RARE CANCERS EUROPE

Joining forces for action

What is needed for better decision-making?

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RARE CANCERS EUROPE

How can we help you ? SEARCH

review

Annals of Oncology 00: 1–7, 2011
doi:10.1093/annonc/mdr458

Rare Cancers Europe (RCE) methodological recommendations for clinical studies in rare cancers: a European consensus position paper

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While they account for one-fifth of new cancer cases, rare cancers are difficult to study. A higher than average degree of uncertainty should be accommodated for clinical as well as for population-based decision making. Rules of rational decision making in conditions of uncertainty should be rigorously followed and would need widely informative clinical trials. In principle, any piece of new evidence would need to be exploited in rare cancers. Methodologies to explicitly weigh and combine all the available evidence should be refined, and the Bayesian logic can be instrumental to this end. Likewise, Bayesian-design trials may help optimize the low number of patients liable to be enrolled in clinical studies on rare cancers, as well as adaptive trials in general, with their inherent potential of flexibility when properly applied. While clinical studies are the mainstay to test hypotheses, the potential of electronic patient records should be exploited to generate new hypotheses, to create external controls for future studies (when internal controls are unpractical), to study effectiveness of new treatments in real conditions. Framework study protocols in specific rare cancers to sequentially test sets of new agents, as from the early post-phase I development stage, should be encouraged. Also the compassionate and the off-label settings should be exploited to generate new evidence, and flexible regulatory innovations such as adaptive licensing could convey new agents early to rare cancer patients, while generating evidence. Though validation of surrogate end points is problematic in rare cancers, the use of an updated notion of tumor response may be of great value in the single patient to optimize the use of therapies, all the more the new ones. Disease-based communities, involving clinicians and patients, should be regularly consulted by regulatory bodies when setting their policies on drug approval and reimbursement in specific rare cancers.

Key words: rare cancers, clinical trials, research methodology

Rare Cancers Conference 2012

Exploring ways to improve clinical research on rare cancers

Date : 01 Mar 2012

Organised by the European Society for Medical Oncology (ESMO) and Rare Cancers Europe, the Rare Cancers Conference, held on 10 February 2012 in Brussels, provided a multi-stakeholder platform for rare cancer and rare disease experts from across Europe to exchange views and share insights into what can be done to improve the methodology of clinical research on rare cancers.

The first two conference sessions offered an overview of rare cancers and associated challenges for clinical research and drug development and also presented a variety of (potential) solutions as well as best practice examples. Where traditional frequent clinical research approaches are not possible, due to the small numbers of patients, it is particularly challenging to make sure that rare cancer patients are not being left without appropriate clinical research and therapeutic progress.

The third session of the conference therefore also highlighted the need for reaching a broad multi-stakeholder consensus on a set of recommendations on improving the methodology of clinical research on rare cancers. These recommendations will be the product of an ongoing multidisciplinary and multi-stakeholder online consensus discussion, promoted by Rare Cancers Europe. They will focus on best methods, including innovative ones, for clinical research on rare cancers, and rare subgroups of frequent cancers, with the goal of encouraging:

- clinical researchers to exploit innovative solutions for the design and analysis of clinical studies;
- clinicians to exploit innovative solutions for the combination of all available knowledge;
- regulators to accept evidence built through these solutions;
- clinicians' and patients' communities to exploit all forms of collaboration to put together as large series as possible for prospective and retrospective clinical and translational research;
- methodologists to advance research into new methodological solutions better fitting the needs of studies on small series

All interested stakeholder groups are encouraged to actively participate in this open discussion, the result of which will be a consensus paper to be publicly presented in autumn 2012. This paper could then be used for related advocacy efforts. All parties interested in joining this discussion are invited to contact Rare Cancers Europe.

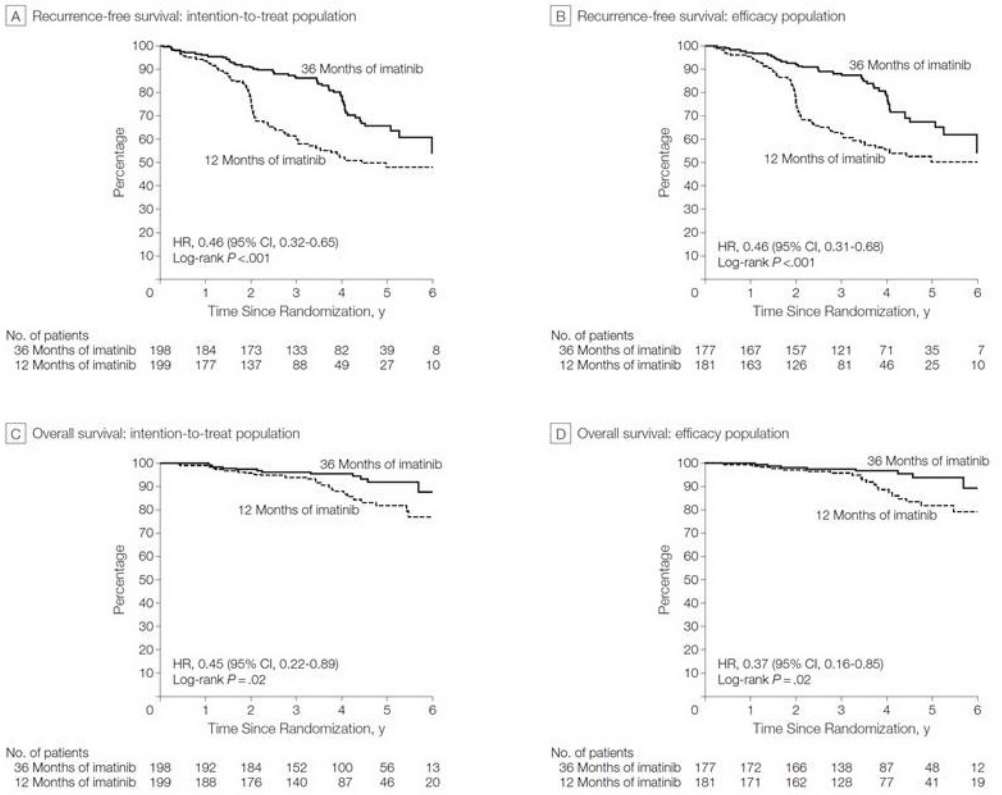
R $p \leq 0.05$


R
p≤0.05

One vs Three Years of Adjuvant Imatinib for Operable Gastrointestinal Stromal Tumor

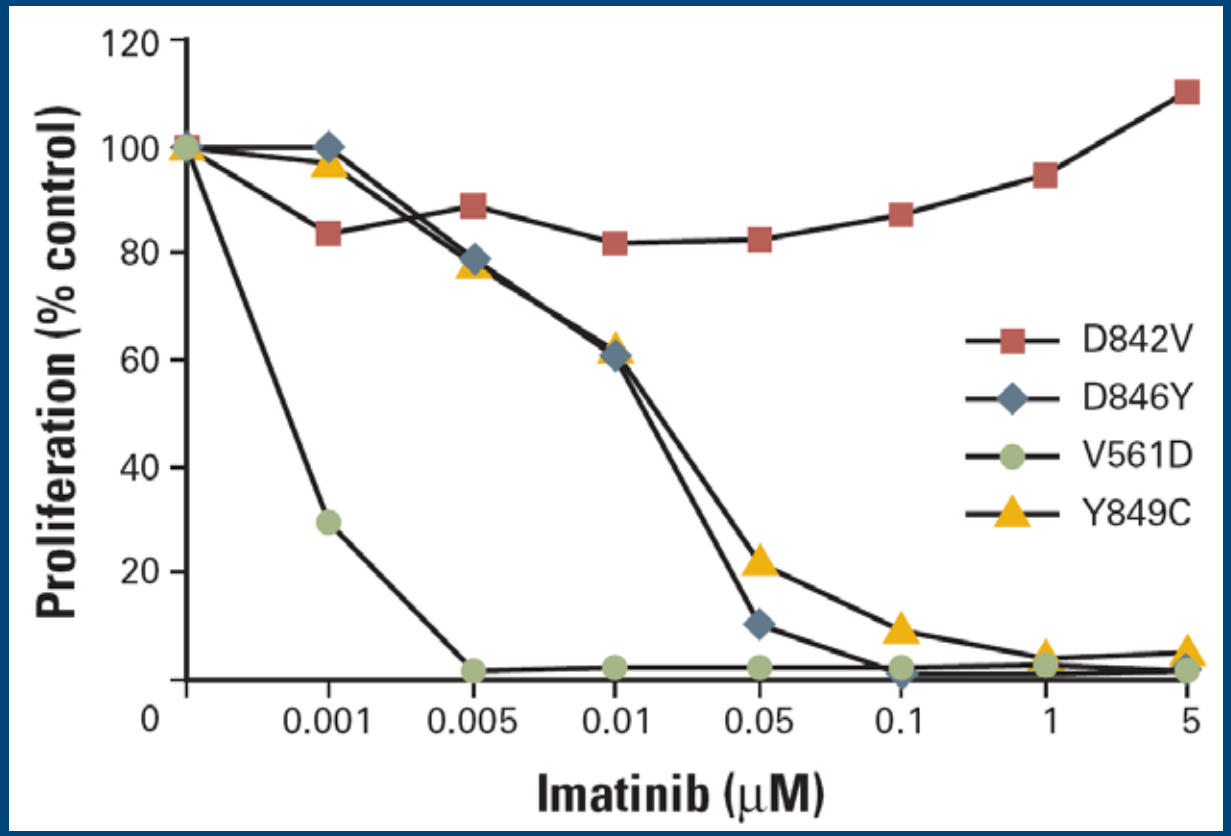
A Randomized Trial

Heikki Joensuu, MD
Mikael Eriksson, MD
Kirsten Sundby Hall, MD
Jörg T. Hartmann, MD
Daniel Pink, MD
Jochen Schütte, MD
Giuliano Ramadori, MD
Peter Hohenberger, MD
Justus Duyster, MD
Salah-Eddin Al-Batran, MD
Marcus Schlemmer, MD
Sebastian Bauer, MD
Eva Wardelmann, MD
Maarit Sarlomo-Rikala, MD
Bengt Nilsson, MD
Harri Sihto, MSc
Odd R. Monge, MD
Petri Bono, MD
Raija Kallio, MD
Aki Vehtari, DSc
Mika Leinonen, MSc
Thor Alvegård, MD
Peter Reichardt, MD



