Cost-Effectiveness Analysis

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Epi 550

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Outline

- Introduction to cost-effectiveness analysis (CEA)
- Choice criteria for CEA
- Incremental cost-effectiveness ratios
- Net benefits (a transformation of CEA) and choice criteria
- Additional topics

What is Commonly Meant by "Cost-Effective"?

- "Super RTL is looking to implement a new 'lean and cost-effective' structure as it slashes about 15 per cent of its 130-person workforce
- Cost effective resolution of small claims: final determination at settlement conference [without a hearing] will eliminate further attendances by all parties and substantially reduce costs of proceeding with low value claims
- "We're called Cost Effective Maintenance because we provid[e] you with the most cost effective solutions to engine maintenance problems…[O]ur [products]…are proven to be highly effective at fixing the problem[s]"
- "Using ETFs To Build A Cost-Effective Portfolio"

Cost-Effectiveness Analysis

- Estimates differences in costs and differences in outcomes between interventions
- Costs and outcomes measured in different units
- Costs usually measured in money terms; outcomes in some other units
- If outcomes aggregated using measures of preference (e.g., quality-adjusted life years saved), referred to as cost utility analysis

Relative Measure

- No program “cost-effective” in abstract
- Results meaningful in comparison with:
  - A predefined threshold for willingness to pay
    - e.g., $50,000 or $100,000 per quality-adjusted life year
  - Other accepted and rejected interventions (e.g., a league tables)

Cost-Effectiveness “History”

- $/Life saved
- $/Year of life saved (YOL)
- $/Quality adjusted life year saved (QALY)

- ??? US Congress and outlawing QALYs ???

Why CEA Rather Than CBA?

- Not precisely clear
  - Potential difficulties in measurement
  - Discomfort with placing a dollar value directly on a particular person's life (rather than years of life in general)
  - QALYs / life years more equally distributed than wealth
  - Health more a “right” than a commodity
    - Implies 1 person 1 vote may be more appropriate than 1 dollar 1 vote
    - Cost-effectiveness analysis uses 1 QALY/year 1 vote

Cost-Effectiveness Ratios

- Incremental Cost-effectiveness ratio

$$\frac{\text{Costs}_1 - \text{Costs}_2}{\text{Effects}_1 - \text{Effects}_2}$$

- Never compare:

$$\frac{\text{Costs}_1}{\text{Effects}_1} \quad \text{VS} \quad \frac{\text{Costs}_0}{\text{Effects}_0}$$

Cost-Effectiveness Ratios (II)

- A ratio can exist for every pair of options (i.e., combinations n things take 2 at a time)
  - 1 option (case series), no ratios calculated
  - 2 options, 1 ratio
  - 3 options, 3 ratios (option 1 versus option 2, option 1 versus option 3, and option 2 versus option 3)
- In efficient selection algorithm, don’t necessarily calculate all possible ratios

Which are the Right Ratios to Consider?

Sixth Stool Guaiac

- Suppose we can use 1 through 6 stool guaiacs when screening for cases of colorectal cancer

# Guaiac Tests	Cost	Cases
1	7.75	.00659469
2	10.77	.00714424
3	13.02	.00719004
4	14.81	.00719385
5	16.31	.00719417
6	17.63	.00719420

Neuhauser and Lewicki, NEJM, 1975;293:226-8.

- What calculations might help make choice between them?

Mistake #1

- Divide therapy's cost by its outcome; compare resulting ratios

# Guaiac Tests	Cost		Cases		C_i / E_i
1	7.75	÷	.00659469	=	1175
2	10.77	÷	.00714424	=	1508
3	13.02	÷	.00719004	=	1811
4	14.81	÷	.00719385	=	2059
5	16.31	÷	.00719417	=	2267
6	17.63	÷	.00719420	=	2460

- Sometimes (mistakenly?) referred to as average cost-effectiveness ratios

Dividing a Therapy's Costs by Its Effects is "Generally Uninformative"

	Cost	QALYs	C_i / Q_i
Example 1			
Rx1	2,800	0.28	10,000
Rx2	5,800	0.29	20,000
Example 2			
Rx1	2,800	0.28	10,000
Rx2	11,200	0.56	20,000

Dividing a Therapy's Costs by Its Effects is "Generally Uninformative"

	Cost	QALYs	C_i / Q_i
Example 1			
Rx1	2,800	0.28	10,000
Rx2	5,800	0.29	20,000
	(5,800-2,800) / (0.29-0.28) = 300,000		
Example 2			
Rx1	2,800	0.28	10,000
Rx2	11,200	0.56	20,000
	(11,200-2,800) / (0.56-0.28) = 30,000		

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	(5,800-2,800) / (0.29-0.28) = 300,000		
Example 2			
Rx1	2,800	0.28	**10,000**
Rx2	11,200	0.56	**20,000**
	(11,200-2,800) / (0.56-0.28) = 30,000		

Mistake #2

- Calculate ratios for all therapies versus 1 guaiac; compare resulting ratios

# Guaiac Tests	Cost	ΔCost	Cases	ΔCases	ACER*
1	7.75	--	.00659469	--	--
2	10.77	3.02	.00714424	.00054955	5495
3	13.02	5.27	.00719004	.00059535	8852
4	14.81	7.06	.00719385	.00059916	11783
5	16.31	8.56	.00719417	.00059948	14279
6	17.63	9.88	.00719420	.00059951	16480

* $(C_i - C_1) / (E_i - E_1)$

Average Cost-Effectiveness Ratio

- Ratios calculated by comparing one therapy to all other therapies (correctly) referred to as average cost-effectiveness ratios
- Definition: Comparison of costs and effects of each intervention with a single option, often "do nothing" or usual care option
  - Sometimes study sponsor's therapy

Average Cost-Effectiveness Ratios

- Goal of algorithm: choose strategy that provides largest health outcome that we are still willing to pay for

# Guaiac Tests	Cost	ΔCost	Cases	ΔCases	ACER
1	7.75	--	.00659469	--	--
2	10.77	3.02	.00714424	.00054955	5495
3	13.02	5.27	.00719004	.00059535	8852
4	14.81	7.06	.00719385	.00059916	11783
5	16.31	8.56	.00719417	.00059948	14279
6	17.63	9.88	.00719420	.00059951	16480

- Why don't average ratios allow identification of this strategy?

What's Wrong with the Average Cost-Effectiveness Ratio?

