The balance of harms and benefits of screening for prostate cancer:

the apples and oranges problem solved

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The Patient-Centered Outcomes Research Institute
April 2,2016

Declarations

Harold Sox is an employee of PCORI but is not representing PCORI policy at this meeting

He has no conflicts of interest to declare.

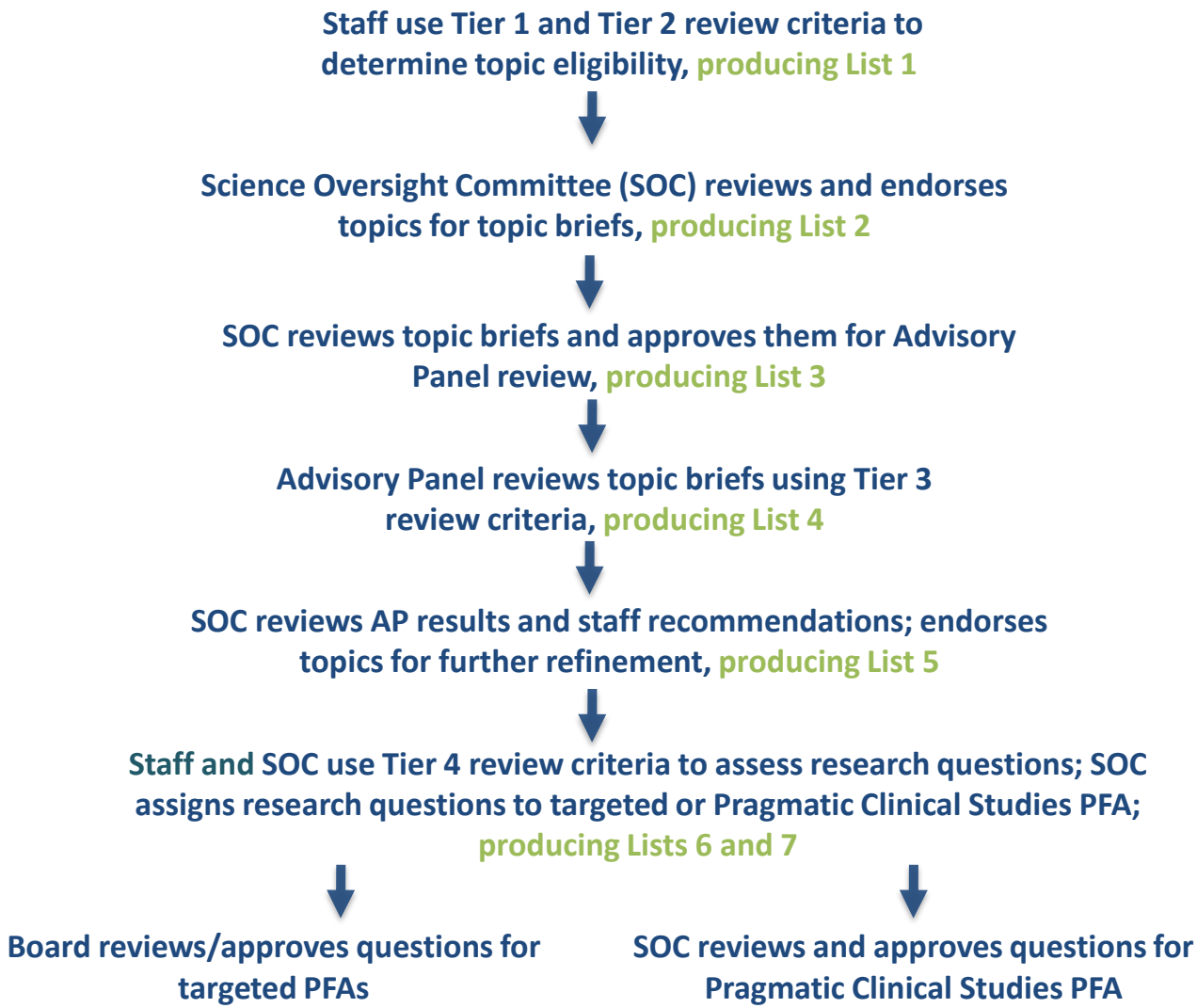
Funding Streams at PCORI

- **"Broad" Funding Announcement:**
  - Topics chosen by the investigator
- **Pragmatic Clinical Studies Funding Announcement:**
  - Topics chosen by PCORI and its stakeholders
- **Targeted Funding Announcement:**
  - Topics chosen by PCORI and its stakeholders

Funding Streams at PCORI

- **"Broad" Funding Announcement**
  - Investigator-initiated; up to $2M and 3 years
  - Based on the 5 broad national priorities
- **Pragmatic Clinical Studies Funding Announcement**:
  - Lists ~25 PCORI High Priority Topics. Choose one or propose a topic; up to $10M over 3-5 years.
  - 3 cycles per year; observational or randomized;
- **Targeted Funding Announcement:**
  - Lists one topic chosen by PCORI; may have multiple research questions; funding varies
    - (HCV: up to $50M; four research questions).

Pathway to a Funding Announcement



Priority Setting Criteria

- Patient-centeredness
- Burden of illness
- Evidence gaps
- What do guidelines say?
- Ongoing studies
- Likelihood of implementation in practice
- Likely durability of research results
- Proposed research questions

AUA-nominated topics in PCORI topic development pathway

- Management of kidney stones:
  - diet and drugs
- BPH:
  - Comparative effectiveness of lifestyle changes, diet modification, behavioral interventions and phytotherapy on the clinical symptoms of BPH
- Castration-resistant prostate cancer

Prostate Cancer screening

Prostate cancer screening GLs in the U.S.

Source	Date	Recommendation
US Preventive Services Task Force	2012	Do not do it
U of Michigan	2011	Discuss at age 50
American Cancer Society	2010	Discuss at age 50
American Urological Association	2009	Discuss at ages 55-69
American College of Preventive Medicine	2008	Discuss; don't screen if patient defers to physician
American College of Physicians	1997	Discuss at age 50
American Academy of Family Physicians	2008	Discuss
National Comprehensive Cancer Network	?	PSA at age 40
American Society for Clinical Oncology	2012	Discuss

All agree that men with life expectancy <10 years shouldn't be screened

Current AUA guidelines

- Age <40-54: do not screen average risk men. (C)
- Age 40-54: do not routinely screen average risk men (C)
  - shared decision making for those at higher risk.
- Age 55-69: shared decision making (B)
- Age 70+: do not screen routinely (C)
- Addenda:
  - Do not screen men with <10-15 year life expectancy
  - Screening every other year (C)

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National Comprehensive Cancer Network	?	PSA at age 40
American Society for Clinical Oncology	2012	Discuss

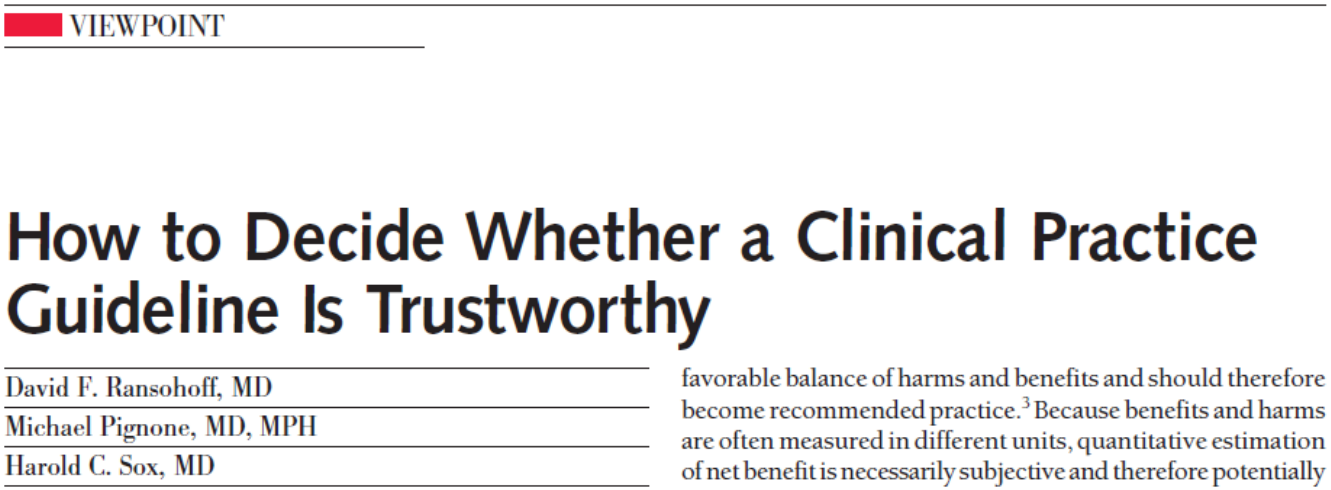
All agree that men with life expectancy <10 years shouldn't be screened

Which of these guidelines shall I choose?

- Which one can I trust to rely on the scientific evidence?
- Which one is the most objective in assessing the balance of harms and benefits?

My interests in guidelines

- Creating a market for high quality guidelines
  - Many guidelines for a topic; varying quality
  - Need a metric of quality to help users choose the most trustworthy guideline.



VIEWPOINT

How to Decide Whether a Clinical Practice Guideline Is Trustworthy

David F. Ransohoff, MD
Michael Pignone, MD, MPH
Harold C. Sox, MD

favorable balance of harms and benefits and should therefore become recommended practice.[3] Because benefits and harms are often measured in different units, quantitative estimation of net benefit is necessarily subjective and therefore potentially

JAMA. 2013;309:139-40.