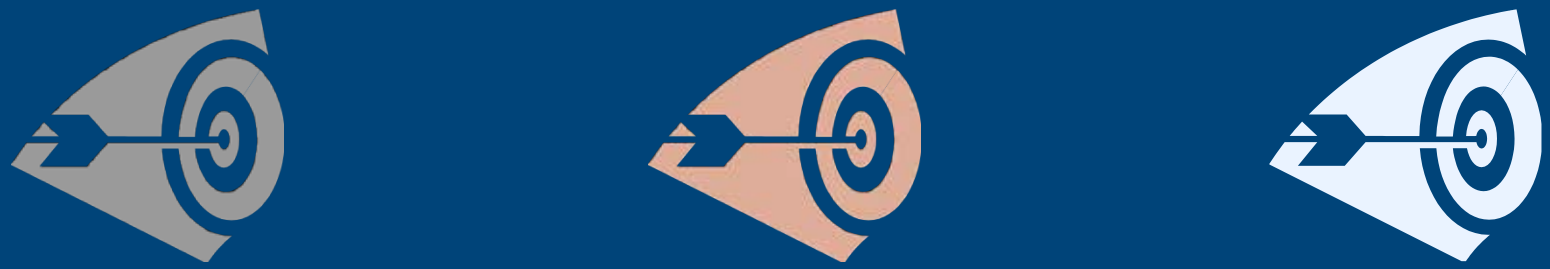
JAMA. 2012;307(12):1265-1272 www.jama.com

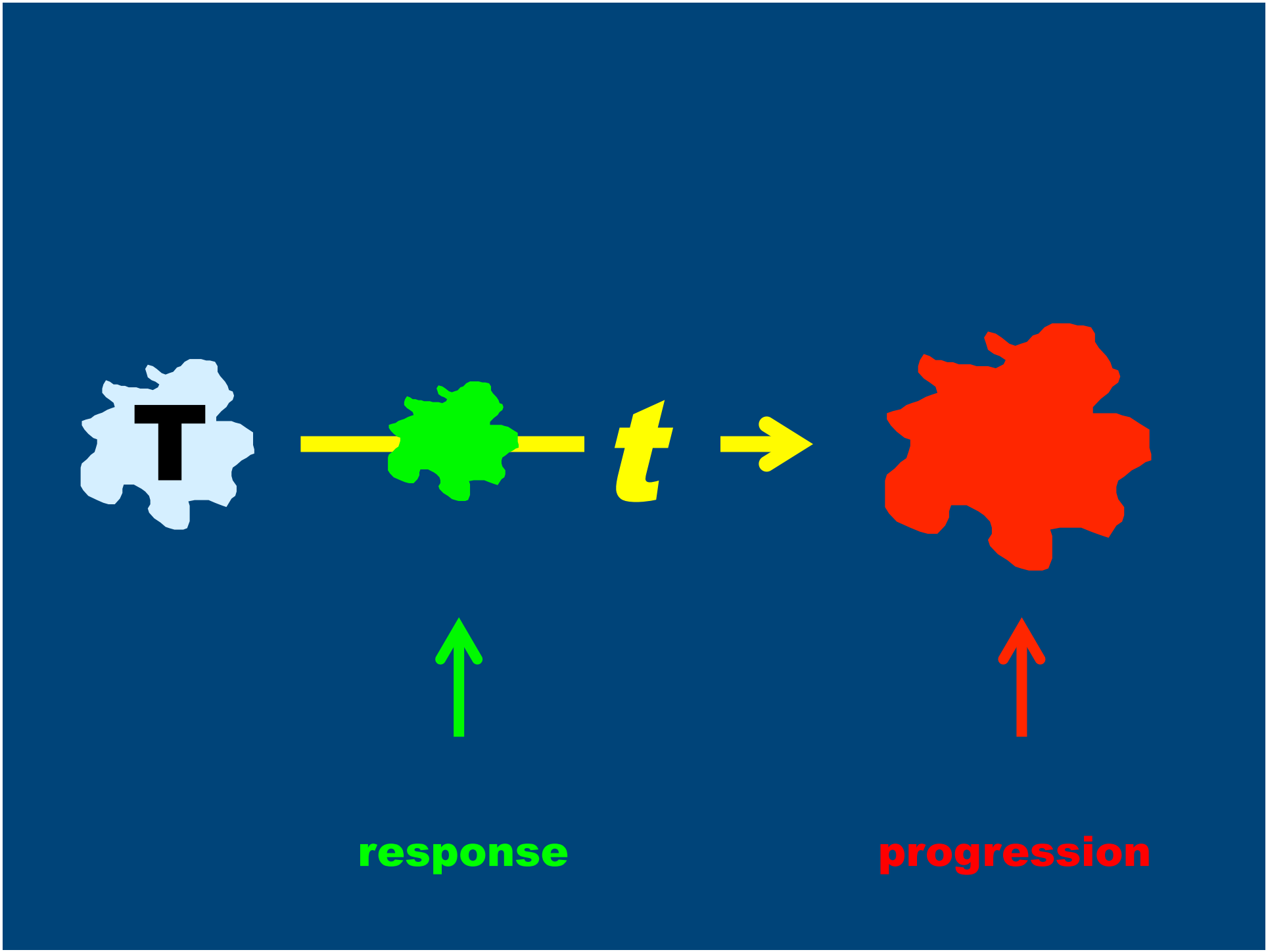
GIST: PDGFRA mutations



Corless CL, J Clin Oncol 2005, 23: 5357

Surrogate end-points




T
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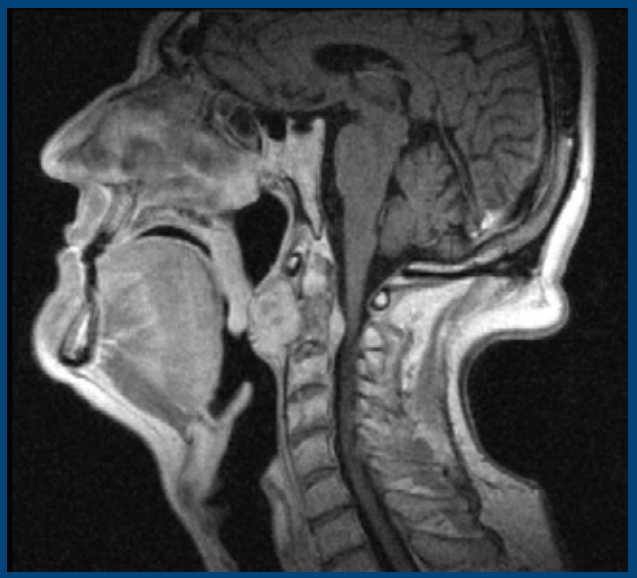
response
progression