# Guaiac Tests	Cost	ΔCost	Cases	ΔCases	ACER
1	7.75	--	.00659469	--	--
5	16.31	8.56	.00719417	.00059948	14279
6	17.63	9.88	.00719420	.00059951	16480

- 16,480 ACER from 6 vs 1 guaiacs gives 6 guaiacs credit for 16.31 already spent and .00719417 cases already detected with 5 guaiacs
- However, if comparing 6 to 5, spending 1.32 (17.63-16.31) more and gaining only 0.00000003 cases detected

  1.32 / 0.00000003 = $44m / incremental case detected

Incremental Cost-Effectiveness Ratios

- Compares costs and effects among alternative options
- When there are only 2 options being evaluated, average and incremental cost-effectiveness ratios are identical

Incremental Cost-Effectiveness Ratio

- Basic idea for correct ratio: calculate ratio for 2 vs 1, 3 vs 2, 4 vs 3, 5 vs 4, and 6 vs 5

# Guaiac Tests	Cost	ΔCost	Cases	ΔCases	ICER*
1	7.75	--	.00659469	--	--
2	10.77	3.02	.00714424	.00054955	5495
3	13.02	2.25	.00719004	.00004580	49.1k
4	14.81	1.79	.00719385	.00000381	470k
5	16.31	1.50	.00719417	.00000032	4.7m
6	17.63	1.32	.00719420	.00000003	44.0m

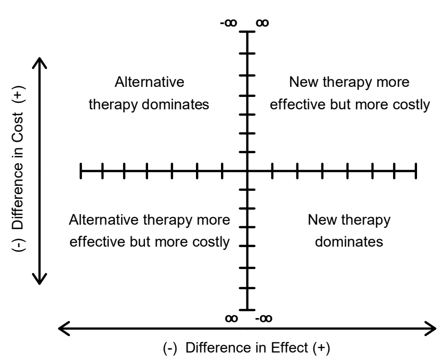
* $(C_i - C_{i-1}) / (E_i - E_{i-1})$

- “Basic idea” correct in this case, but can have problems

Potential Problems With Calculating ICERS

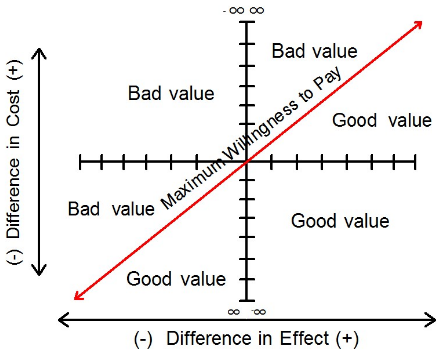
- Problem 1: Treatments must be correctly ordered
- Problems 2: Never want to spend more and obtain less outcome
- Problem 3: Don’t want to buy less outcome for a higher cost per unit of outcome

Cost-Effectiveness Plane



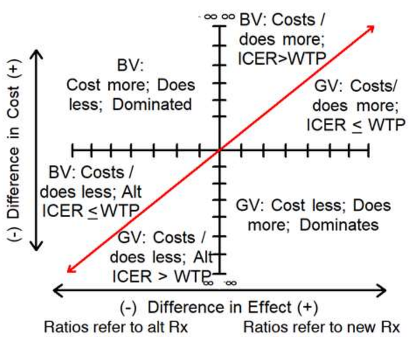
- Axes
- Origin
- Average ratios
- Incremental ratios

Good and Bad Value



- Willingness to pay "line"
- Reasons for good and bad value differ per quadrant

Reasons for Good and Bad Value



Choice Criteria, Simple Examples

Choice Criteria For Cost-Effectiveness Ratios

- Choose options with acceptable average and incremental cost-effectiveness ratios (i.e., whose ratios with all other options are acceptable)
- Subject to:
  - Budget Constraint?
  - Acceptable Ratio?
- Not accounting for uncertainty around ratios
- Consider 3 mutually exclusive options and a willingness to pay of 40k/50k

Choice Criteria, Example 1

	Option 1	Option 2	Option 3
Expected Costs	10,000	135,000	270,000
Expected QALYs	20	25	30

Ratios	Option 2	Option 3	
Option 1	25,000	26,000	
Option 2	--	27,000	Adopt?

Choice Criteria, Example 2

	Option 1	Option 2	Option 3
Expected Costs	10,000	135,000	235,000
Expected QALYs	20	25	26

Ratios	Option 2	Option 3	
Option 1	25,000	37,500	
Option 2	--	100,0000	Adopt?

Choice Criteria, Example 3

	Option 1	Option 2	Option 3
Expected Costs	10,000	210,000	230,000
Expected QALYs	20	21	21.5

Ratios	Option 2	Option 3	
Option 1	200,000	146,667	
Option 2	--	40,000	Adopt?

Fairness of Criteria?

- In example 2 above, 3 options available; if WTP = 40,000, reject Option 3
- Suppose options are drugs, and patient 1 can take any of 3, but patient 2 is allergic to drug 2 and can't take it
- What do we choose?

	Drug 1	Drug 2	Drug 3
Patient 1			
Exp Costs	10,000	135,000	235,000
ExpQALYs	20	25	26
Patient 2			
Exp Costs	10,000	--	235,000
Exp QALYs	20	--	26

Fairness (2)

Patient 1	Option 2	Option 3	
Option 1	25,000	37,500	
Option 2	--	100,0000	Adopt?

Patient 2	Option 3		
Option 1	37,500		Adopt?

4+ Formal Methods for Choosing Between Rx

Multitherapy Example

- Suppose 5 screening strategies have following discounted costs and life expectancies:

Treatment	Cost	YOLS
S1 Sig Q10	1290	17.378
S2 U+Sig, Q10	1810	17.402
S3 C Q(10)	2030	17.396
S4 Sig Q5	1535	17.387
S5 U+Sig, Q5	2035	17.407

Frazier AL, et al. JAMA. 2000;284:1954-61.