About Guidelines

- They have become powerful because they influence many aspects of practice.
  - Insurance coverage
  - Practice measures
  - Quality of care improvement goals
- The recommendations are susceptible to bias
  - Conflict of interest
  - Selective use of evidence
  - Subjectivity in assessing the balance of harms and benefits is largely unavoidable.

Guideline recommendations of the National Academy of Medicine

- Manage panel members' and sponsors' conflicts of interests
- Do a systematic review of the evidence
- Describe the logic that connects the evidence to the recommendation
- Describe the magnitude of the benefits and harms and discuss the balance between them → recommendations.

The process for making a guideline

Choose topic

↓

Form guidelines panel

↓

Define key questions

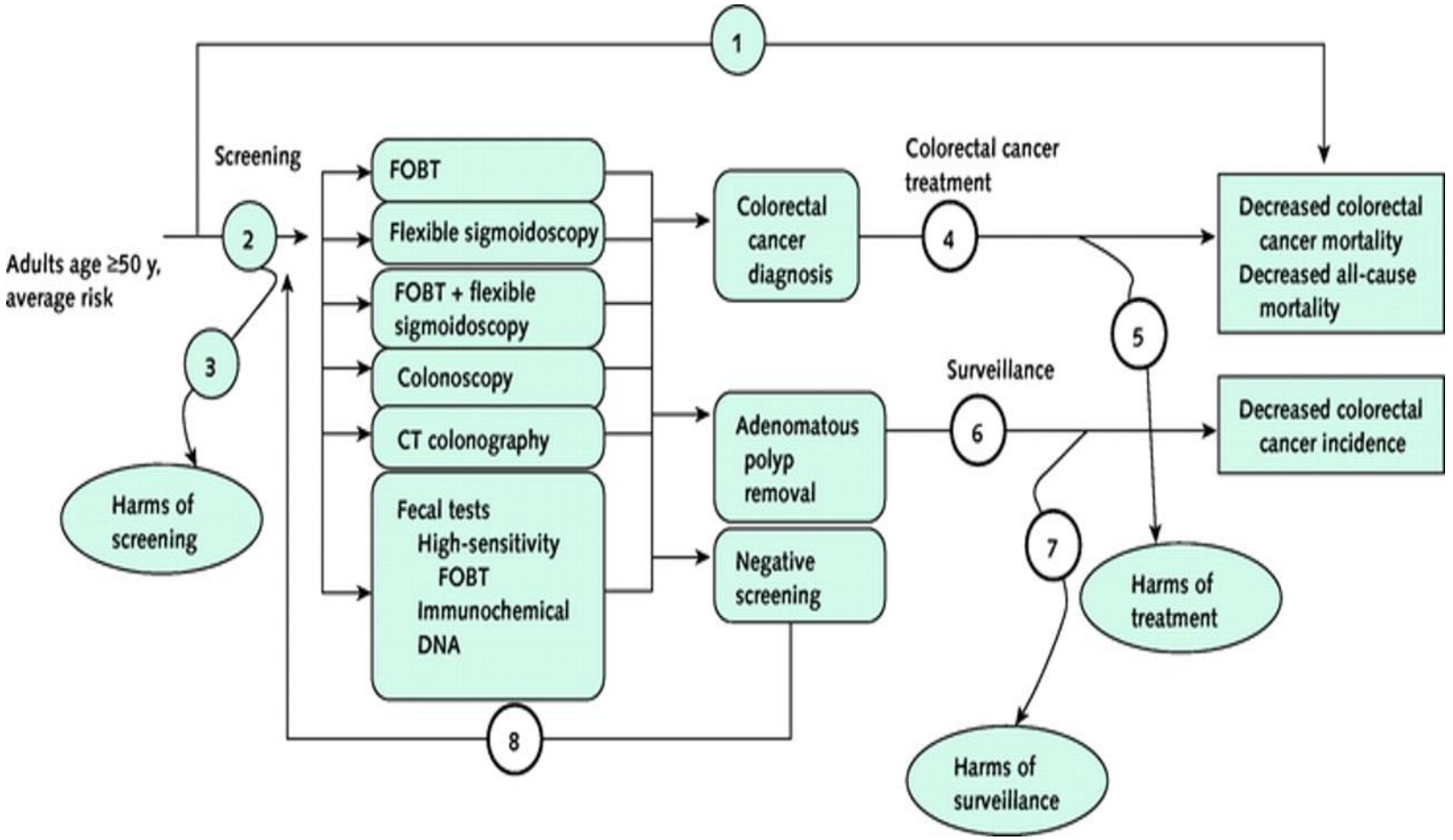
↓

Do a systematic review of the evidence for each key question → Harms, Benefits

↓

Panel makes recommendations

Analytic framework and key questions (KQs)



Whitlock, E. P. et. al. Ann Intern Med 2008;149:638-658

Annals of Internal Medicine

The process for making a guideline

Choose topic

↓

Form guidelines panel

↓

Define key questions

↓

Do a systematic review of the evidence for each key question → **Harms Benefits**

↓

Panel makes recommendations

The US Preventive Services Task Force on prostate cancer screening

Evidence and recommendations

2011-2012

2011-12 US Preventive Services Task Force Recommendation for Prostate Cancer screening.

- Benefits:
  - Treatment: surgery > watchful waiting in <65 year olds
  - Screening: 2 controlled trials of PSA screening
    - US trial: no effect on prostate cancer mortality
    - European trial: 22% reduction in PC mortality
- Harms
  - Urinary incontinence: ↑18-28 percentage points by surgery
  - Erectile Dysfunction: ↑ 26-36 percentage points by surgery

Assessment of Harms and Benefits of Screening for Prostate Cancer

- In its recommendation statement, the USPSTF said: “ Assessing the balance of benefits and harms requires weighing a moderate to high probability of persistent harm from treatment against the low probability of preventing a death from prostate cancer in the long-term”
- “The USPSTF concludes that there is moderate certainty that the benefits of PSA-based screening for prostate cancer do not outweigh the harms.”

2011-12 US Preventive Services Task Force Recommendation for Prostate Cancer screening.

- Conclusion:
  - "reduction in PC mortality is at most very small; harms of screening and treatment are common and often persistent. Moderate certainty that benefits of screening do not outweigh harms."
- Recommendation:
  - Recommend against screening

Options for weighing the balance of harms and benefits

- Look at a table of outcomes, their frequency with and without screening, and a description of the health states → a subjective judgment.
  - The preferred approach for an individual patient
  - Such tables appear in many decision aids
  - The patient's choice is utility-maximizing.

- Given the variation in a population, making a subjective estimate of the balance of harms and benefits for a population is hard to imagine as an instrument for policy-making. But it happens.

Screening outcomes: 60 year old man*

Outcome	Effect (vs. no screening)	Units
Prostate cancer cured, if present	Longer life	Years gained; QOL
Anxiety relieved	Happier	Better QOL for rest of life
Prostate biopsy	Pain for a few days; anxiety	Reduced QOL for few days
Urinary incontinence	Pads or diaper	% needing pad/diapers
Erectile dysfunction	Less sex	% w/ worse erectile function
Bowel dysfunction	Unpredictable urge to…..	% w/ poor bowel function
Over-diagnosis	In those with adverse effects of Rx, chagrin at knowing Rx might not have been needed	Reduction in QOL, adverse effects of treatment

*Life expectancy 21.0 years

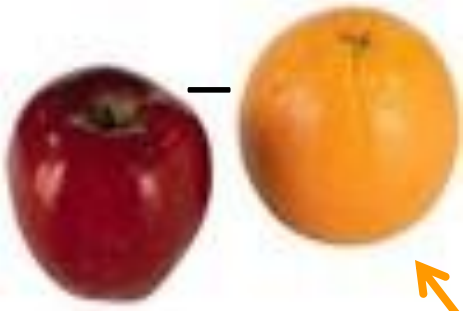
Benefits:

Treatment: surgery > watchful waiting in <65 year olds

Screening: 2 controlled trials of PSA screening

US trial: no effect on prostate cancer mortality

European trial: 22% reduction in PC mortality



= ???

Harms

Urinary incontinence: ↑18-28 percentage points surgery

Impotence: ↑ 26-36 percentage points by surgery

Options for using outcomes data to decide whether to recommend screening

- Look at a table of outcomes, their frequency with and without screening, and a description of the health states → a subjective judgment.
- Create a model that uses a common metric to quantitate the gains and losses from screening.
  - Heijnsdijk et al: used quality-adjusted life years (QALYs) as a common metric for benefits and harms in their microsimulation model.
    - QALY: time in a health state x quality of life in it