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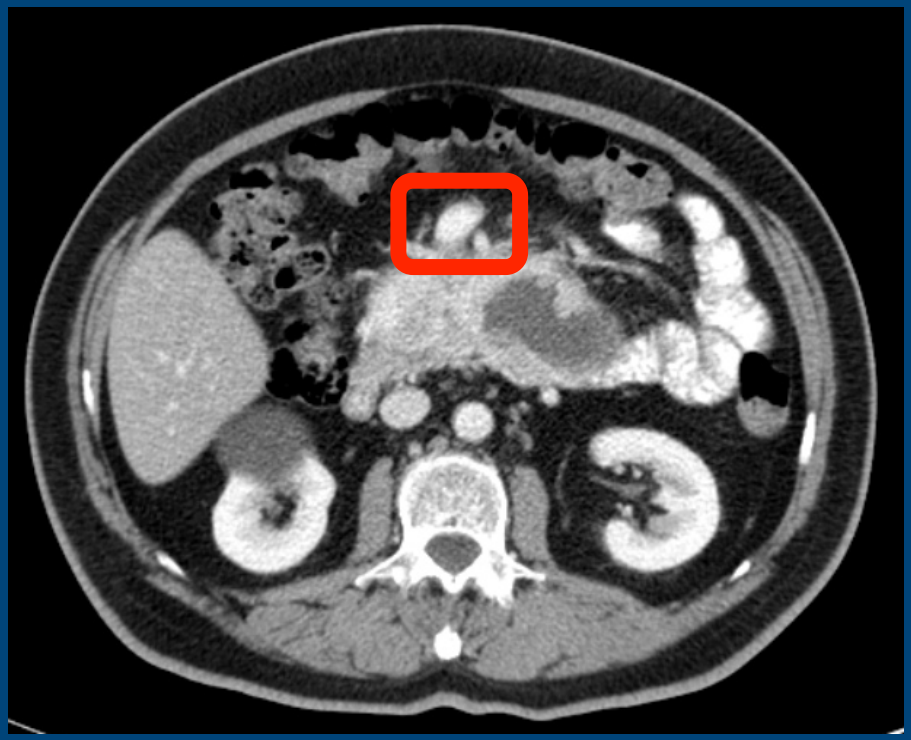
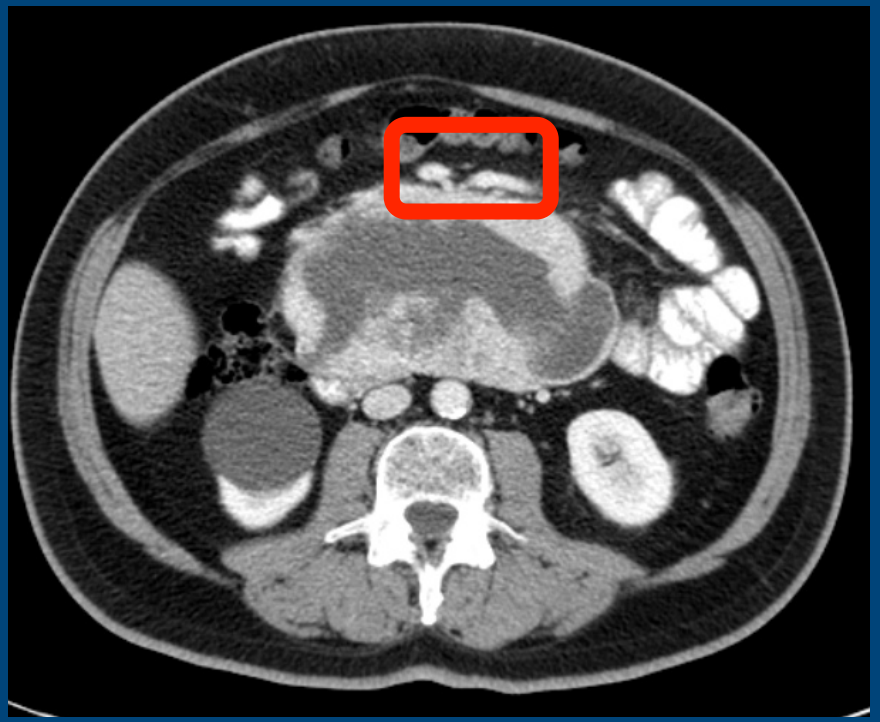
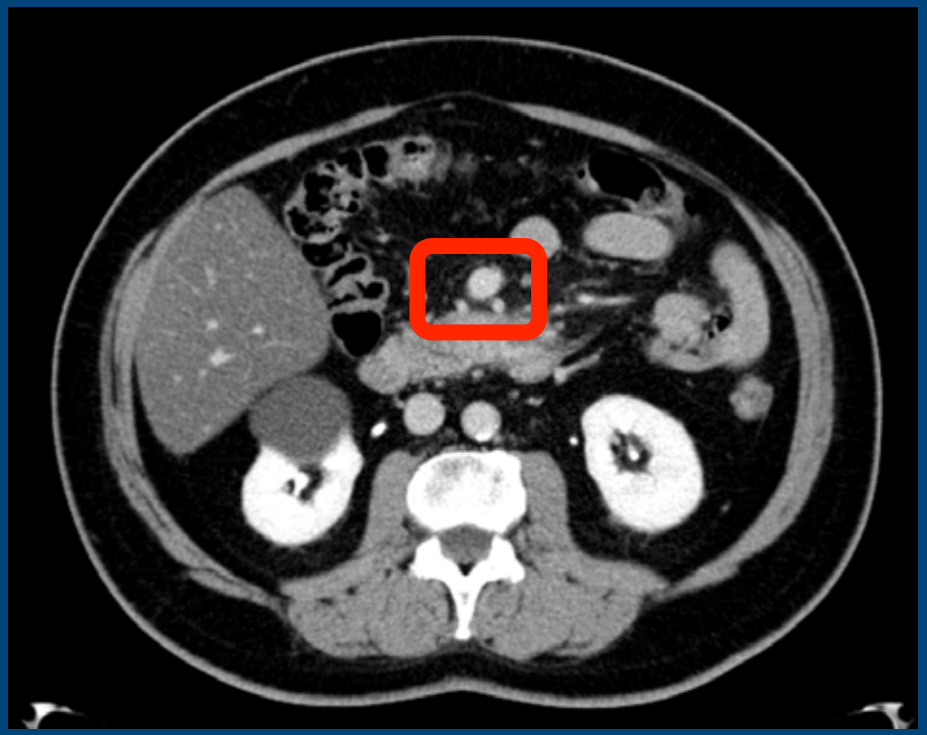
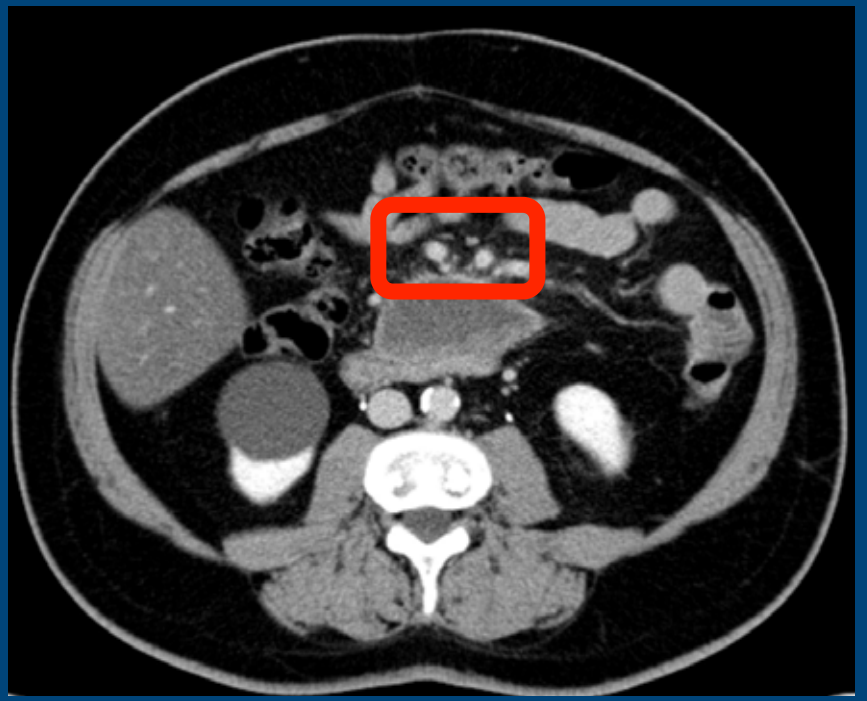








Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Gordon C S Smith, Jill P Pell

Parachutes reduce the risk of injury after gravitational challenge, but their effectiveness has not been proved with randomised controlled trials

topic

Parachutes are widely used to prevent death and major injury after gravitational challenge

Parachute use is associated with adverse effects due to failure of the intervention and iatrogenic injury

Studies of free fall do not show 100% mortality

What this study adds

No randomised controlled trials of parachute use have been undertaken

The basis for parachute use is purely observational, and its apparent efficacy could potentially be explained by a "healthy cohort" effect

Individuals who insist that all interventions need to be validated by a randomised controlled trial need to come down to earth with a bump

BMJ 2003;327:1459

European Action Against Rare Cancers

Recommendations Addressing Regulatory Barriers in Rare Cancer Care

We:

1. Acknowledge that while the process for establishing the efficacy of new medicines is in principle the same for all cancers, the strength of the evidence – intended as level and quality of evidence and statistical precision – that is achievable in common cancers is difficult to achieve in rare conditions and, therefore, a higher degree of uncertainty should be accepted for regulatory as well as clinically informed decision-making.