Choice Among Screening Strategies

- Which therapy should be adopted if acceptability criterion is 20,000/ YOL saved? 40,000 / YOL saved? 50,000 / YOL saved?
- Demonstrate 4(+) methods for selecting single therapy from among 5 candidate therapies
  - Methods all based on selecting therapy with acceptable ratio
  - All 4(+) are transformations of one another -- use same information in slightly different ways -- and all recommend identical cost-effective strategy

Method 1: Incremental Cost-Effectiveness Ratio

- Previously indicated basic idea was to calculate ratio for 2 vs 1, 3 vs 2, 4 vs 3, 5 vs 4
- Also noted 3 problems/complications:
  1. For incremental cost-effectiveness ratios and incremental NMB, treatments must be correctly ordered
  2. Never want to spend more and obtain less outcome
  3. Don't want to buy less outcome for a higher cost per unit of outcome

Problem/Complication 1

- Treatments must be correctly ordered

Treatment	Cost	YOLS
S1 Sig Q10	1290	17.378
S2 U+Sig, Q10	1810	17.402
S3 C Q(10)	2030	17.396
S4 Sig Q5	1535	17.387
S5 U+Sig, Q5	2035	17.407

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Efficient Algorithm: Step 1

- By convention, rank order therapies in ascending order of either outcomes or cost

Treatment	Cost	YOLS
S1 Sig Q10	1290	17.378
S4 Sig Q5	1535	17.387
S3 C Q(10)	2030	17.396
S2 U+Sig, Q10	1810	17.402
S5 U+Sig, Q5	2035	17.407

- 5 strategies not in ascending order of either cost or effect
- Revised so correctly ordered by effect
- Final recommendation unaffected by ranking variable

Problem/Complication 2

- Never want to spend more (increased cost) and obtain less outcome (reduced effects) than at least one other alternative
  - Referred to as “strong” dominance

Efficient Algorithm: Step 2

- Eliminate therapies that are strongly dominated

Treatment	Cost	YOLS
S1 Sig Q10	1290	17.378
S4 Sig Q5	1535	17.387
S3 C Q(10)	**2030**	**17.396**
S2 U+Sig, Q10	**1810**	**17.402**
S5 U+Sig, Q5	2035	17.407

- S2 strongly dominates S3
- Eliminate S3 from consideration for adoption

Efficient Algorithm: Step 3

- Compute incremental cost-effectiveness ratios for each remaining adjacent pair of outcomes
  - i.e., between options S1 and S4; options S4 and S2; and options S2 and s5

Treatment	Cost	Δ	YOLS	Δ	ICER
S1 Sig Q10	1290	--	17.378	--	--
S4 Sig Q5	1535	245	17.387	.009	27,222
~~S3 C, Q10~~	~~2030~~	~~495~~	~~17.396~~	~~.009~~	~~SDOM~~
S2 U+Sig, Q10	1810	275	17.402	.015	18,333
S5 U+Sig, Q5	2035	225	17.407	.005	45,000

Alternative Ranking

- Ignoring convention and rank ordering from highest to lowest doesn't change results

Treatment	Cost	Δ	YOLS	Δ	ICER
S5 U+Sig, Q5	2035	225	17.407	.005	45,000
S2 U+Sig, Q10	1810	275	17.402	.015	18,333
~~S3 C, Q10~~	~~2030~~	~~495~~	~~17.396~~	~~.009~~	~~SDOM~~
S4 Sig Q5	1535	245	17.387	.009	27,222
S1 Sig Q10	1290	--	17.378	--	--

Efficient Algorithm: Step 3 (2)

- If resulting incremental ratios ranked from lowest to highest (alternative ranking, highest to lowest), skip to Step 6
- If not, need to address problem/complication 3

Treatment	Cost	Δ	YOLS	Δ	ICER
S1 Sig Q10	1290	--	17.378	--	--
S4 Sig Q5	1535	245	17.387	.009	**27,222**
~~S3 C, Q10~~	~~2030~~	~~495~~	~~17.396~~	~~.009~~	~~SDOM~~
S2 U+Sig, Q10	1810	275	17.402	.015	18,333
S5 U+Sig, Q5	2035	225	17.407	.005	45,000

Problem/complication 3

- Rather buy more outcome for a lower cost per unit than less outcome for a higher cost per unit
  - Referred to as "extended" or "weak" dominance
- May need to repeat evaluation of weakly dominated therapies several times

Efficient Algorithm: Step 4

- Eliminate therapies that are weakly dominated

Treatment	Cost	Δ	YOLS	Δ	ICER
S1 Sig Q10	1290	--	17.378	--	--
S4 Sig Q5	**1535**	**245**	**17.387**	**.009**	**27,222**
~~S3 C, Q10~~	~~2030~~	~~--~~	~~17.396~~	~~--~~	~~SDOM~~
S2 U+Sig, Q10	**1810**	**275**	**17.402**	**.015**	**18,333**
S5 U+Sig, Q5	2035	225	17.407	.005	45,000

- S4 weakly dominated by S2
  - S2 more effective than S4: .015 vs .009
  - Ratio for S2 vs S4 (18,333) less than ratio for S4 vs S1 (27,222)

Efficient Algorithm: Step 5

- Eliminate S4 **AND RECALCULATE RATIO** for S2 vs S1

Treatment	Cost	Δ	YOLS	Δ	ICER
S1 Sig Q10	1290	--	17.378	--	--
~~S4 Sig Q5~~	~~1535~~	~~--~~	~~17.387~~	~~--~~	~~WDOM~~
~~S3 C, Q10~~	~~2030~~	~~--~~	~~17.396~~	~~--~~	~~SDOM~~
S2 U+Sig, Q10	1810	520	17.402	.024	21,667
S5 U+Sig, Q5	2035	225	17.407	.005	45,000

- Resulting ratio will always be less than ratio of weakly dominated therapy and greater than weakly dominating therapy's original incremental ratio
  - E.g., 18,333 < 21,667 < 27,222

Resulting incremental ratios now ranked from lowest to highest (alternative ranking, highest to lowest),

Efficient Algorithm: Step 6

Maximum WTP	Therapy
<21,667	S1
21,667 to 45,000	S2
45,000+	S5

- ICERs from selection algorithm define a set of ranges of values of willingness to pay for which different therapies are preferred
- Identify acceptable therapy from among 3 candidate therapies by comparing W with ranges
- NMB algorithms do not provide these ranges directly
  - Require additional calculations of which calculation of ICERs possibly easiest

Defining Cost-Effectiveness Ranges

Maximum WTP	Therapy
<21,667	S1
21,667 to 45,000	S2
45,000+	S5

- NMB algorithm provides point estimates/CI for a given willingness to pay
- Don't directly define a set of ranges of values of willingness to pay for which different therapies are preferred
- Requires additional calculations
  - Calculation of ICERs possibly being easiest of these calculations

Full Cost-Effectiveness Table

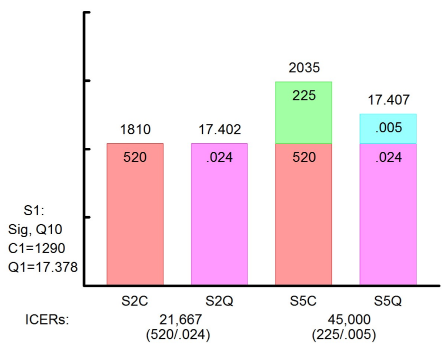
Treatment	Cost	ΔC	YOLS	Δ Y	ICER
S1 Sig Q10	1290	--	17.378	--	--
~~S4 Sig Q5~~	~~1535~~	~~--~~	~~17.387~~	~~--~~	~~WD~~
~~S3 C Q(10)~~	~~2030~~	~~--~~	~~17.396~~	~~--~~	~~SD~~
S2 U+Sig, Q10	1810	520	17.402	0.024	21,667
S5 U+Sig, Q5	2035	225	17.407	0.005	45,000