Heijnsdijk et al. New Engl J Med. 2012;367;659-668

Original Article

Quality-of-Life Effects of Prostate-Specific Antigen Screening

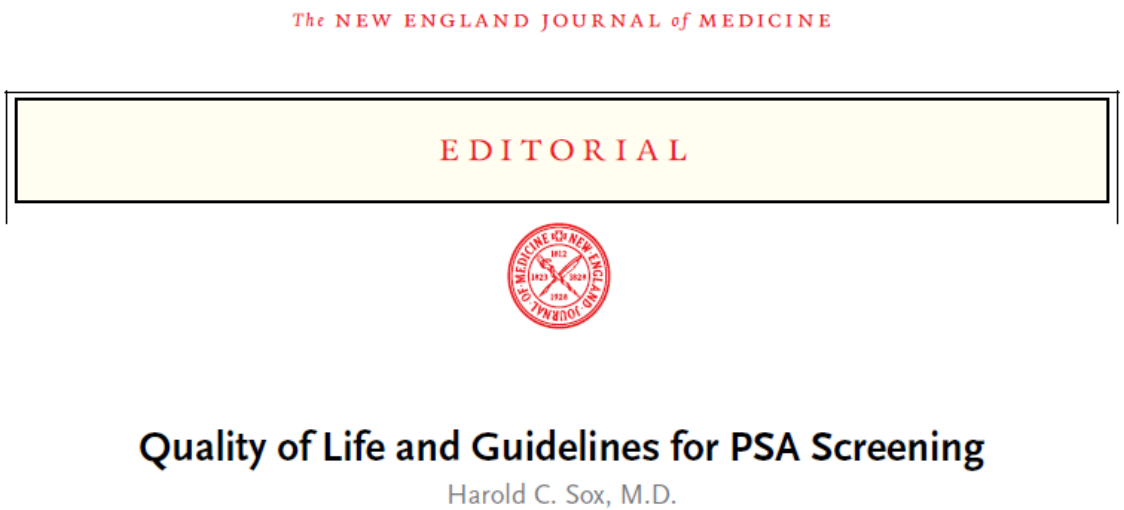
Eveline A.M. Heijnsdijk, Ph.D., Elisabeth M. Wever, M.Sc., Anssi Auvinen, M.D., Jonas Hugosson, M.D., Stefano Ciatto, M.D., Vera Nelen, M.D., Maciej Kwiatkowski, M.D., Arnauld Villers, M.D., Alvaro Páez, M.D., Sue M. Moss, Ph.D., Marco Zappa, M.D., Teuvo L.J. Tammela, M.D., Tuukka Mäkinen, M.D., Sigrid Carlsson, M.D., Ida J. Korfage, Ph.D., Marie-Louise Essink-Bot, Ph.D., Suzie J. Otto, Ph.D., Gerrit Draisma, Ph.D., Chris H. Bangma, M.D., Monique J. Roobol, Ph.D., Fritz H. Schröder, M.D., and Harry J. de Koning, M.D.

N Engl J Med
Volume 367(7):595-605
August 16, 2012

The NEW ENGLAND JOURNAL of MEDICINE

My interests in guidelines

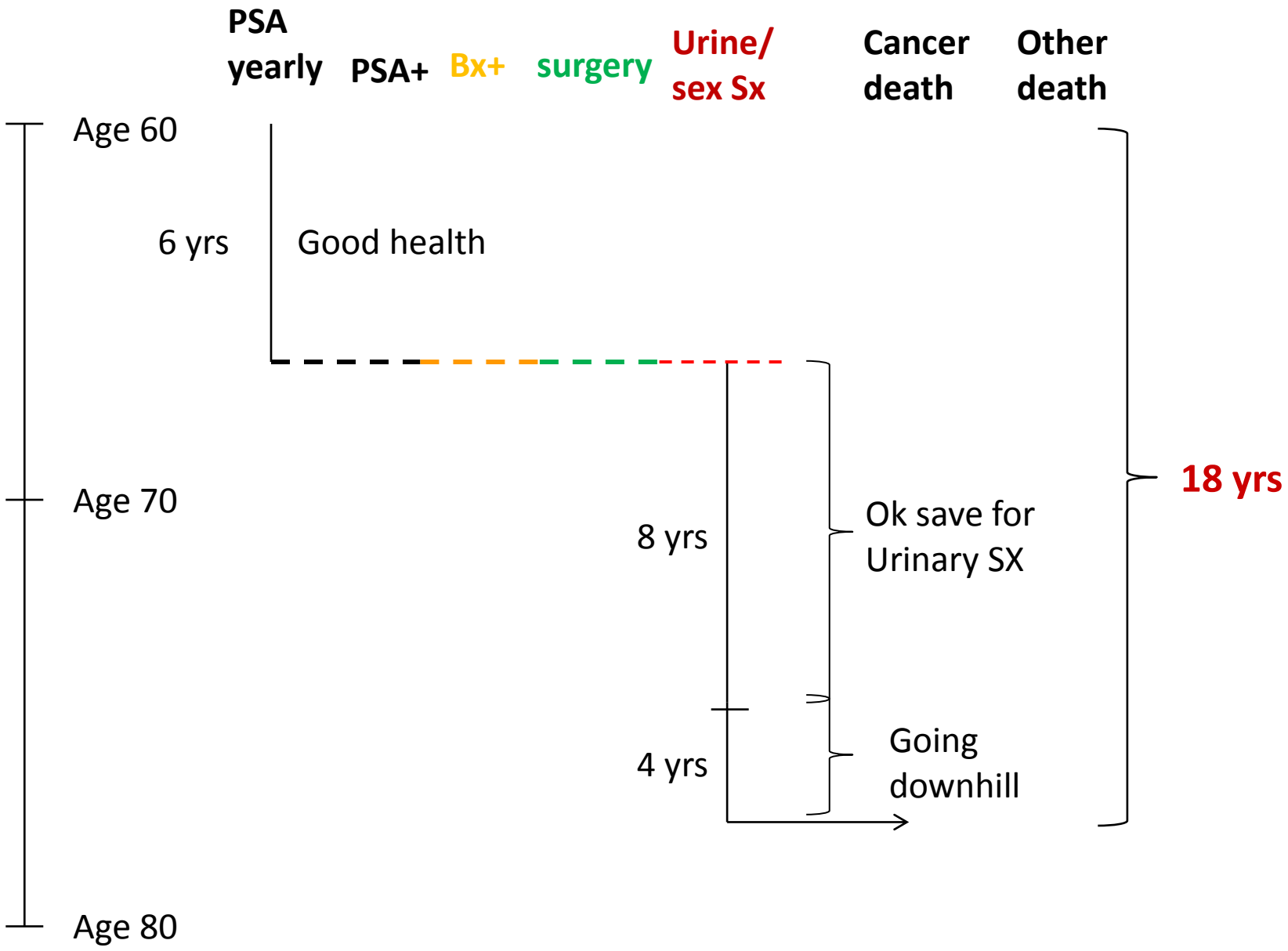
- Finding objective methods to estimate net benefits (i.e. benefits minus harms)
  - Reduce subjectivity/bias in assessing balance of H and B
  - Take account of patient's preferences for the outcome states that they may experience



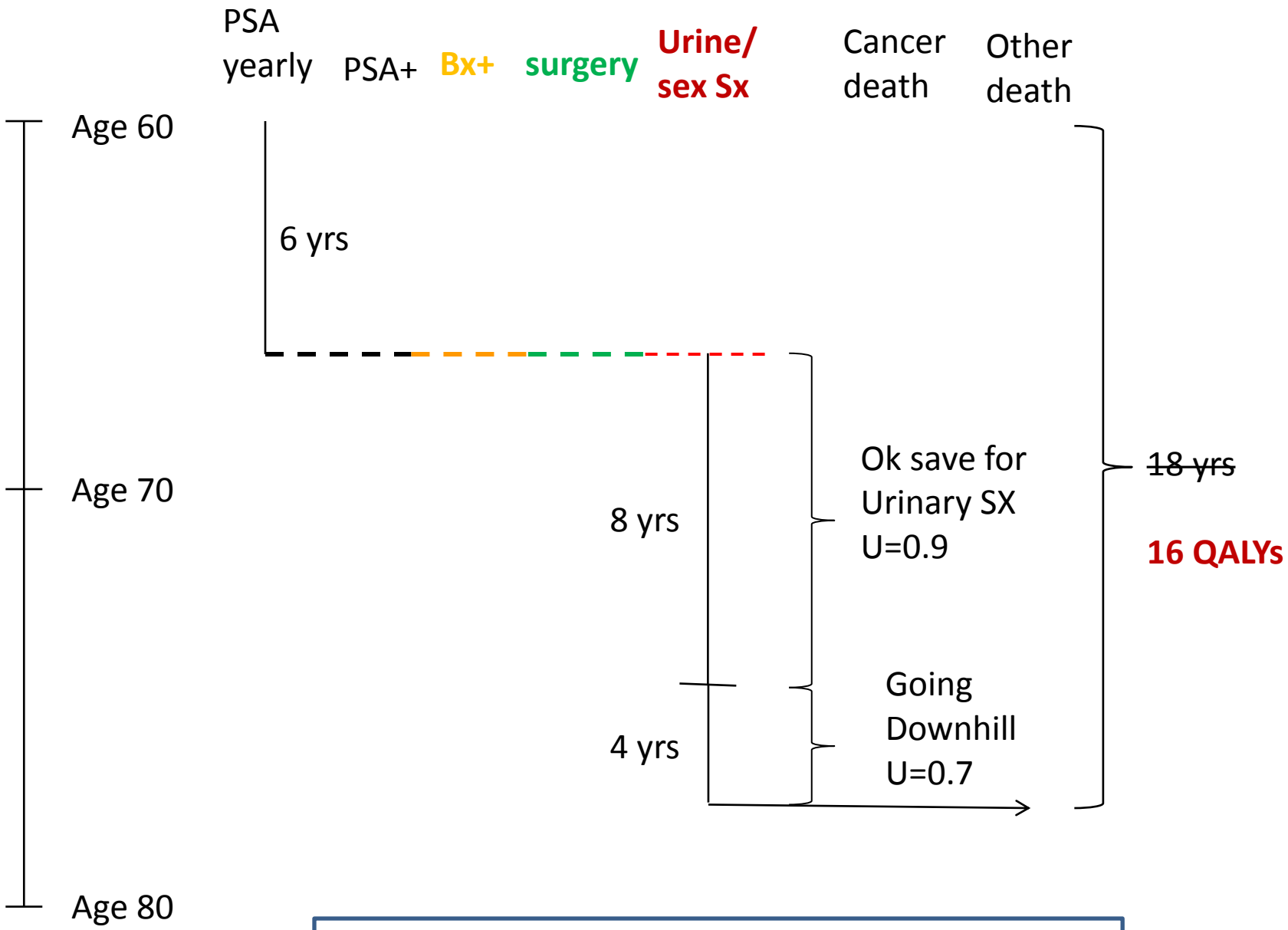
New Engl J Med. 2012;367:669-71.