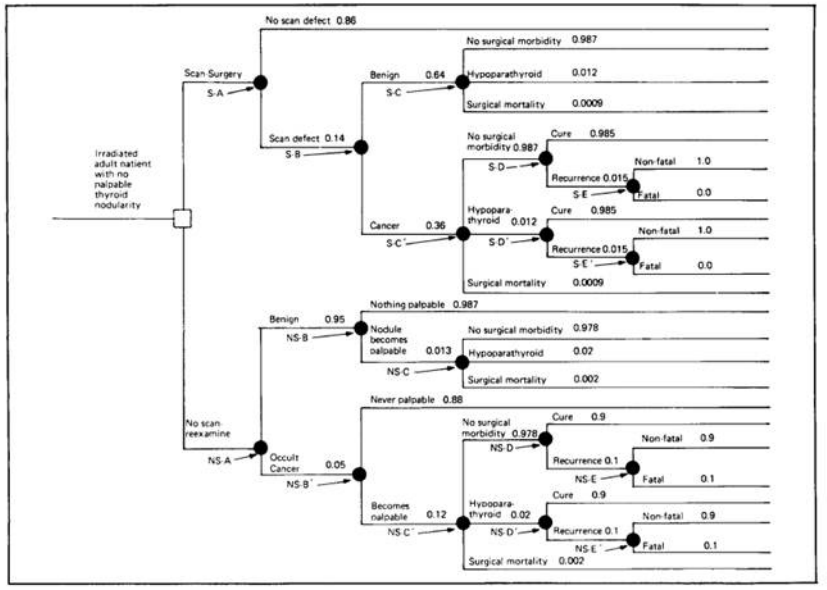

R
p≤0.05

MEDICAL PROGRESS

DECISION ANALYSIS

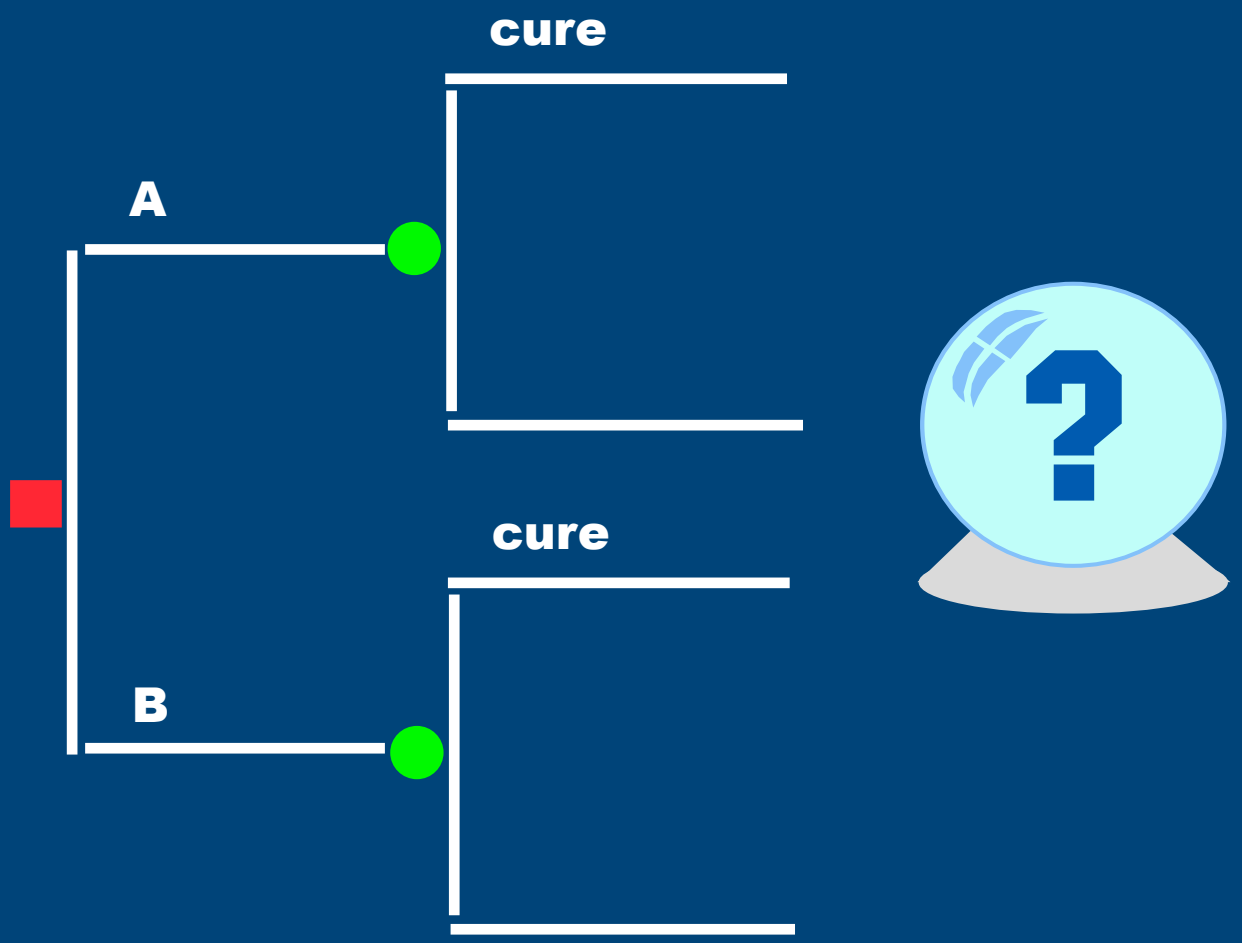
STEPHEN G. PAUKER, M.D., AND JEROME P. KASSIRER, M.D.

$$* \quad P_{dis|find} = \frac{P_{dis} \times P_{find|dis}}{\sum_{i=1}^{n} P_{dis\ i} \times P_{find|dis\ i}},$$



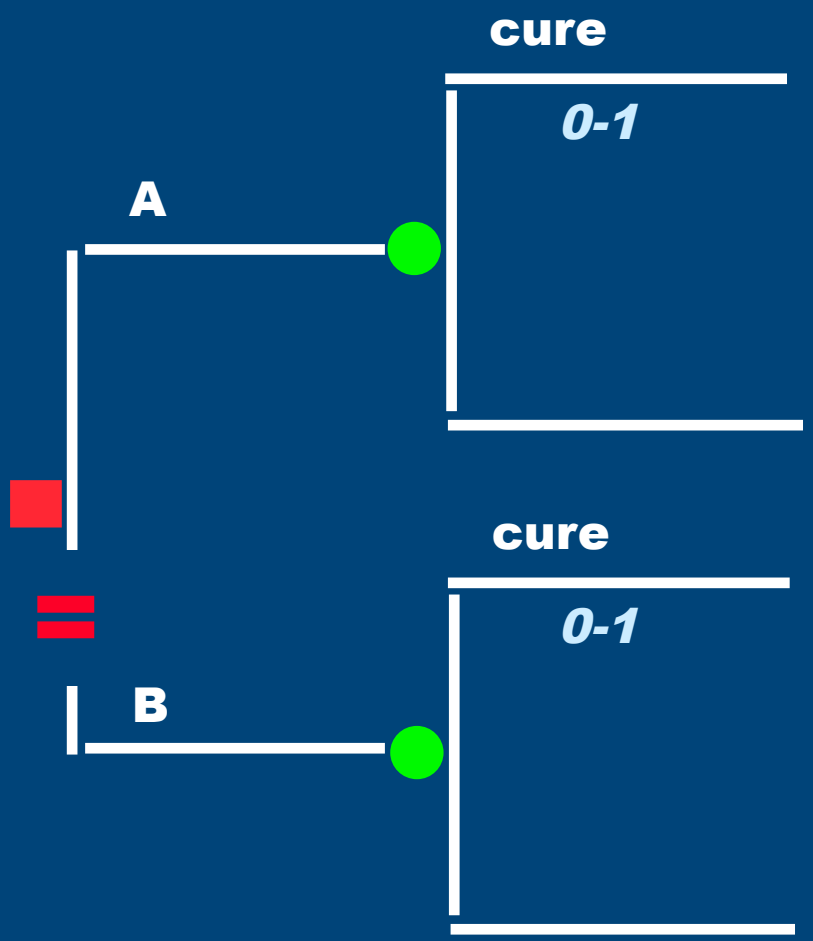
N Engl J Med 1987;316:250

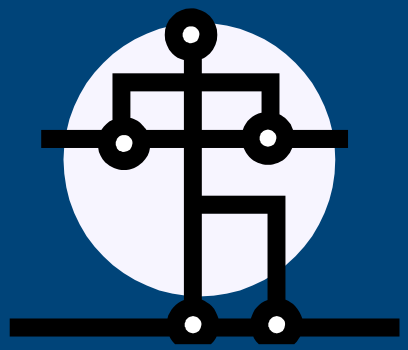
Uncertainty



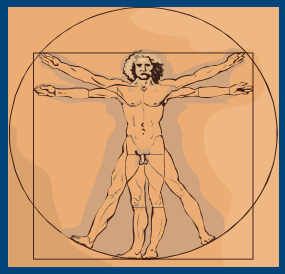
Risk

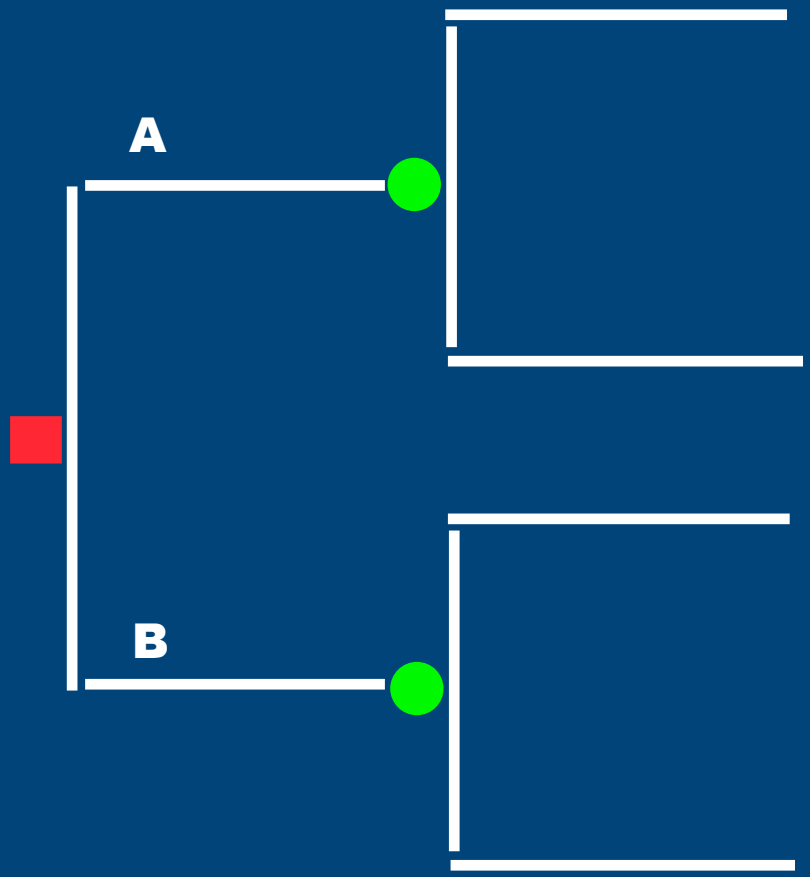
probabilities!