SD = strong dominance; WD = weak dominance

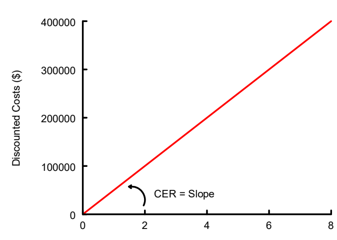
Reduced Cost-Effectiveness Table

Treatment	Cost	ΔC	YOLS	Δ Y	ICER
S1 Sig Q10	1290	--	17.378	--	--
S2 U+Sig, Q10	1810	520	17.402	0.024	21,667
S5 U+Sig, Q5	2035	225	17.407	0.005	45,000

Compared S2 to S1 and S5 to S2; Do We Also Need to Compare S5 to S1?

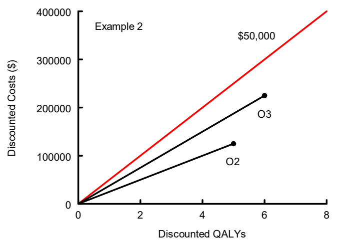


Introduction to Method 2: Frontier Analysis (Geometry of Choice)



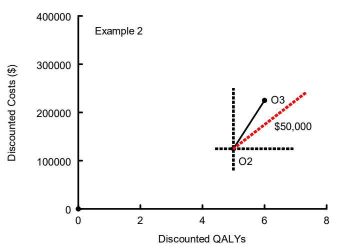
- Can also identify optimal strategy using cost-effectiveness plane
- Often focus on upper right quadrant, where new therapies increase both costs and outcomes

Choosing Among Frontier Options (1)



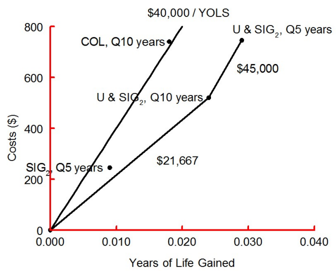
- Options 2 and 3 both have acceptable average cost-effectiveness ratios (e.g., below $50,000/YOLS)
  - Slopes of lines be origin and points on plane

Choosing Among Frontier Options (2)



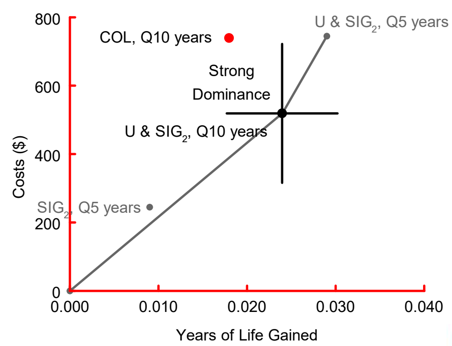
- To evaluate incremental ratio, shift origin to option with lowest acceptable average cost-effectiveness ratio, and reimpose $50,000 acceptability criterion

Colorectal Cancer Screening Example

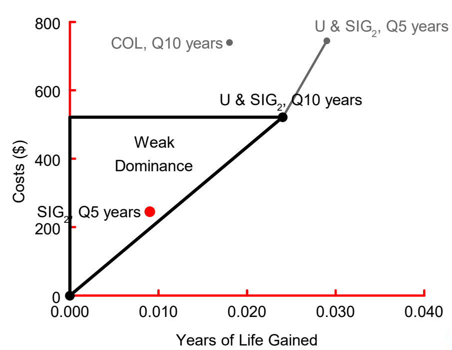


- Convex hull represents therapies that for a given level of effect have lowest cost (or for a given level of cost have highest effect)

Strong Dominance



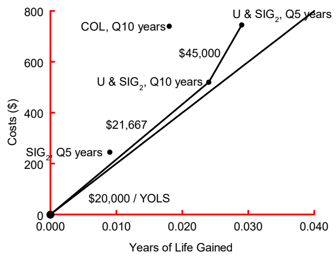
Weak Dominance



Sig_2,q5 and Frontier

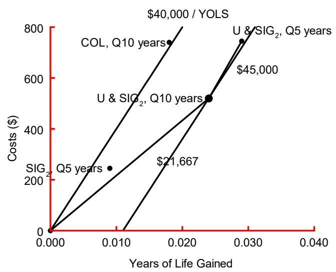
- Weakly dominated, but
  - Uncertainty (i.e., confidence region) might be such that we may not be able to exclude it from frontier
  - Weakly dominated therapies that lie close to frontier, "might be considered [a] reasonable alternative...if there were noneconomic reasons to prefer them, such as patient or physician acceptability, availability, or other factors." Mark D. JAMA. 287;202:2428-9.

Method 2. Choice Using a 20,000 Willingness to Pay

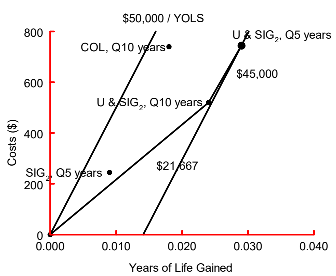


- Choose therapy with tangency between frontier and lowest line with slope defined by maximum willingness to pay for health outcome

Method 2. Choice Using a 40,000 Willingness to Pay



Method 2. Choice Using a 50,000 Willingness to Pay

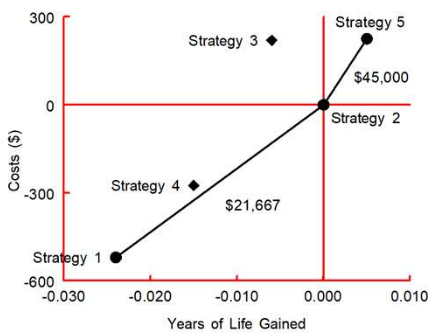


Method 2 Recommendations

Maximum WTP	Therapy
<21,667	S1
21,667 to 45,000	S2
45,000+	S5

- As with Method 1, ICERs from selection algorithm define (same) set of ranges of values of willingness to pay for which different therapies are preferred
- Identify acceptable therapy from among 3 candidate therapies by comparing W with ranges
- NMB algorithms do not directly provide these ranges

Reach Same Conclusions Whether or Not Lowest Ranked Strategy Used As Reference



Introduction to Methods 3 - 5: Net Benefits

- A composite measure (part cost-effectiveness, part cost benefit analysis), usually expressed in dollar terms, that is derived by rearranging cost-effectiveness decision rule:

$$W > \Delta C / \Delta Q$$

where W = willingness to pay (e.g., 50 or 100K)