What the Dutch model does

- Simulates life history of a person
- At any time, chance events may occur:
  - A patient may develop a prostate nodule or an elevated PSA (or the PSA may continue to be normal)
  - The prostate biopsy may positive (or not)
  - The patient may choose surgery, radiation, or active surveillance (a choice, not a chance)
  - Treatment may be curative or not
  - The patient may develop complications of treatment (or not)
- Using a computer, a large number of cases can be created very quickly
  - Depending on chance, events may occur early, later, or not at all → a distribution of life expectancies.
- Screening compared to no screening →difference in outcomes

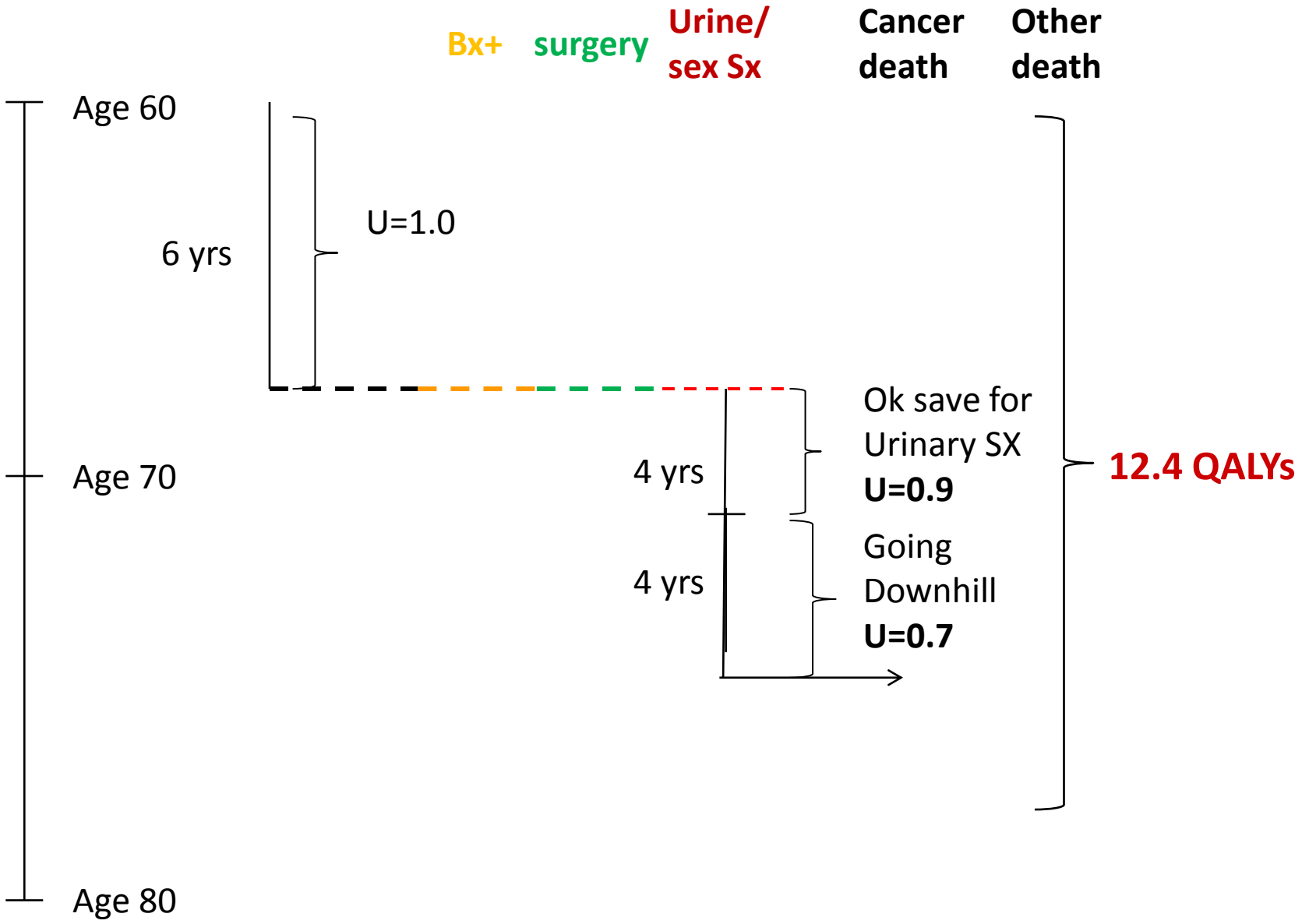

PSA yearly
PSA+
Bx+
surgery
Urine/ sex Sx
Cancer death
Other death
Age 60
6 yrs
Good health
Age 70
8 yrs
Ok save for Urinary SX
4 yrs
Going downhill
18 yrs
Age 80

Screening



Screening

6 + 0.9 x 8 + 0.7 x 4 = 16 quality-adjusted years



No Screening

6 + 0.9 x 4 + 0.7 x 4 = 12.4 quality-adjusted years

Modeling outcomes of prostate cancer screening

- Generate 1000 cases like the examples
  - The probabilities of transition between health states come from the literature → how long each case stays in a health state → a distribution of lengths of time in the state.
  - The distribution of utilities for the health states come from the literature.
- The result is a *distribution* of lengths of time in the various health states and utilities for those health states → distribution of QALYS.

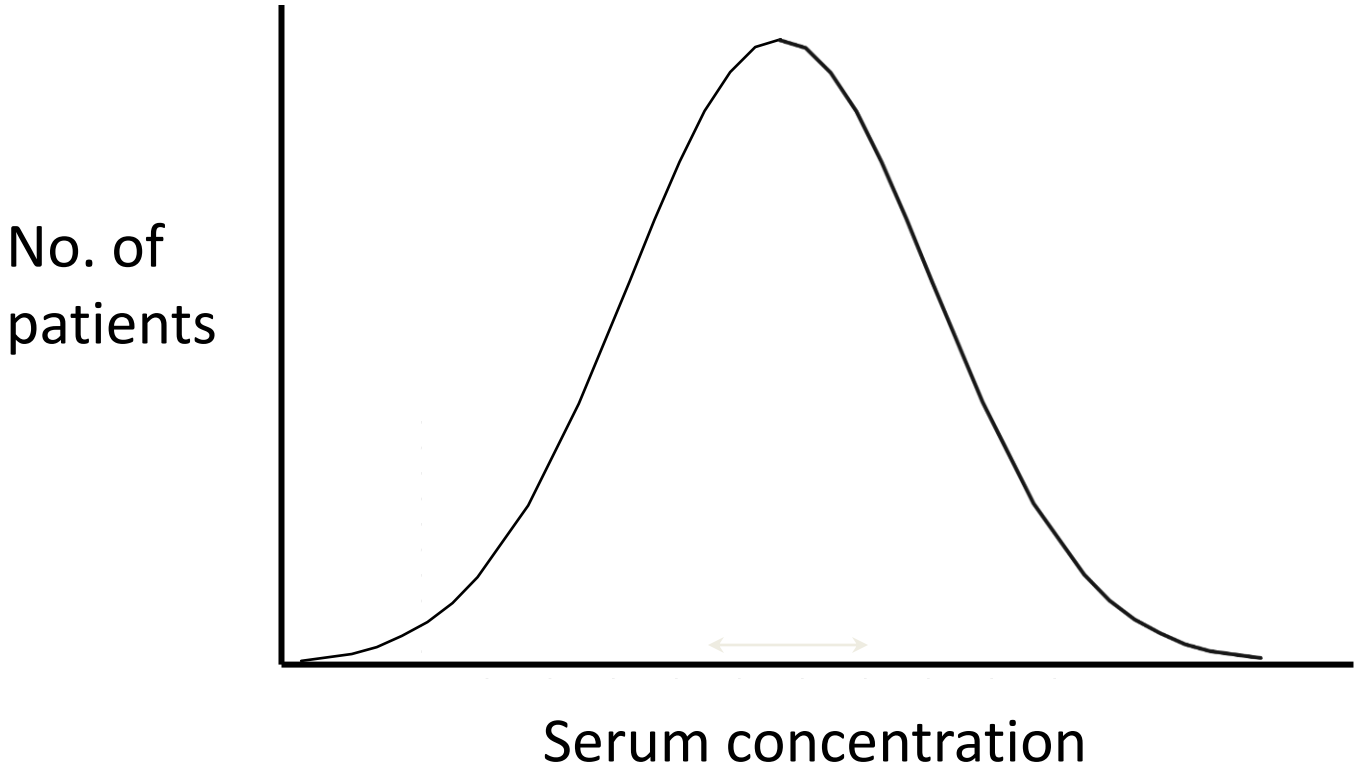
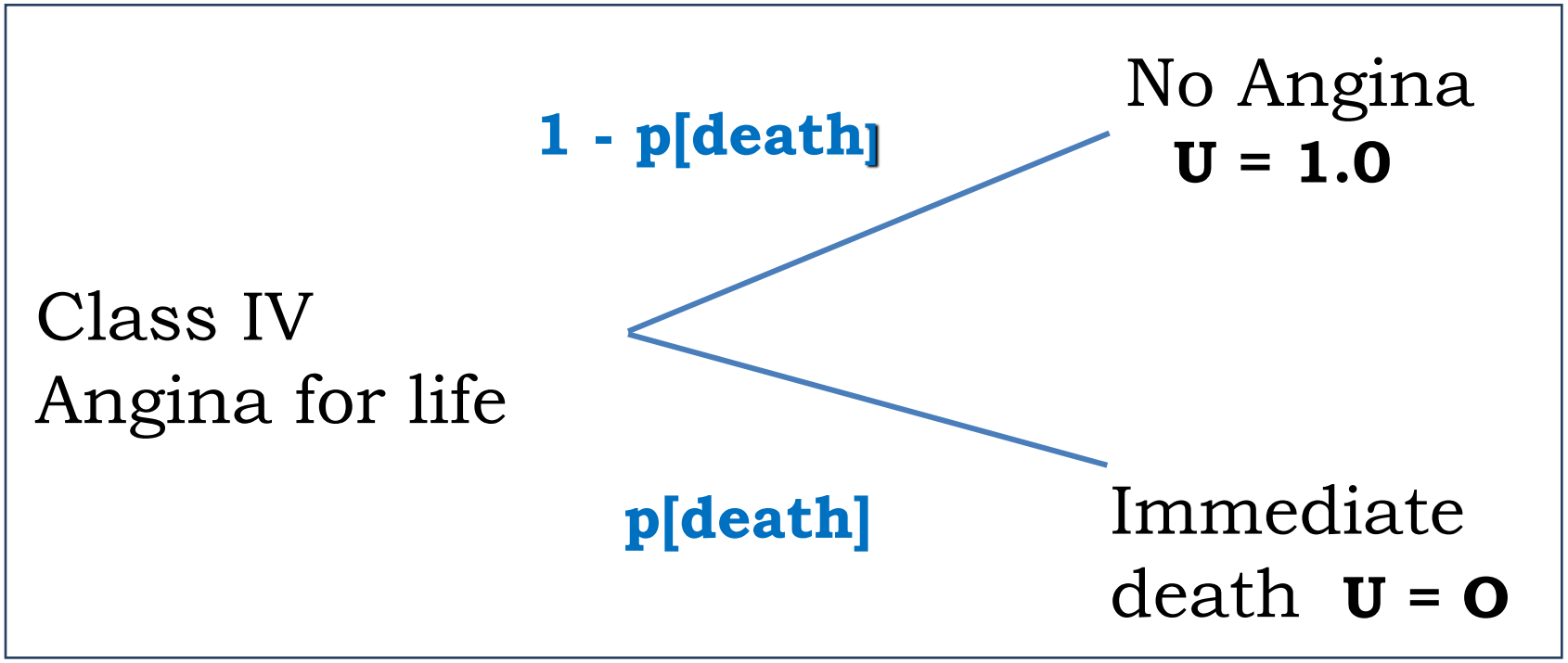