Utility





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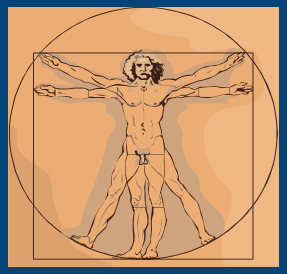
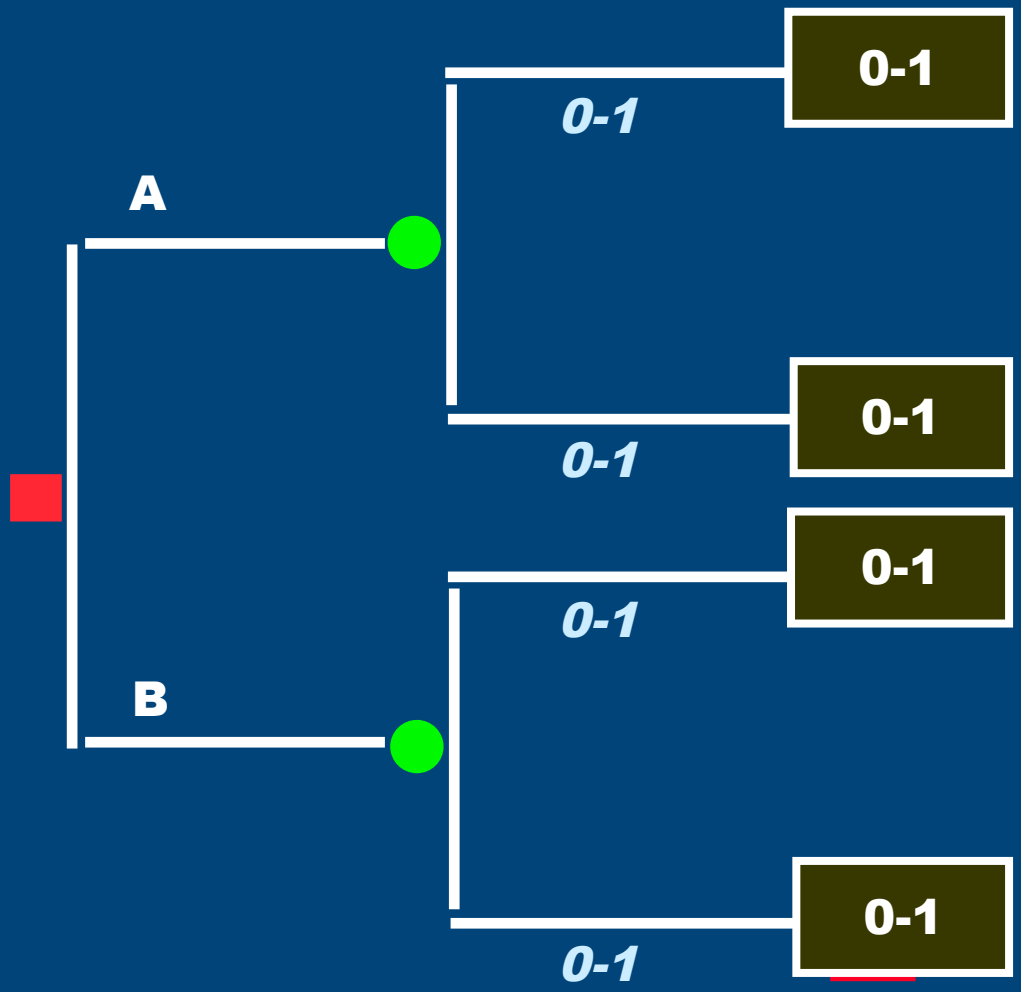
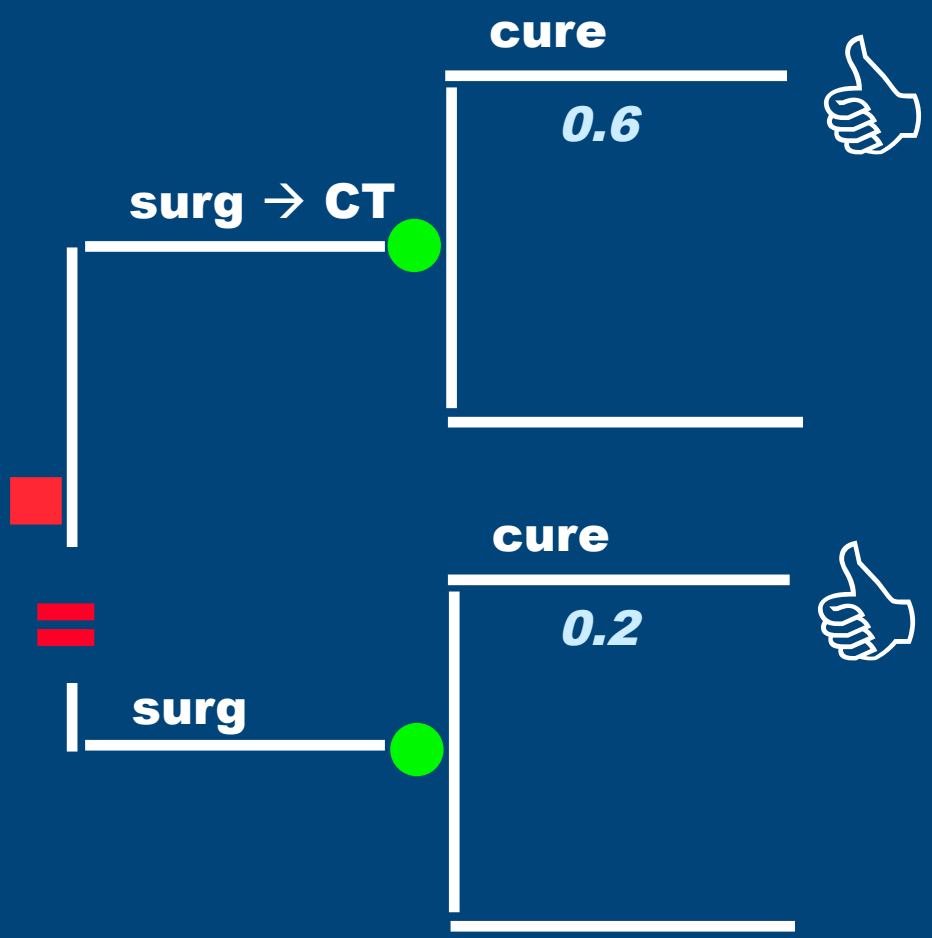
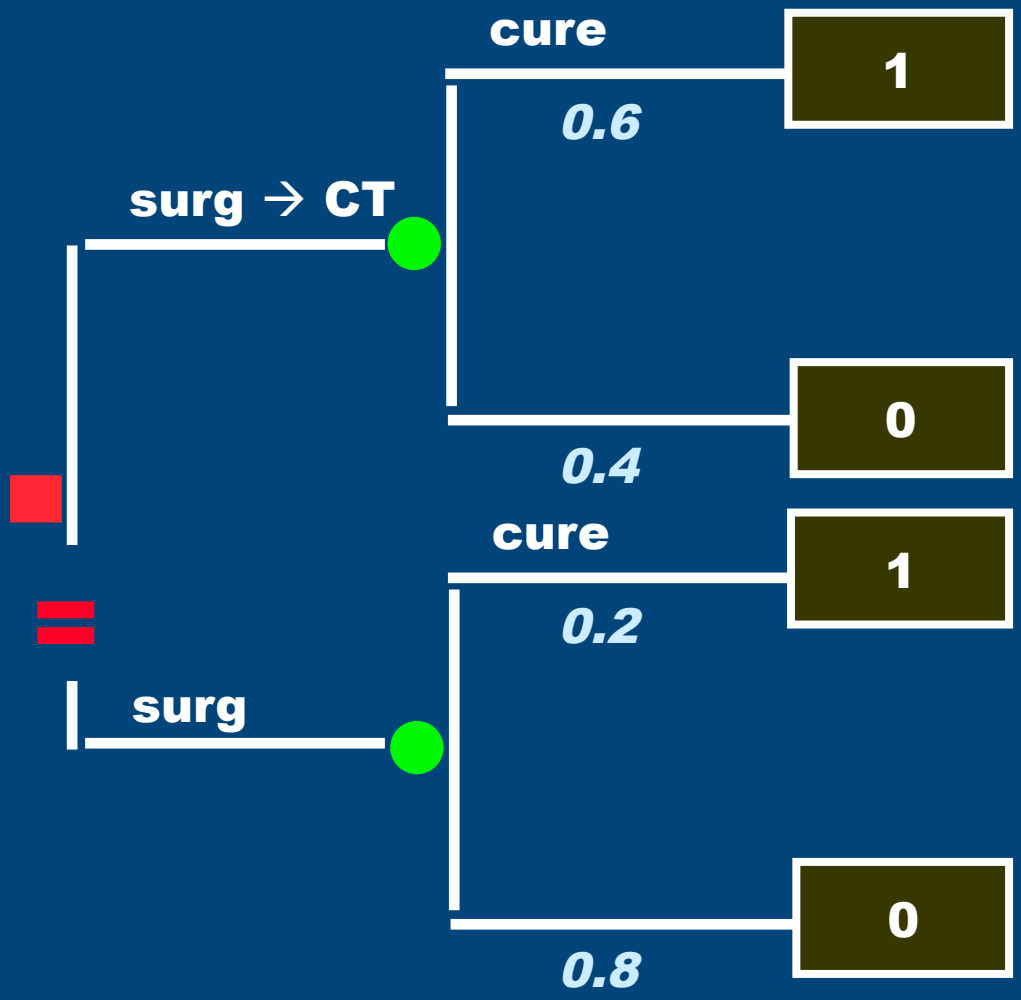
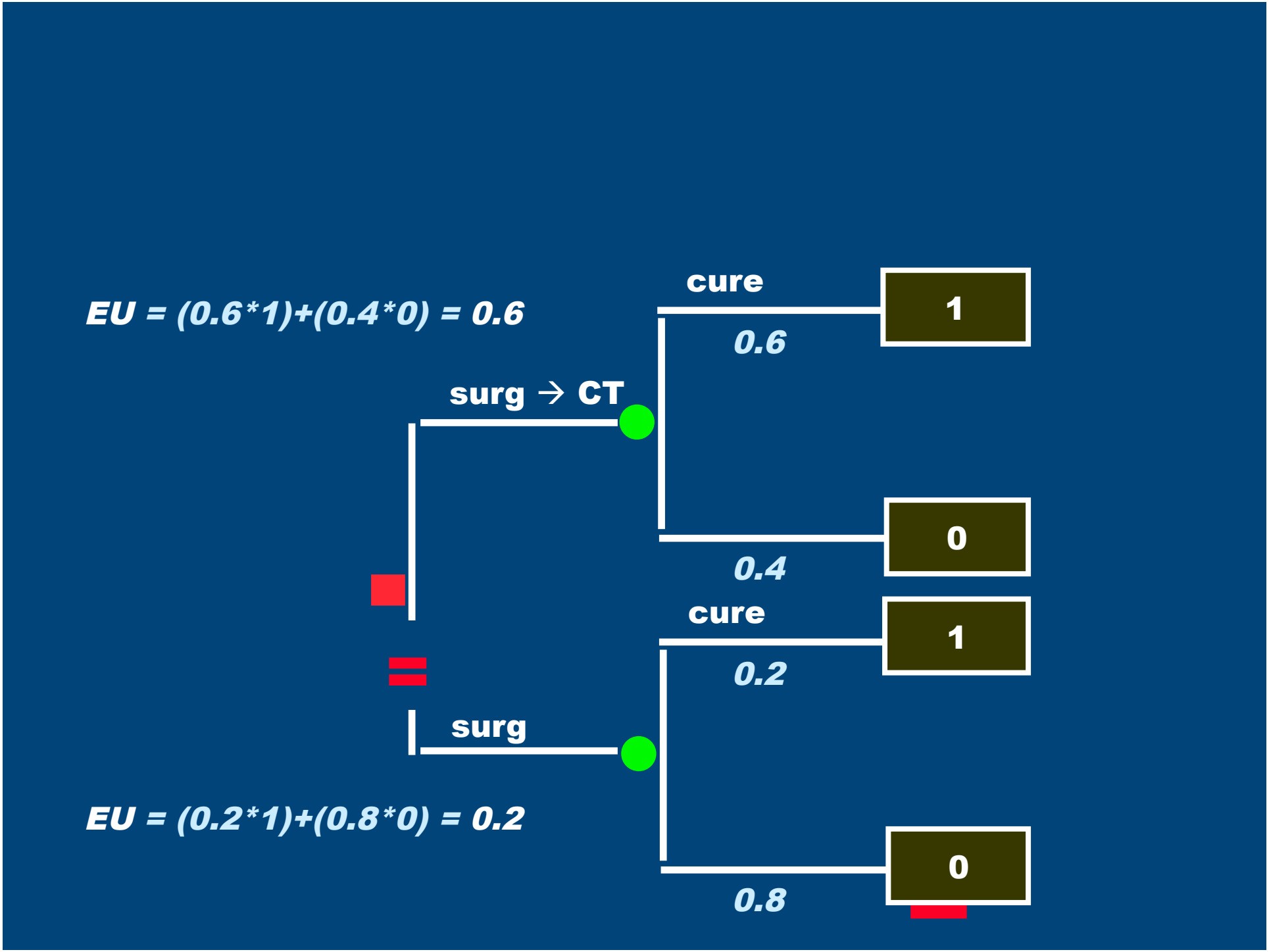
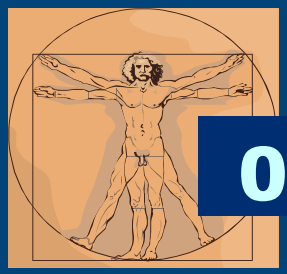