Net Benefits (II)

- Two forms of net benefit expression exist depending on rearrangement of decision rule
  - Most commonly used net monetary benefits expressed on cost scale (NMB)

    $$(W * \Delta Q) - \Delta C$$

  - OR alternatively net health benefits (NHB) expressed on health outcome scale:

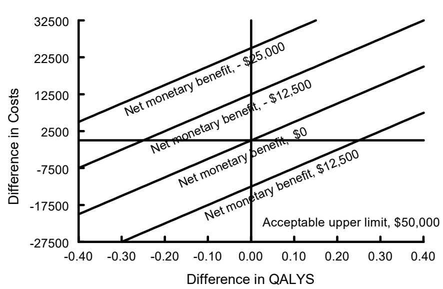
    $$\Delta Q - (\Delta C / W)$$

    - Potential disadvantage: NHB undefined when WTP equals 0
- Both expressions = formulas for a line

NMB Rationale

- Overcomes problems associated with parametric tests of ratio
  - Study result is a difference in means, not a ratio of means, and is always defined and continuous
- Substitutes “poor-person’s” willingness to pay measure (the acceptability criterion) for more theoretically correct individually-measured willingness to pay
  - Differs from cost-benefit analysis in that it does not aggregate individuals' willingnesses to pay for health
- All else equal, adopt programs with net monetary (health) benefits greater than 0
  - i.e., programs with incremental cost-effectiveness ratios less than WTP

NMB Rationale (2)



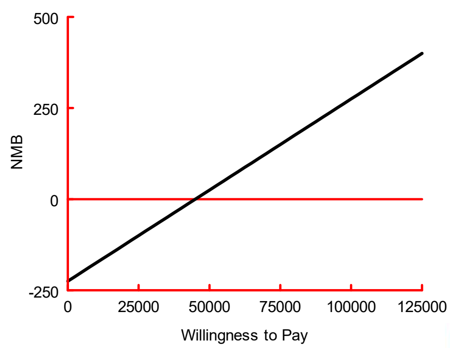
- As with OOS and ROC curve, on CE plane, NMB ($-\Delta C + W\Delta Q$) represented by a family of lines all with slope equal to W

Different Lines Have Different Values of Net Benefit

- For NMB, line's net benefits = -intercept = –ΔC (because at origin, W = 0, thus W ΔQ = 0)
- For line passing through origin, NMB = 0
  - Lines below and to right of net benefit=0 line have positive net benefits (i.e., acceptable cost-effectiveness ratios)
  - Lines above and to left have negative net benefits

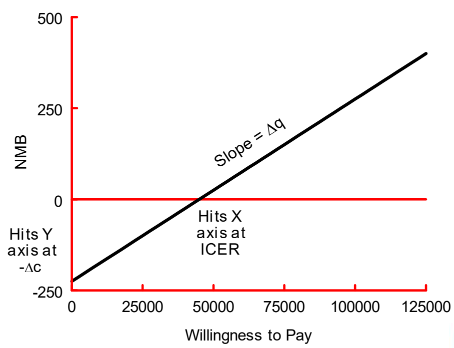
*** Method 2, above, is equivalent to selecting the therapy with largest valued NMB ***

NMB Graph, S5 V S2



- ΔC = 225; ΔQ = 0.005

NMB Graph, S5 V S2



- ΔC = 225; ΔQ = 0.005

Diagnostic Test: P* and Cost-Effectiveness/NMB

- Cost-benefit notation

$$p^* = \frac{\Delta O_{D-}}{\Delta O_{D-} + \Delta O_{D+}}$$

- Cost-effectiveness/NMB notation

$$p^* = \frac{W\ \Delta e_{D-} - \Delta c_{D-}}{W\left(\Delta e_{D-} + \Delta e_{D+}\right) - \left(\Delta c_{D-} + \Delta c_{D+}\right)}$$

Diagnostic Test: Do Nothing / Test Threshold

- Cost-benefit notation

$$p_{tt} = \frac{\left(1\text{-spec}\right)\ \Delta O_{D-} + T_c}{\left(1\text{-spec}\right)\ \Delta O_{D-} + \text{sens}\ \Delta O_{D+}}$$

- Cost-effectiveness/NMB notation

$$p_{tt} = \frac{\left(1\text{-spec}\right)\left(W\ \Delta e_{D-} - \Delta c_{D-}\right) + T_C}{\left(1\text{-spec}\right)\left(W\ \Delta e_{D-} - \Delta c_{D-}\right) + \text{sens}\left(W\ \Delta e_{D+} - \Delta c_{D+}\right)}$$

Method 3. Monetary Benefit

- Probably easiest of NMB methods but least used
- Step 1. Calculate each therapy's MB (also referred to as NB) by multiplying therapy's average (NOT incremental) effect times WTP and subtracting therapy's average cost
- For therapy i:

$$MB_i = W\bar{Q}_i - \bar{C}_i$$

- Select therapy with largest MB
- Yields therapy choice consistent with Method 1, BUT
  - Need additional calculations to obtain boundaries between ranges of W where each therapy is best
    - With calculations of ICERs possibly easiest

Example Method 3: Monetary Benefit (MB)

- Multiply W * Effect; subtract cost; compare resulting MB
  - Uses cost and effect, not ∆cost and ∆effect

	Cost	YOLS	MB, 20K	MB, 40K	MB, 50K
S1 Sig, Q10	1290	17.378	**346,270**	693,830*	867,610
S4 Sig, Q5	1535	17.387	346,205	693,945	867,815
S2 U+Sig, Q10	1810	17.402	346,230	**694,270**	868,290
S3 C,Q10	2030	17.396	345,890	693,810	867,770
S5 U+Sig,Q5	2035	17.407	346,105	694,245	**868,315**

* (40,000 * 17.378) = 695,120; subtracting 1290 = 693,830

MB Advantages

- Don't need to reorder therapies
- Don't need algorithm to select cost-effective therapy
  - i.e., Choose therapy with largest MB
- Allows calculation of magnitude of difference in MB between therapies
  - By simple subtraction of different therapies' MBs
  - Not available from ICER calculations

MB Disadvantages

- Need to recalculate MB for every policy relevant W
- Even though we can draw frontier (see Method 4), willingness to pay cut-offs where each therapy is preferred over others not directly reported by any single MB calculation
  - Calculation of ICERs may be easiest method for identifying ranges
- Can't always identify weakly dominated therapies
  - Identification useful because there is no value of W for which they represent best value (i.e., aren't in the choice set)