Fig. 5-1

Health State	Utility for health state (best, worst case estimate)	Duration of health state
Screening attendance	0.99 (1.0-0.99)	1 wk
Biopsy	0.90 (0.94-0.87)	3 wk
Cancer diagnosis	0.80 (0.85-0.75)	1 mo
Radiation Rx	0.73 (0.91-0.71) 0-2 mos 0.78 (0.88-0.61) 2-12 mos	2 mos 10 mos
Radical prostatectomy	0.67 (0.90-0.56) 0-2 mos 0.77 (0.91-0.70) 2-12 mos	2 mos 10 mos
Active surveillance	0.97 (1.0-0.85)	7 yr
Post-recovery period	0.95 (1.0-0.93)	9 yrs
Palliative Rx	0.60 (0.24-0.86)	30 mos
Terminal illness	0.40 (0.24-0.40)	6 mos

Heijnsdijk et al. New Engl J Med. 2012;367;659-668)

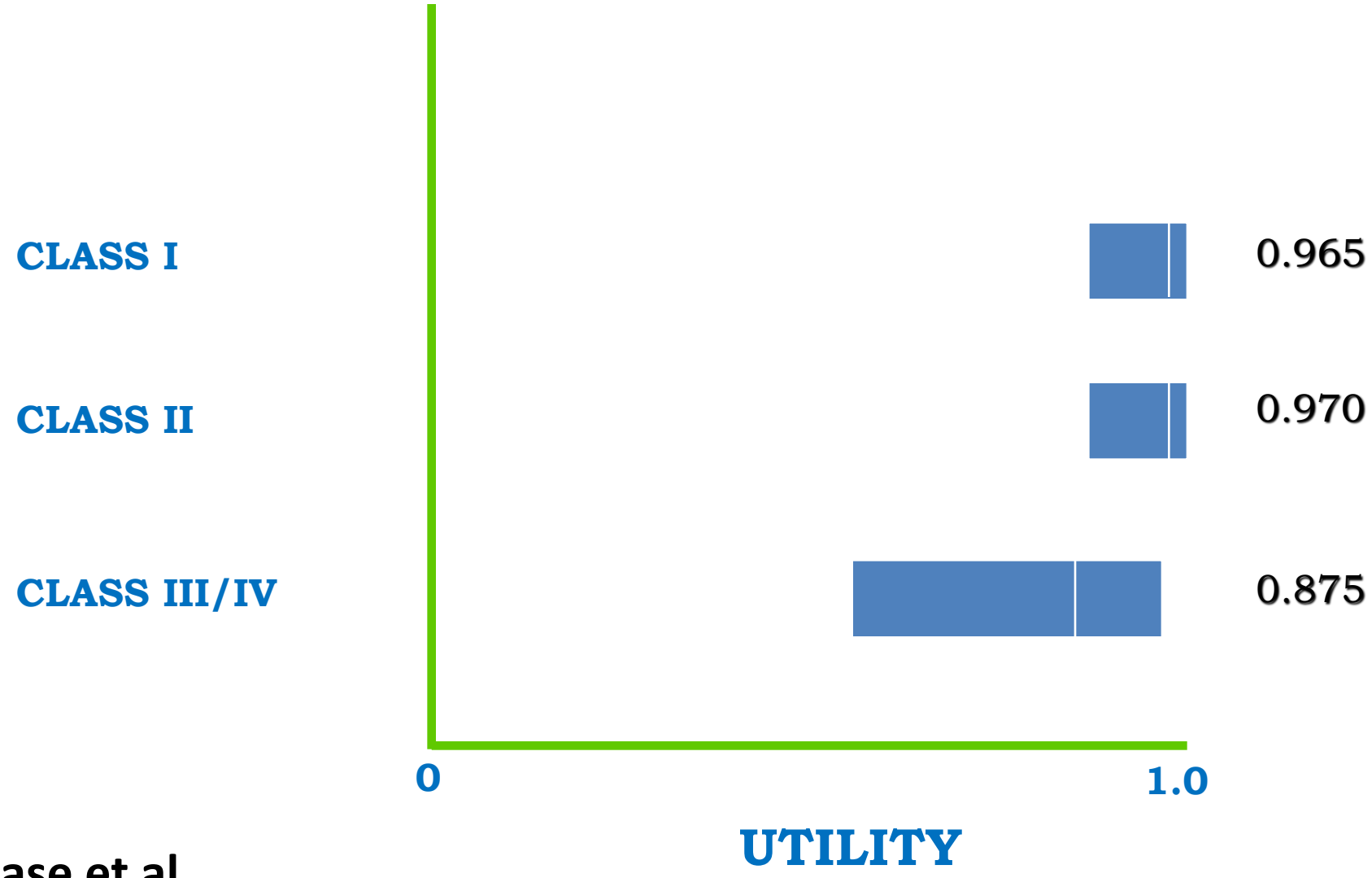
THE STANDARD REFERENCE GAMBLE



Suppose you are indifferent between the gamble and the sure thing when p[death] is 0.10. Then,

U[Class IV Angina] = .10 x 0 + .90 x 1.0 = .90

UTILITIES FOR ANGINA PECTORIS



Nease et al.
JAMA 1995;273:1185-90

QUALITY-ADJUSTED LIFE EXPECTANCY

QUALITY-ADJUSTED LIFE EXPECTANCY = =

LIFE EXPECTANCY x **UTILITY FOR AN OUTCOME STATE**

LIFE IN CLASS IV ANGINA

= 20 YEARS X 0.90

= 18 HEALTHY YEARS (QALYs)

Health State	Utility for health state (best, worst case estimate)	Duration of health state
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Terminal illness	0.40 (0.24-0.40)	6 mos

Heijnsdijk et al. New Engl J Med. 2012;367;659-668)

