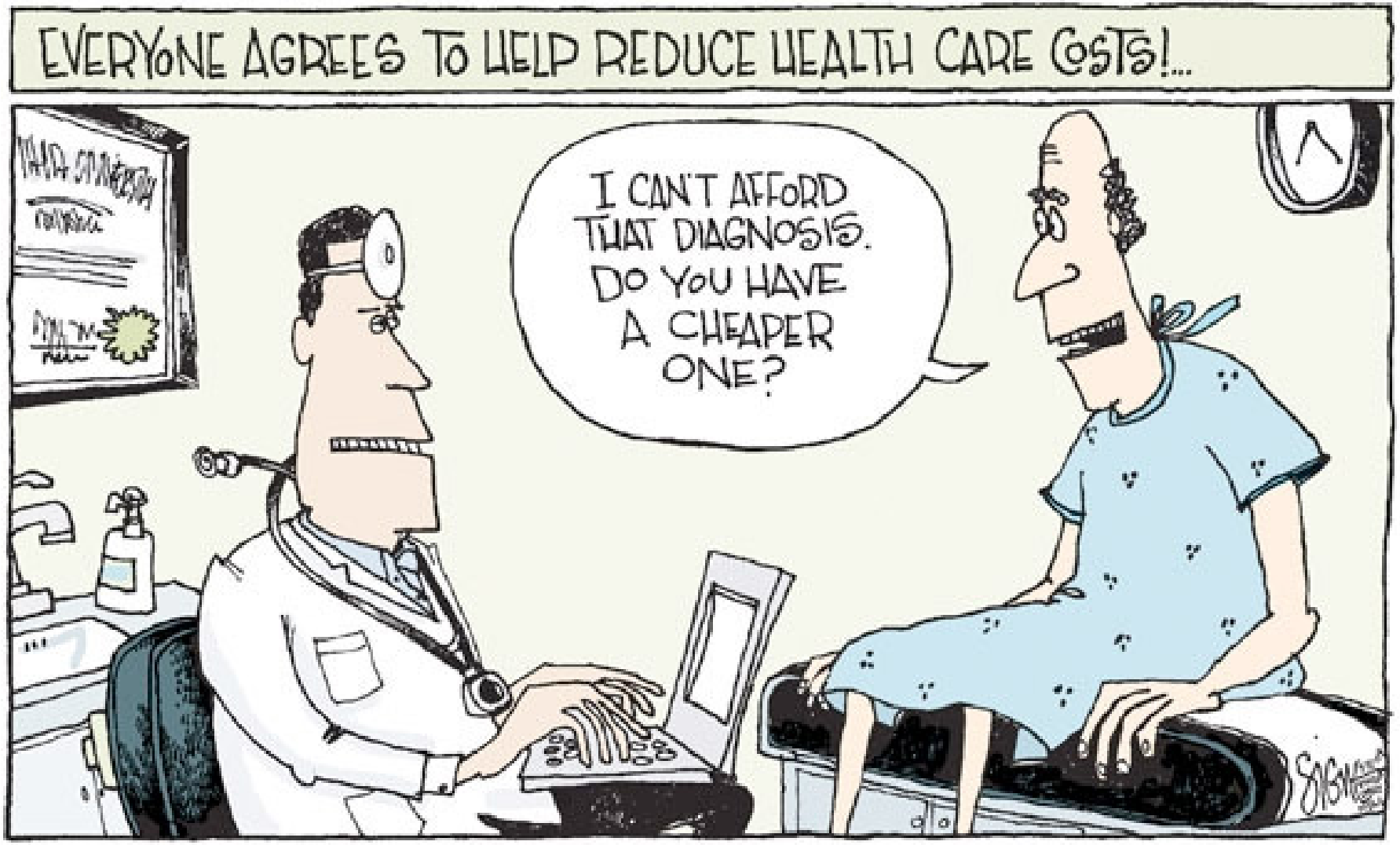
- Specific challenges are often encountered in oncology economic evaluations
  - choice of outcome to be used (e.g., overall survival [OS] versus other measures of disease control, such as progression-free survival);
  - the best method to estimate survival gain (e.g., mean survival, median survival, area under the curve);
  - time horizon, especially because most clinical trials report early results;
  - which toxicities to include in the resource utilization data (e.g., mild versus severe);
  - which perspective to take (e.g., the perspective of the payer in a publicly funded federal/provincial/territorial health care system versus a societal perspective).

Why Interventions Fail Economics 101…

- Cost: ICER, budget impact too high (>70-100K/QALY)
- Benefits – not enough clinical benefit (survival); sometimes not enough advocacy…
- Methodologic/Process Issues
  - Pharmacoeconomic submission poor quality
  - Clinical data hard (for non-oncologists) to interpret
    - outcome not OS but surrogate (PFS, RR) – how to value?
    - Trial design – Phase II not III, crossover allowed, outdated/wrong comparator
    - Unpublished data or abstract/ASCO presentation only

Economic Analyses in Clinical Trials

- Important addition to strengthen, complement results of ongoing clinical trials
- Helps clinicians, patients and policy-makers interpret value of novel interventions
- Critical part of Canadian oncology drug funding process (pan Canadian Oncology Drug Review)
- Timely economic evaluation of CTG interventions may facilitate uptake of novel therapies


EVERYONE AGREES TO HELP REDUCE HEALTH CARE COSTS!...
I CAN'T AFFORD THAT DIAGNOSIS. DO YOU HAVE A CHEAPER ONE?