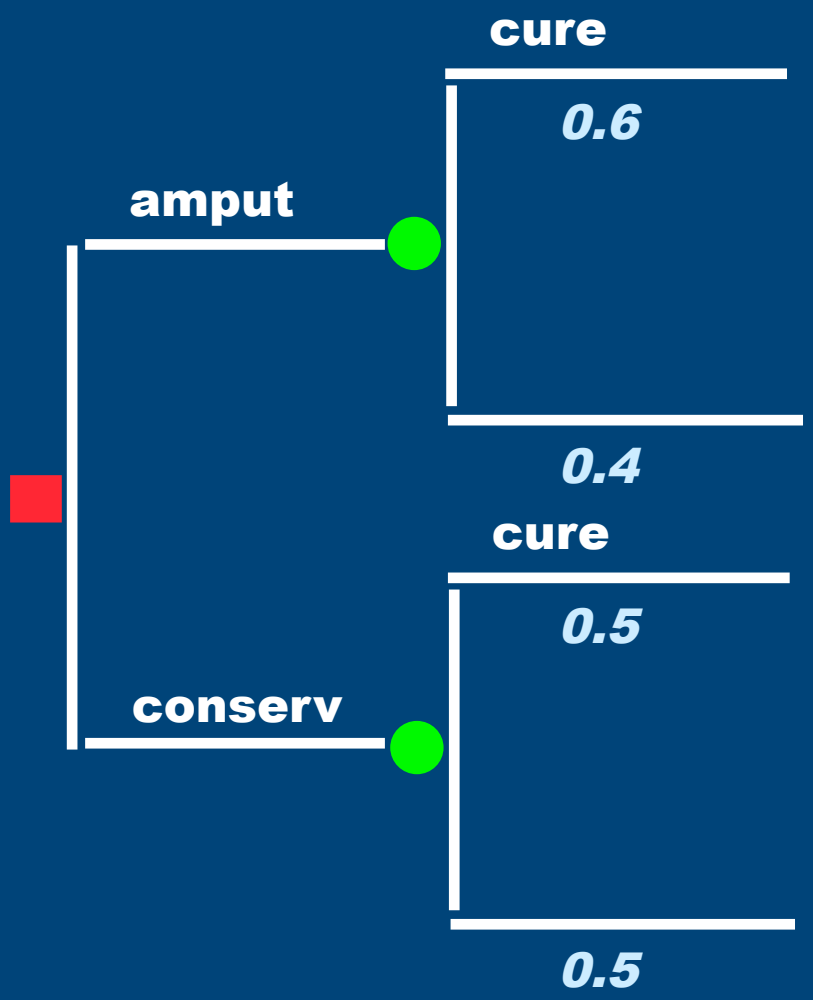

cure
0.6
surg → CT
cure
0.2
surg

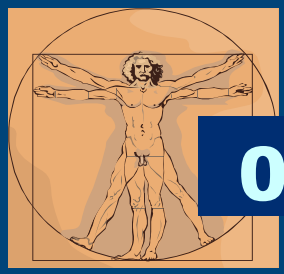

cure
1
0.6
surg → CT
0
0.4
cure
1
0.2
surg
0
0.8


EU = (0.6*1)+(0.4*0) = 0.6
cure
1
0.6
surg → CT
0
0.4
cure
1
0.2
surg
EU = (0.2*1)+(0.8*0) = 0.2
0
0.8



0 - 1





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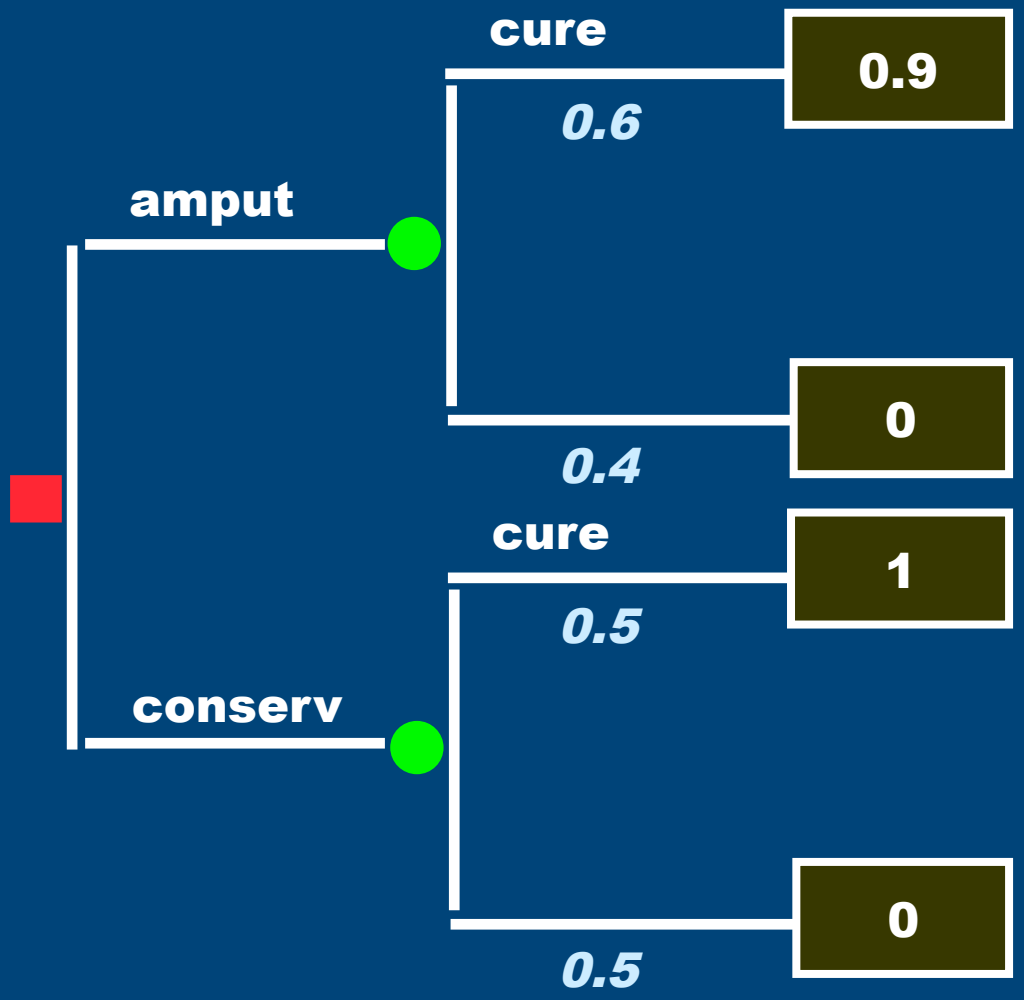
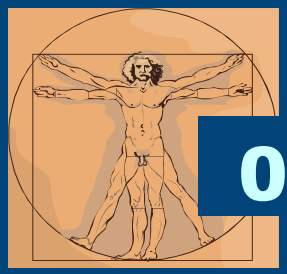