Method 4, Average Net Monetary Benefit (ANMB)

- Akin to average cost-effectiveness ratio (ACER)
  - All calculations compared to 1 comparator
- Because there are no ratios, doesn't yield mistaken recommendations that use of ACER does
- In literature, ANMB typically referred to as NMB
- NMB/ANMB most commonly reported measure of NMB in literature

Steps in Calculating NMB/ANMB

- Subtract one therapy's costs from all other therapies (including itself)
- Subtract same therapy's effects from all other therapies (including itself)
- Multiply the W times difference in effect and subtract out difference in cost
- Select therapy with largest NMB/ANMB

Example: Method 4, NMB/ANMB

	ΔCost*	ΔYOLS*	ANMB, 20K	ANMB, 40K	ANMB, 50K
S1 Sig, Q10	0	0	**0**	0	0
S4 Sig, Q5	245	0.009	-65	115	205
S2 U+Sig, Q10	520	0.024	-40	**440**	680
S3 C,Q10	740	0.018	-380	-20	160
S5 U+Sig,Q5	745	0.029	-165	415	**705**

Δcost = $C_i - C_1$; ΔYOLS = $YOLS_i - YOLS_1$

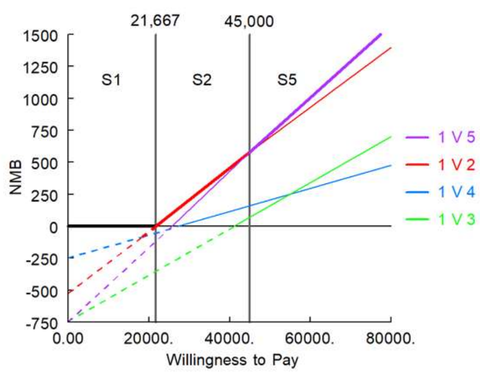
- For values of W of 20k, 40k, and 50k, reach same conclusions as methods 1 - 3

Subtracting S1's MB from MB Also Yields ANMB

	Cost	YOLS	MB, 20K	S1 MB, 20K	ANMB, 20K
S1 Sig, Q10	1290	17.378	**346,270**	**346,270**	**0**
S4 Sig, Q5	1535	17.387	346,205	346,270	-65
S2 U+Sig, Q10	1810	17.402	346,230	346,270	-40
S3 C,Q10	2030	17.396	345,890	346,270	-380
S5 U+Sig,Q5	2035	17.407	346,105	346,270	-165

- Magnitude of benefit of choice: S1's net benefit at least 40 greater than any other therapy

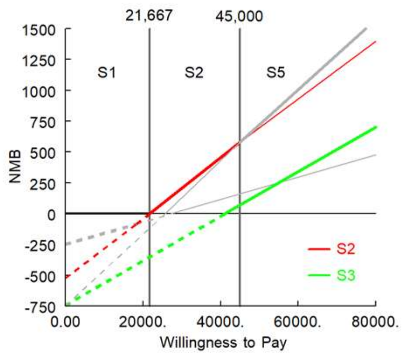
(A)NMB Frontier / Convex Hull



Frontier Selection Algorithm

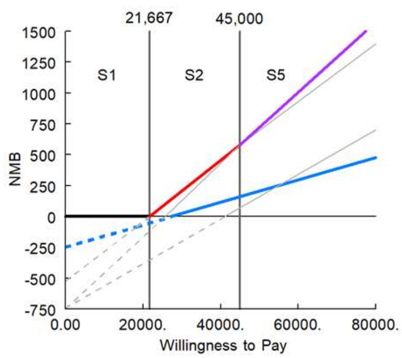
- For a given W, select therapy with highest nonnegative point on NMB lines
  - E.g., select strategy 5 if W = 50,000
- For a given W, if points on all NMB lines are negative, reference therapy is preferred
  - Below 21,667 black line on X axis is highest, so therapy 1 preferred
    - E.g., select strategy 1 if W = 15,000

(A)NMB and Strong Dominance



- One NMB curve (S2, red) is every-where above strongly dominated therapy's NMB curve (S3, green)

(A)NMB and Weak Dominance



- No one NMB curve is everywhere above weakly dominated therapy's NMB curve (S4, blue)
- But there's no value of W for which weakly dominated therapy is preferred

(A)NMB Advantages

- Don't need to reorder therapies
- Don't need algorithm to select cost-effective therapy
  - i.e., Choose therapy with largest (A)NMB
- Provides estimate of magnitude of difference in (A)NMB between therapies
  - Magnitude unavailable from ICER calculations

ICERs, Like SSLRs, Throw Away Information

- An infinite number of combinations of estimates of ΔC and ΔQ all have same ICER (e.g., 30,000)
- If ICER = W, they all have the same NMB
- Example:
  - Assume W = 30.000, therapy A's ΔC = 3000 and ΔQ = 0.1, and therapy B's ΔC = 6000 and ΔQ = 0.2
  - Both have same ICER (30,000), and same NMBs.
    - Therapy A: 30,000*0.1 – 3000 = 0
    - Therapy B: 30,000*0.2 – 6000 = 0

ICERs, Like SSLRs, Throw Away Information (2)

- If ICER ≠ W, each ΔC/ΔQ pair that has an ICER of 30,000 will have a different NMB
- Example:
  - Assume W = 50.000, therapy A's ΔC = 3000 and ΔQ = 0.1, and therapy B's ΔC = 6000 and ΔQ = 0.2
  - Both have same ICER (30,000), but different NMBs.
    - If W = 50,000
      - Therapy A: 50,000*0.1 – 3000 = 1,000
      - Therapy B: 50,000*0.2 – 6000 = 4,000
      - Difference in net monetary benefit = 3,000

(A)NMB Disadvantages

- Need to recalculate (A)NMB for every policy relevant W
- Even though we can draw frontier, cut-offs for ranges of willingness to pay where each therapy is preferred over others not directly reported by any single (A)NMB calculation
  - Calculation of ICERs may be easiest method for identifying range cut-offs
- Can't always identify weakly dominated therapies
  - Identification useful because there is no value of W for which they represent best value (i.e., aren't in the choice set)

Method 5. INMB Selection

- Can follow a modified version of method 1 to calculate incremental NMB (INMB)
- Modifications include:
  - In step 3, calculate INMB rather than cost-effectiveness ratios
  - Proceed to selection algorithm if:
    - All INMB are positive, OR
    - All INMB are negative, OR
    - First N_i therapies have positive INMB and remaining N_j therapies have negative INMB
  - Otherwise, continue to step 4

See Appendix for Explicit Steps

Method 3-5 Recommendations

Maximum WTP	Therapy
10,000	S1
20,000	S1
40,000	S2
50,000	S5

Exercise: Selecting a Therapy

- Suppose you evaluated 5 therapies and observed the following costs and effects
- Using method 1, which strategy would you recommend if WTP = 30,000, 50,000, 75,000 and 150,000?