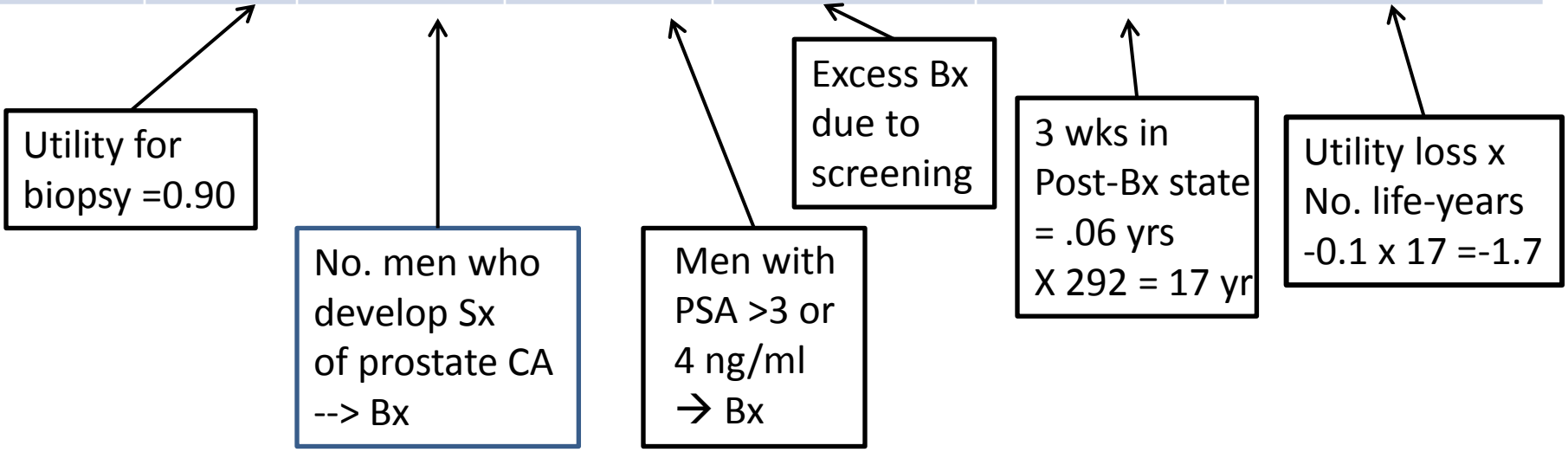
Table 3. Effect of Various Health States with and without Annual Screening for Prostate Cancer over the Lifetime of 1000 Men between the Ages of 55 and 69 Years.*

Health State	Utility Loss	No Screening	Screening	Difference between Screening and No Screening	Quality Adjustment
		no. of men		*no. of life-yr*†	*no. of life-yr (range)*‡
Screening attendance	−0.01	0	8242	8242	158	−1.6 (−1.9 to −0.3)
Biopsy	−0.10	313	605	292	17	−1.7 (−2.2 to −1.0)
Cancer diagnosis	−0.20	112	157	45	4	−0.7 (−0.9 to −0.6)
Radiation therapy						
At 2 mo after procedure	−0.27	43	48	5	1	−0.2 (−0.2 to −0.1)
At >2 mo to 1 yr after procedure	−0.22	43	48	5	4	−0.9 (−1.6 to −0.5)
Radical prostatectomy						
At 2 mo after procedure	−0.33	32	68	35	6	−2.0 (−2.7 to −0.6)
At >2 mo to 1 yr after procedure	−0.23	32	68	35	30	−6.9 (−9.1 to −2.7)
Active surveillance	−0.03	28	48	20	106	−3.2 (−15.8 to 0)
Postrecovery period						
No overdiagnosis	−0.05	75	71	−4	109	−5.5 (−36.4 to 0)
Overdiagnosis	−0.05	0	45	45	215	−10.8 (−30.3 to 0)
Palliative therapy	−0.40	40	26	−14	−35	14.1 (5.1 to 26.9)
Terminal illness	−0.60	31	22	−9	−4	2.6 (2.6 to 3.3)

* The rate of attendance at screenings was assumed to be 80%. The total adjustment in the number of life-years owing to all health effects was −16.7 (range, −93.8 to 24.4).
† The difference in the number of men who underwent screening and those who did not undergo screening has been multiplied by the duration of the health states (as shown in Table 1).
‡ The difference in life-years for each health state has been multiplied by the utility loss to calculate the adjustment for quality of life.

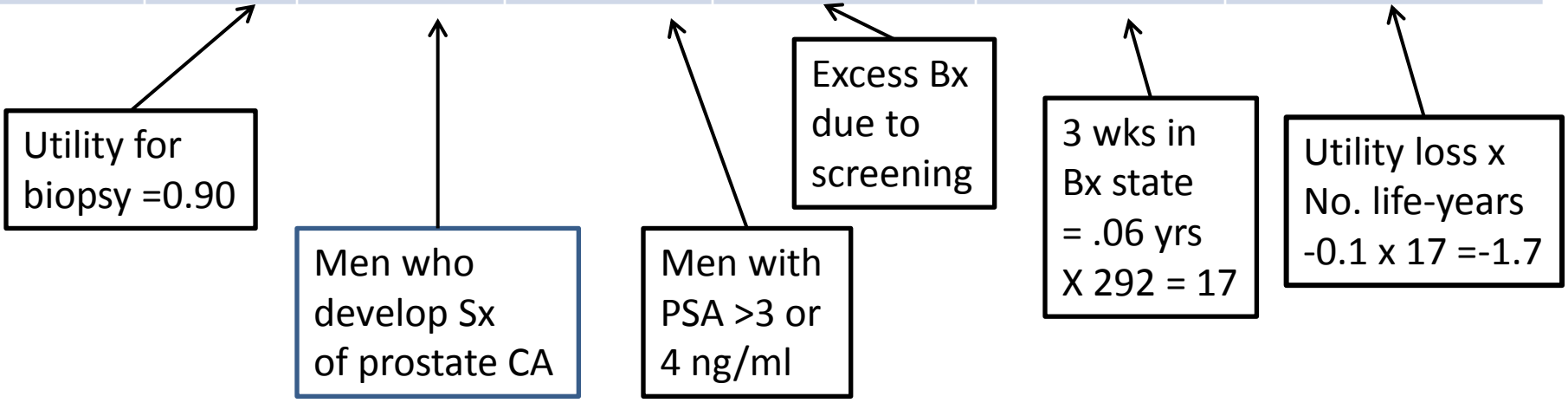
Source: Heijnsdijk et al. New Engl J Med. 2012;367;659-668.

Health state	Utility loss	No Screening	Screening	Screen minus No Screen (No. men)	Screen minus No Screen (No. life-years	Quality-adjustment (range)
Biopsy	-0.10	313	603	292	17	-1.7 (-1.9 to -0.3)



Denominator: 1000 screened men aged 55-69 years

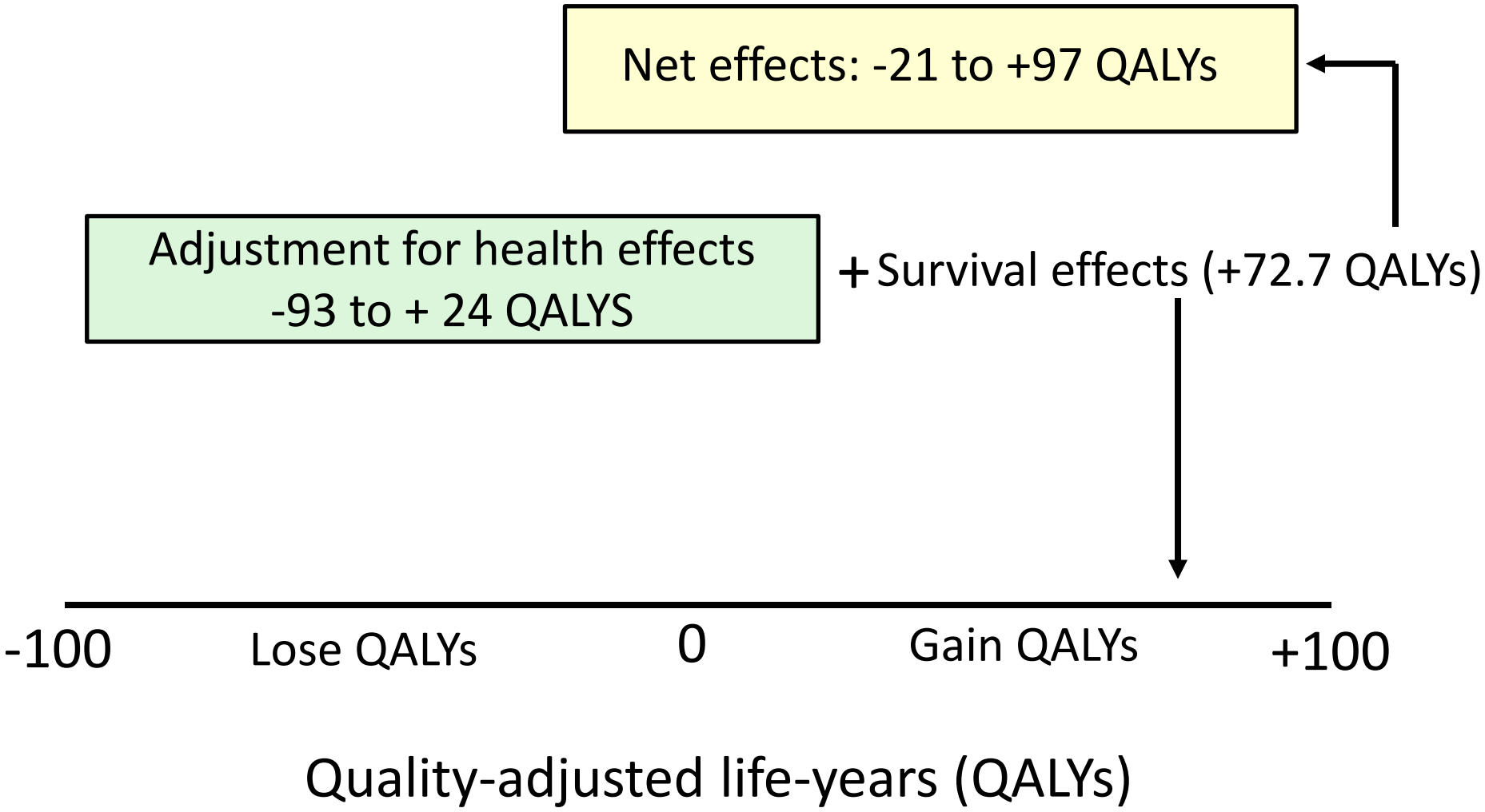
Health state	Utility loss	No Screening	Screening	Screen minus No Screen (No. men)	Screen minus No Screen (No. life-years	Quality-adjustment (range)
Biopsy	-0.10	313	603	292	17	-1.7 (-2.2 to -1.0)



Interpretation: in 1000 screened men 55-69 years old, prostate biopsy results in a loss of 1.7 quality-adjusted (i.e., healthy) years of life.