0 - 1

*EU = (0.6*0.9)+(0.4*0) = 0.54*

amput

cure

0.6

0,9

0.4

0

*EU = (0.5*1)+(0.5*0) = 0.5*

conserv

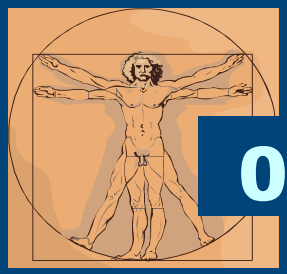
cure

0.5

1

0.5

0



0 - 1

*EU = (0.6*0.8)+(0.4*0) = 0.48*

amput

cure

0.6

0,8

0.4

0

*EU = (0.5*1)+(0.5*0) = 0.5*

conserv

cure

0.5

1

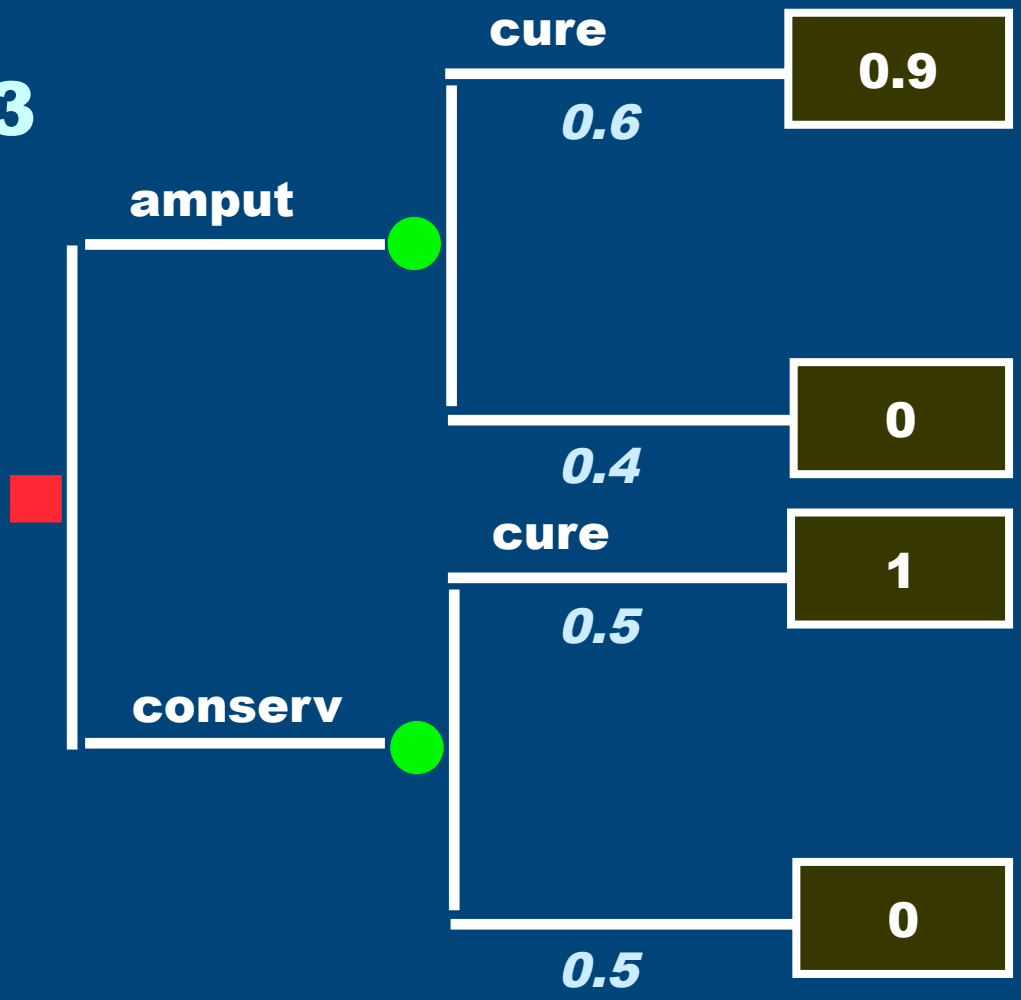
0.5

0

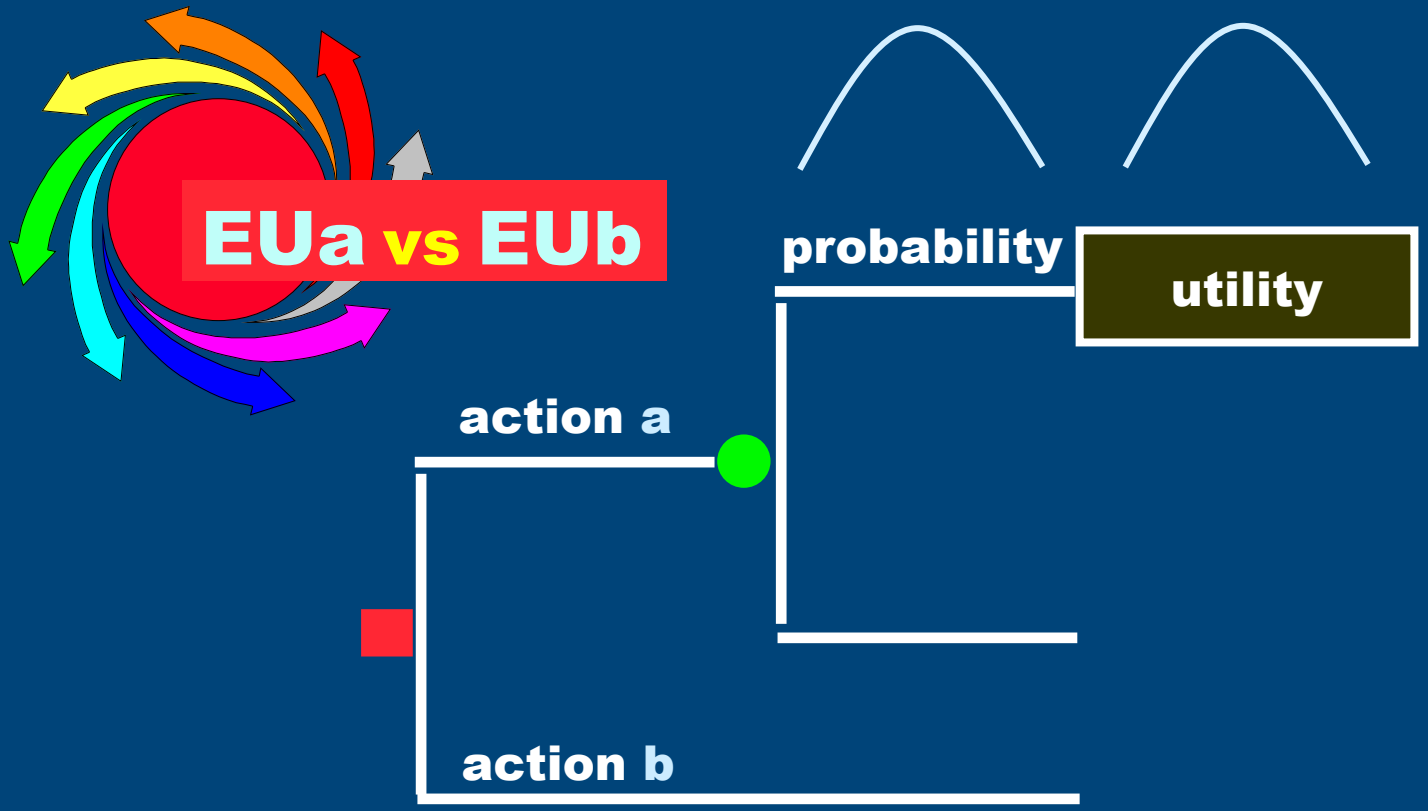
Sensitivity analysis

Pa1 = 0.55

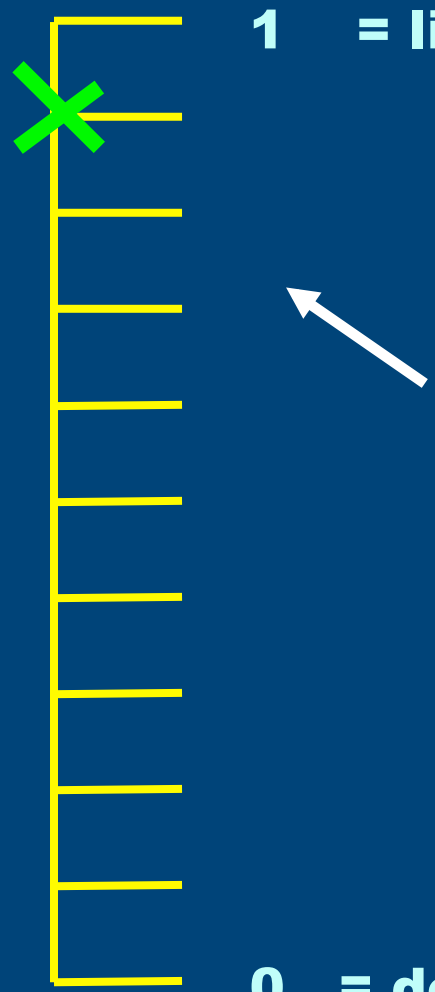
Ua1 = 0.83

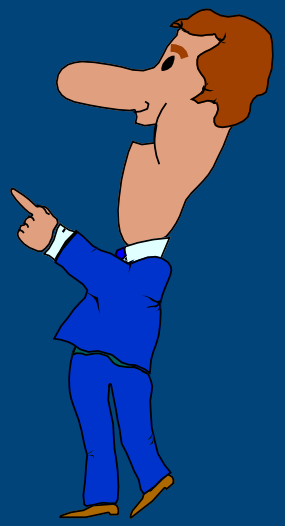


Sensitivity analysis

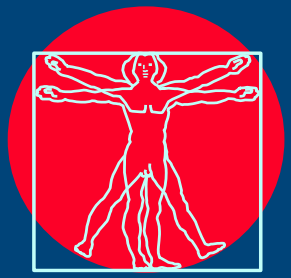


“Value”





“Utility”



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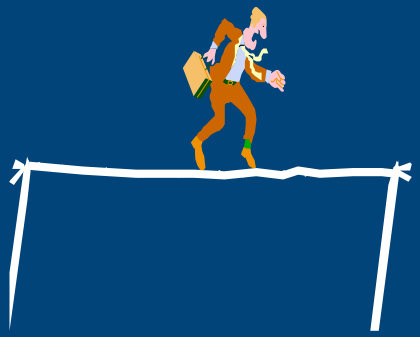
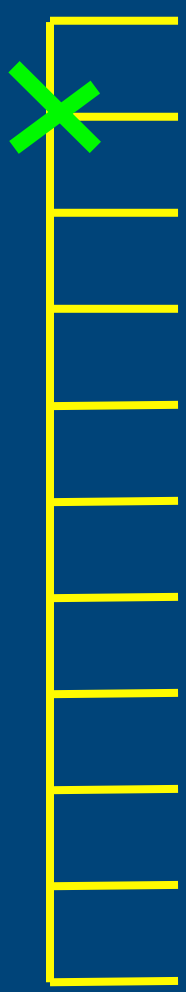