Strategy	Total Cost	QALYs
1	678	35.6656
2	635	35.6650
3	655	35.6655
4	644	35.6653
5	683	35.6657

Step 1

- Step 1. ???

Strategy	Total Cost	QALYs
1	678	35.6656
2	635	35.6650
3	655	35.6655
4	644	35.6653
5	683	35.6657

Rank Order

- Step 1. Rank order therapies by increasing cost or effect

Strategy	Total Cost	QALYs
2	635	35.6650
4	644	35.6653
3	655	35.6655
1	678	35.6656
5	683	35.6657

Step 2

- Step 2. ???

Strategy	Total Cost	QALYs
2	635	35.6650
4	644	35.6653
3	655	35.6655
1	678	35.6656
5	683	35.6657

Dominated Therapies

- Step 2. Eliminate any strongly dominated therapies

Strategy	Total Cost	QALYs
2	635	35.6650
4	644	35.6653
3	655	35.6655
1	678	35.6656
5	683	35.6657

- There are no strongly dominated therapies

Step 3

- Step 3. ???

Strategy	Total Cost	QALYs
2	635	35.6650
4	644	35.6653
3	655	35.6655
1	678	35.6656
5	683	35.6657

Calculate ICERS

- Step 3. Calculate incremental cost-effectiveness ratios

Strategy	Total Cost	QALYs	ICER
2	635	35.6650	--
4	644	35.6653	30,000
3	655	35.6655	55,000
1	678	35.6656	230,000
5	683	35.6657	50,000

Step 4

- Step 4. ???

Strategy	Total Cost	QALYs	ICER
2	635	35.6650	--
4	644	35.6653	30,000
3	655	35.6655	55,000
1	678	35.6656	230,000
5	683	35.6657	50,000

Weakly Dominated Therapies

- Step 4. Eliminate any weakly dominated therapies

Strategy	Total Cost	QALYs	ICER
2	635	35.6650	--
4	644	35.6653	30,000
3	655	35.6655	55,000
~~1~~	~~678~~	~~35.6656~~	~~230,000~~
5	683	35.6657	50,000

- Eliminate strategy 1 with an ICER of 230k because strategy 5 is more effective and has a lower ICER

Step 5

- Step 5. ???

Strategy	Total Cost	QALYs	ICER
2	635	35.6650	--
4	644	35.6653	30,000
3	655	35.6655	55,000
~~1~~	~~678~~	~~35.6656~~	~~230,000~~
5	683	35.6657	50,000

Recalculate ICERS

- Step 5. Recalculate ICERS

Strategy	Total Cost	QALYs	ICER
2	635	35.6650	--
4	644	35.6653	30,000
3	655	35.6655	55,000
~~1~~	~~678~~	~~35.6656~~	~~230,000~~
5	683	35.6657	140,000

Step 6

- Step 6. ???

Strategy	Total Cost	QALYs	ICER
2	635	35.6650	--
4	644	35.6653	30,000
3	655	35.6655	55,000
~~1~~	~~678~~	~~35.6656~~	~~230,000~~
5	683	35.6657	140,000

Therapy Selection

- Step 6. Select option with largest ICER that is lower than maximum WTP

Strategy	Total Cost	QALYs	ICER
2	635	35.6650	--
4	644	35.6653	30,000
3	655	35.6655	55,000
~~1~~	~~678~~	~~35.6656~~	~~230,000~~
5	683	35.6657	140,000

- #2 if WTP<30,000; #4 if WTP=50,000; #3 if WTP=75,000; #5 if WTP=150,000

Recommendation?

Maximum WTP	Therapy
<30,000	S2
30,000 to <55,000	S4
55,000 to <140,000	S3
140,000+	S5

Simultaneous Comparison

- Description of selection algorithm may suggest a path through different options, with adoption of lower cost/ effect pairs before adoption of higher cost/effect pairs
- Not true
  - All 4 algorithms are simply step-by-step procedures that simultaneously compare all options as done by:
    - Identifying tangency between NMB lines and " health production" frontier, or
    - Comparing MBs

What Is Maximum Acceptable Ratio?

- Traditionally, cost-effectiveness ratios less than $40,000 to $50,000 per QALY saved (or NMB cost lines defined using these ratios) have been considered acceptable
- Little analytic attention has been given to identifying an appropriate acceptability criterion
- Continuing debate about whether threshold in U.S. has increased (e.g., at a minimum to $100,000 per QALY)
- Not clear that thresholds derived for point estimate of cost-effectiveness ratio should be used to determine threshold for upper limit of confidence interval for CE ratio

Additional Issues

Are All Ratios of Equal Value?

- Mortal, relatively incurable diseases vs. diseases that principally affect quality of life
  - Are acceptable ratios for former higher than for latter?
    - NICE, appraisal committees can consider 'giving greater weight to QALYs achieved in later stages of terminal diseases'" (Nature, 09/2009)
  - As more treatments become available and disease appears less incurable, does acceptable incremental ratio for new therapies begin to approach "standard" acceptable ratio?
- Small budgetary impact

Are All Ratios of Equal Value? (II)

- Identifiable individuals
- Do individuals have a set of "social preferences" that differ from their "individual preferences"
  - $1,000,000 to cure 100 blind invalids
  - $1,000,000 to cure 100 blind healthy individuals
- Compensation for risks imposed by society

Acceptability and Lower Left Quadrant?