Health State	Utility	Quality Adjustment (years per 1000 men 55-69 yrs)
Screening attendance	0.99	-1.6 (-1.9 to -0.3)
Biopsy	0.90	-1.7 (-2.2 to -1.0)
Cancer diagnosis	0.80	-0.7 (-0.9 to -0.6)
Radiation Rx	0.73 0.78	-0.2 (-0.2 to -0.1) first 2 mos -0.9 (-1.6 to -0.5) 2-12 mos
Radical prostatectomy	0.67 0.77	-2.0 (-2.7 to -0.6) first 2 mos -6.9 (-9.1 to -2.7) 2-12 mos
Active surveillance	0.97	-3.2 (-15.9 to 0)
Post-recovery period	0.95	-5.5 (-36.4 to 0) no overdiagnosis -10.8 (-30.3 to 0) overdiagnosis
Palliative Rx	0.60	+14.1 (+5.1 to +26.9)
Terminal illness	0.40	+2.6 (+2.6 to +3.3)

Total adjustment for health effects of Rx = -16.7 QALYs (range, -93.8 to +24.4)


Net effects: -21 to +97 QALYs
Adjustment for health effects
-93 to + 24 QALYS
+ Survival effects (+72.7 QALYs)
-100
Lose QALYs
0
Gain QALYs
+100
Quality-adjusted life-years (QALYs)

Net effects of screening

Effect	QALYs per 1000 men 55-69 yrs
Survival effects: Life-years (assumes all health states have a utility of 1.0) gained from screening (vs. not screening)	+72.7
Adjustment for health effects of screening	-16.7 QALYs (range, -93.8 to +24.4)
Net effect (benefits – harms)	+56 (range, -20.7 to +97.1)

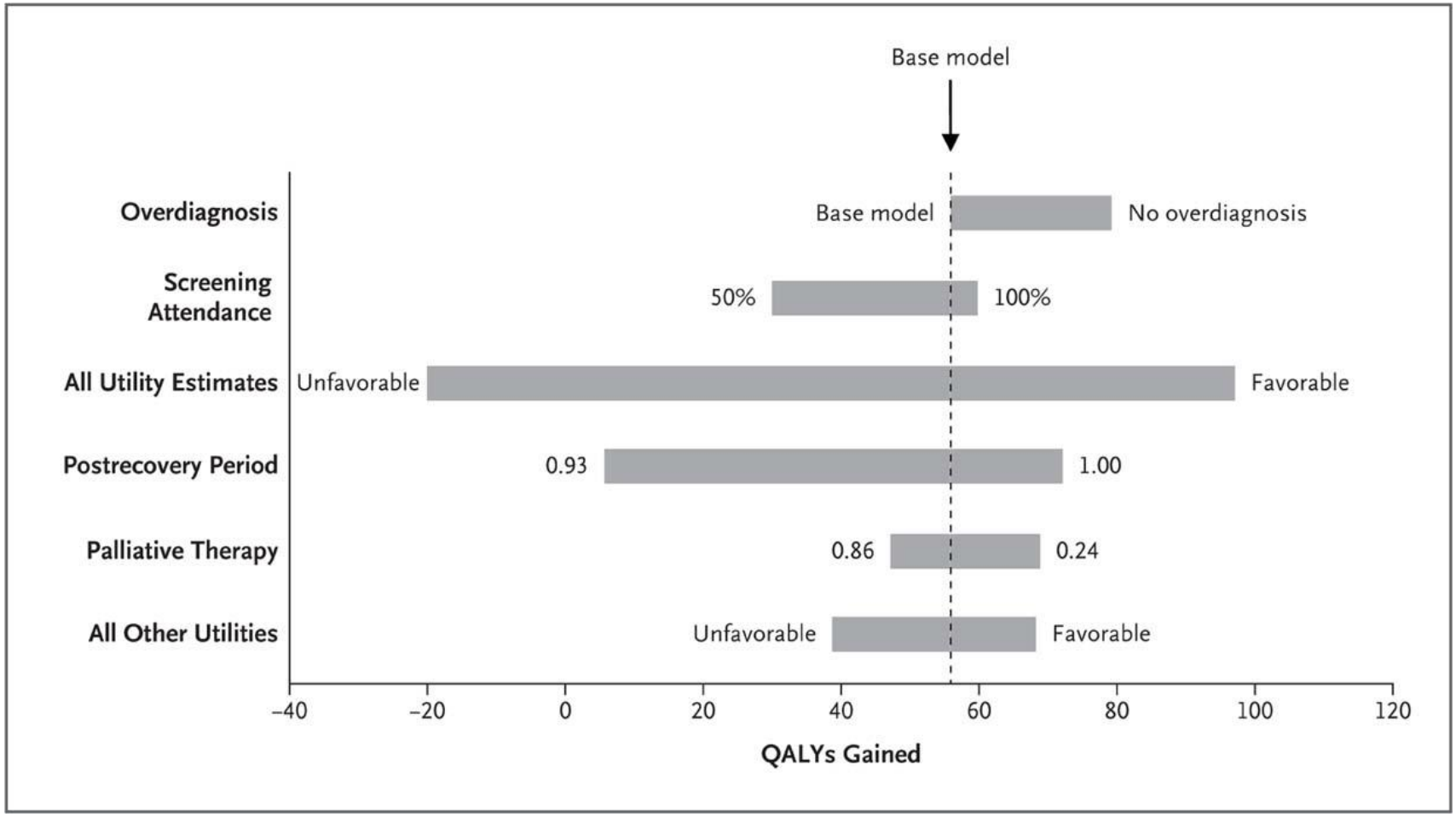
What does this result say about screening policy?