- Economists usually treat ratios in upper right and lower left quadrants symmetrically
  - If won't spend more than $50,000 per QALY saved for a more costly and more effective new therapy in upper right quadrant, then won't spend more than $50,000 per death averted for more costly, more effective alternative therapy in lower left quadrant
  - i.e., adopt a less costly and less effective new therapy if its ratios of savings per QALY lost were greater than $50,000 compared with alternative

Acceptability and Lower Left Quadrant? (II)

- Some have suggested that preferences for gains and losses of health are asymmetric
  - Common assumption: people need to be paid more to give up health than they are willing to pay to gain health (possibly an income effect)
- Such asymmetries can be incorporated into decision making for individual therapies, but complicates NMB calculation, construction of acceptability curves, and league-table decision making

Negative Cost-Effectiveness Ratios

- If point estimates for differences in costs and effects are of opposite signs (either increased costs and decreased effectiveness or decreased costs and increased effectiveness), resulting cost-effectiveness ratio will be negative
- Magnitude of negative point estimates for ratios in same quadrant does not provide information about relative preferability of these different therapies

Negative Ratios (II)

- When comparing two options and resulting cost-effectiveness ratio (or CI of ratio) is negative, do not report negative value (because magnitude conveys little if any information)
  - Instead simply report that ratio represents that therapy is dominant/dominated
- If lower and upper limits of confidence interval (CI) for CE ratio are both negative, relative magnitude of the two limits provides information about whether or not CI includes Y axis of CE plane (return to this idea when we discuss sampling uncertainty for CERs)

Take Home Messages (I)

- Decision making using cost-effectiveness ratios requires attention to average and incremental cost-effectiveness ratios
- To make decisions using these ratios, compare them to:
  - A predefined standard (i.e., a threshold) against which they can be compared (e.g., $50,000 per year of life saved might be considered largest acceptable ratio), or
  - Other accepted and rejected interventions (e.g., against league tables), or
  - (Rarely or never:) Utility curves trading off health and cost

Appendix:
Method 5. INMB Selection

INMB Selection

- Can follow a modified version of method 1 to calculate incremental NMB (INMB)
- Modifications include:
  - In step 3, calculate INMB rather than cost-effectiveness ratios
  - Proceed to selection algorithm if:
    - All INMB are positive, OR
    - All INMB are negative, OR
    - First N_i therapies have positive INMB and remaining N_j therapies have negative INMB
  - Otherwise, continue to step 4

Method 5: Step 1

- Rank order therapies in ascending order of either outcomes or cost

Treatment	Cost	YOLS
S1 Sig Q10	1290	17.378
S4 Sig Q5	1535	17.387
S3 C Q(10)	2030	17.396
S2 U+Sig, Q10	1810	17.402
S5 U+Sig, Q5	2035	17.407

- 5 strategies not in ascending order of either cost or effect
- Revised so correctly ordered by effect
- Final recommendation unaffected by ranking variable

Method 5: Step 2

- Eliminate therapies that are strongly dominated

Treatment	Cost	YOLS
S1 Sig Q10	1290	17.378
S4 Sig Q5	1535	17.387
~~S3 C Q(10)~~	**~~2030~~**	**~~17.396~~**
S2 U+Sig, Q10	**1810**	**17.402**
S5 U+Sig, Q5	2035	17.407

- S2 strongly dominates S3
- Eliminate S3 from consideration for adoption

Method 5: Step 3

- Compute INMB for each remaining adjacent pair of outcomes
  - i.e., INMB for options S1 vs S4; S4 vs S2; and S2 vs s5

Treatment	Cost	Δ	YOLS	Δ	$INMB_{40k}$
S1 Sig Q10	1290	--	17.378	--	--
S4 Sig Q5	1535	245	17.387	.009	115
~~S3 C, Q10~~	~~2030~~	~~495~~	~~17.396~~	~~.009~~	~~SDOM~~
S2 U+Sig, Q10	1810	275	17.402	.015	325
S5 U+Sig, Q5	2035	225	17.407	.005	-25

Method 5: Step 4

- Eliminate any obviously weakly dominated therapies for this or any other value of W
  - Obvious weak dominance: Lower ranked therapy with negative INMB followed by higher ranked therapy with positive INMB
- No obvious weak dominance for 40,000 (is for 20,000)

Treatment	Cost	Δ	YOLS	Δ	$INMB_{40k}$
S1 Sig Q10	1290	--	17.378	--	--
S4 Sig Q5	1535	245	17.387	.009	115
~~S3 C, Q10~~	~~2030~~	~~495~~	~~17.396~~	~~.009~~	~~SDOM~~
S2 U+Sig, Q10	1810	275	17.402	.015	325
S5 U+Sig, Q5	2035	225	17.407	.005	-25

Nonobvious Weak Dominance

- May not calculate INMB for value of W for which weak dominance is obvious
  - In colorectal screening example evidence of weak dominance of S4 exists for values of W between approximately 19,000 and 27,000
    - E.g., for W=20,000 NMB for lower ranked S4, and higher rantked S2, and S5 equal –65, 25, and -125
- Fact that there was no obvious weak dominance for W=40,000 does not mean that S4 is not weakly dominated
  - Therapy that is weakly dominated for 1 W, is a weakly dominated therapy and should be removed from all analyses

Nonobvious Weak Dominance (2)

- Good news: Therapies which are weakly dominated but which have no obvious evidence of weak dominance will never be identified as best therapy even if not removed from analysis
- But will affect magnitudes of calculated INMB
  - INMB for weakly dominated therapy should be added to INMB for next highest ranked therapy
- Alternate definition of weak dominance for INMB: There is no value of WTP for which therapy has greatest effectiveness among therapies with 0 or positive INMB

INMB and Weak Dominance

- As with CE algorithm:
  - Step 4: Drop weakly dominated therapies
    - In current example eliminate S4 and recalculate INMB for S2
  - Repeat until there are no therapies with negative INMB interspersed among positives
  - Proceed to selection algorithm

Result of Step 4. for 20K

	Δcost	ΔYOLS	INMB, $20K
S1 Sig, Q10	0	0	**0**
S4 Sig, Q5	WD	WD	WD
S2 U+Sig, Q10	520	.024	-40
S3 C,Q10	SD	SD	SD
S5 U+Sig,Q5	225	0.005	-125

- After elimination of S4, all INMB are 0 or negative
- Can proceed to selection algorithm
  - Because all strategies are less than or equal to 0, adopt S1

INMB Recommendations

	INMB, 10k	INMB, 20K	INMB, 40K	INMB, 50K
S1 Sig, Q10	**0**	**0**	0	0
S4 Sig, Q5	-155	WD	115	205
S2 U+Sig, Q10	-125	-40	**325**	475
S3 C,Q10	SD	SD	SD	SD
S5 U+Sig,Q5	-175	-125	-25	**25**

- May or may not assess value of W that allows identification of weak dominance

INMB Selection Algorithm

- If all INMB are 0 or positive, select therapy with largest effectiveness
  - e.g., when W=50,000, select S5
- If all INMB are less than or equal to 0, select therapy with greatest effectiveness among therapies with 0 INMB
  - e.g., when W=10,000, select S1
- If first N_i therapies have 0 or positive INMB and remaining N_j therapies have negative INMB, select therapy with greatest effectiveness among therapies with 0 or positive INMB
  - e.g., when W=40,000, select S2

Method 3-5 Recommendations

Maximum WTP	Therapy
10,000	S1
20,000	S1
40,000	S2
50,000	S5

Unlike ICERs, Monotonicity Not Required for INMB