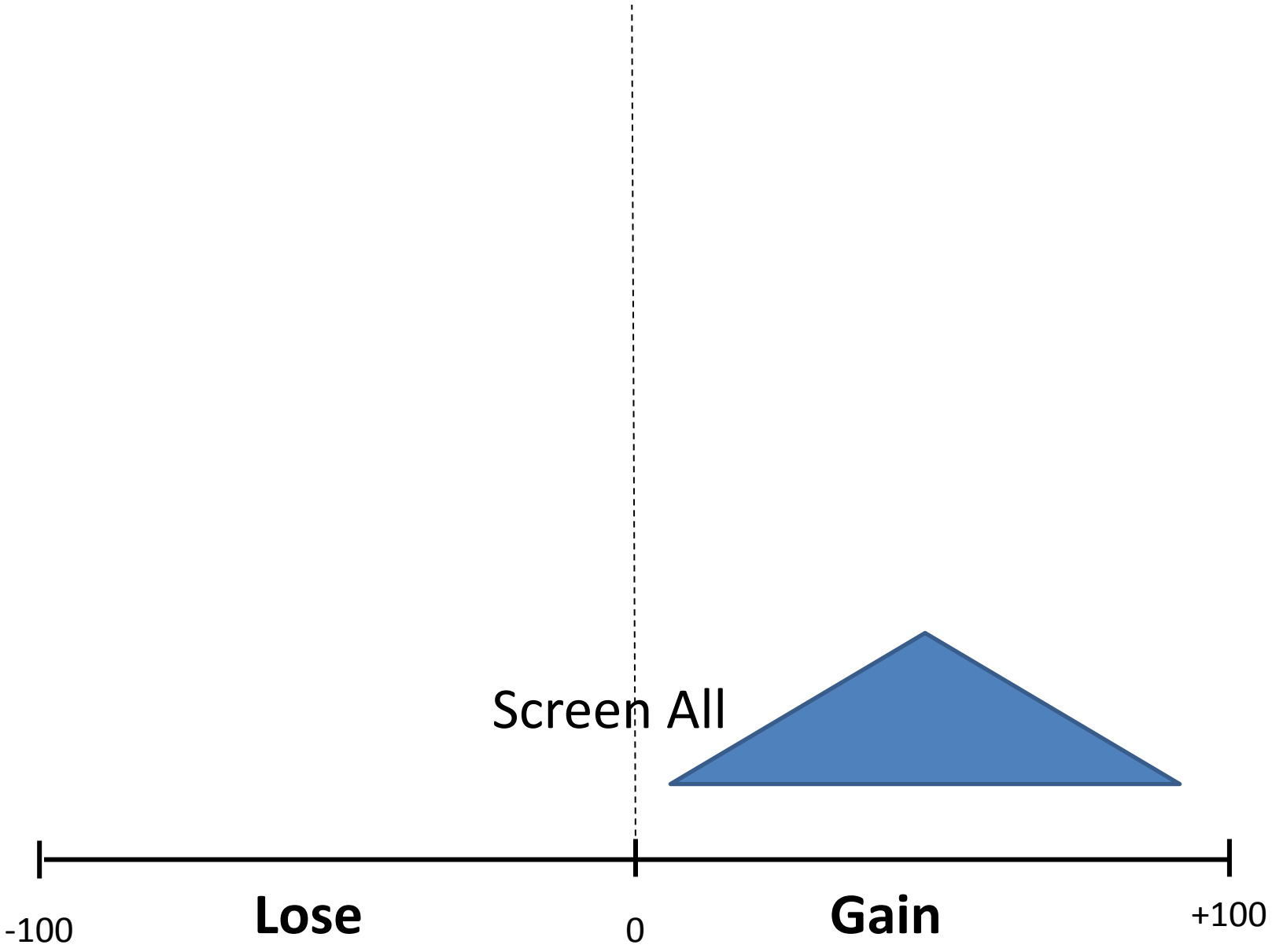
Net effects of screening

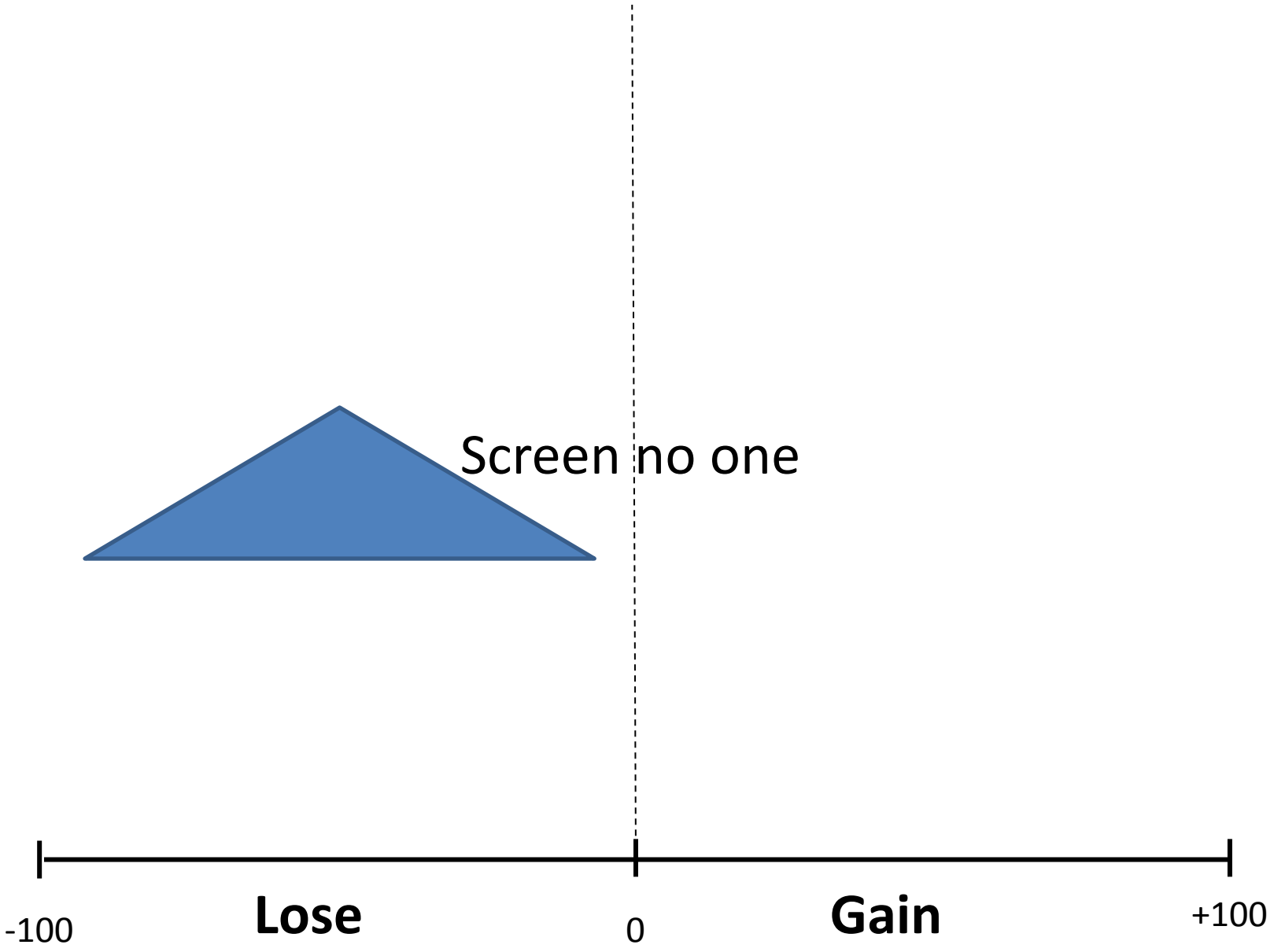
Effect	QALYs
QALYs gained from screening (vs. not screening)	+72.7
Adjustment for health effects of screening	-16.7 QALYs (range, -93.8 to +24.4)
Net effect (benefits – harms)	+56 (range, **-20.7 to +97.1**)

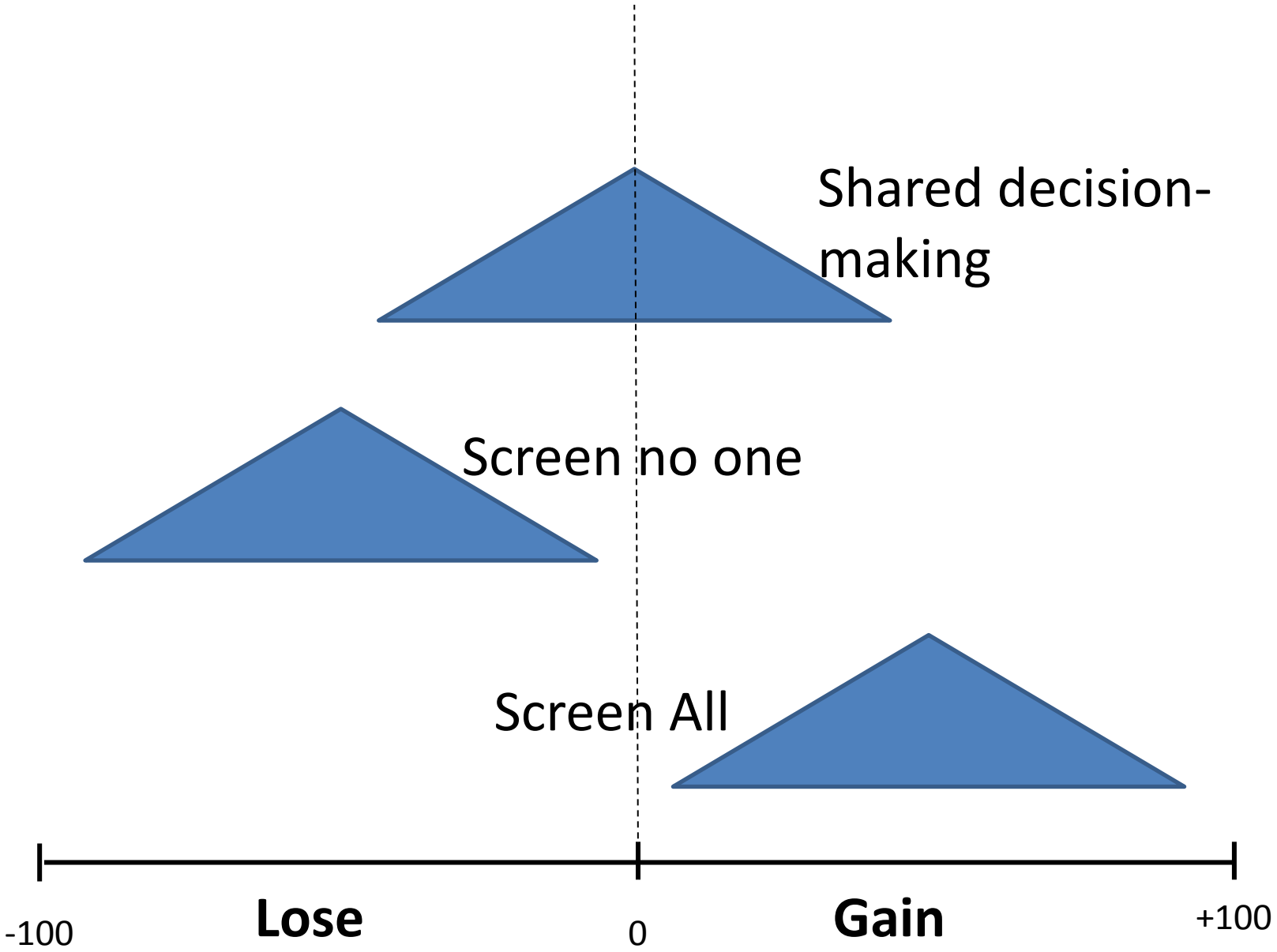
What does this result say about screening policy?

Some gain and some lose from prostate cancer screening. The same recommendation for everyone is not appropriate.




Screen All
-100
Lose
0
Gain
+100
Net benefit (quality adjusted years/1000 screened men)


Screen no one
-100
Lose
0
Gain
+100
Net benefit (quality adjusted years/1000 screened men)


Shared decision-making
Screen no one
Screen All
-100
Lose
0
Gain
+100
Net benefit (quality adjusted years/1000 screened men)

Prostate cancer screening GLs in the U.S.

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American Academy of Family Physicians	2008	Discuss
National Comprehensive Cancer Network	?	PSA at age 40
American Society for Clinical Oncology	2012	Discuss

All agree that men with life expectancy <10 years shouldn't be screened

The approach taken here is a solution to the problem of estimating net benefit.

It would remove much of the subjectivity involved in making recommendations for guidelines.

A decision support system based on this model could help to individualize screening recommendations.

Conclusions

- The balance of benefits and harms of an intervention are a touchstone for decision making.
- Benefits and harms are usually measured in different units → hard to assess the balance in close calls.
- Benefits and harms can be expressed as their impact on length and quality of life (QALYs).

Conclusions

- Depending on their utilities for adverse effects of treatment, prostate cancer patients may gain or lose QALYs by undergoing PSA screening.
- At a population level, this means that shared decision making is the preferred intervention for prostate cancer screening.
- At an individual level, patients need to make up their own minds about the downstream health states --> SHARED DECISION MAKING
  - Their likelihood
  - Their meaning for their lives