U

value
in conditions of risk

“Utility”

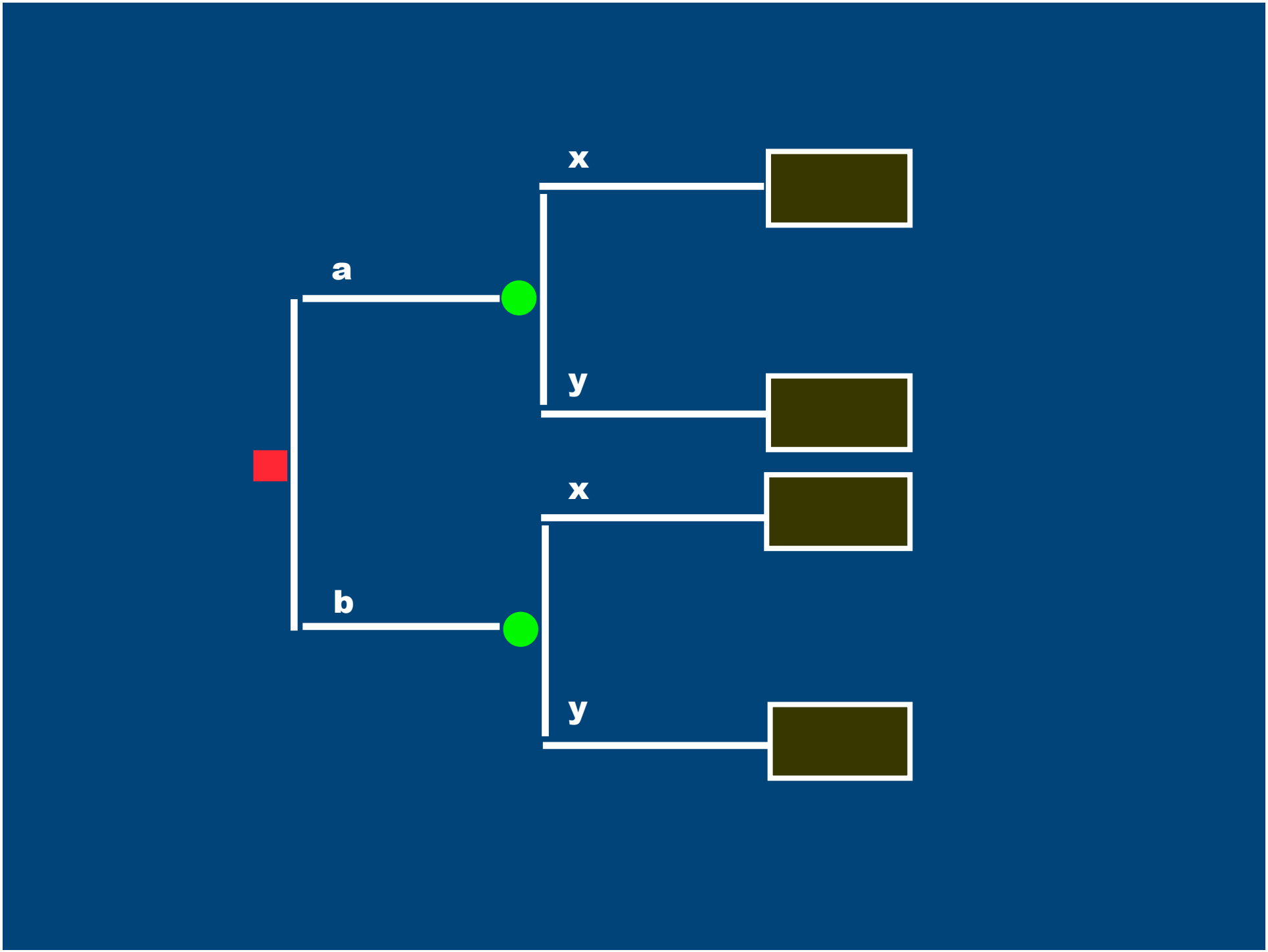


1 = life

1 - risk
=
utility

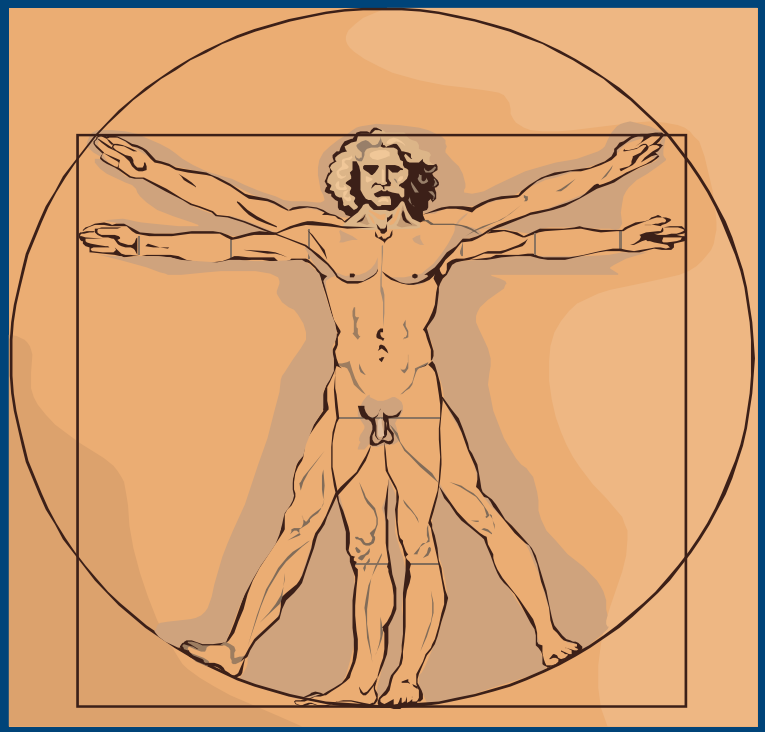
0 = death

“Which risk of dying would you accept to avoid this outcome?”

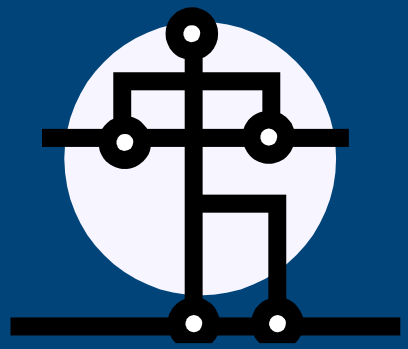

x
a
y
x
b
y

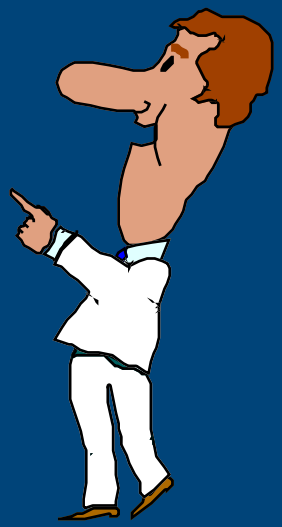
Required:

Studying quality of life in a descriptive fashion!

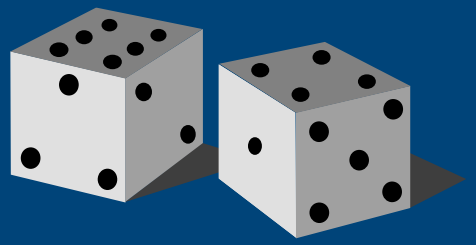


Required:
Easy elicitation of probabilities!



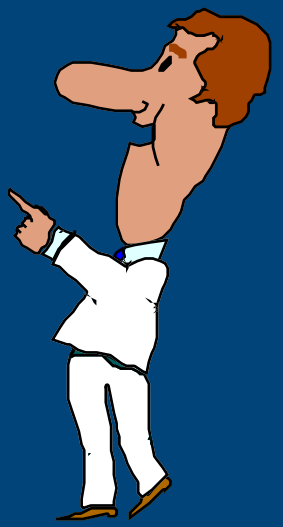


The notion of probability...

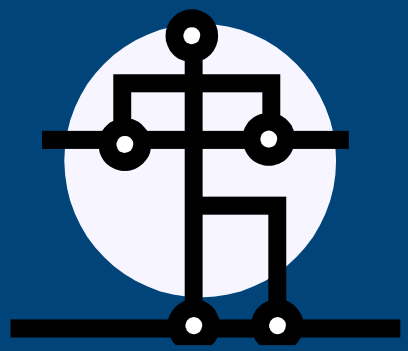


objective
frequency

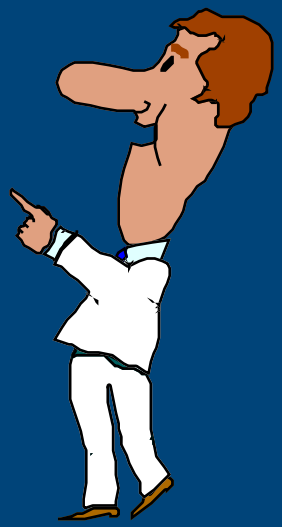
P[E]



degree of belief



subjective probability

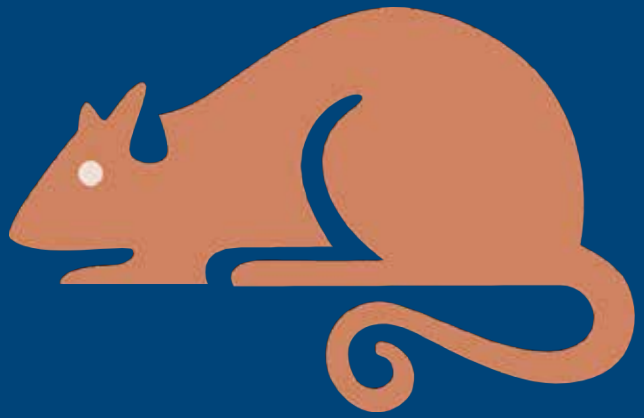


The Bayes theorem...

$$P[A|B] = P[A] \times \frac{P[B|A]}{P[B]}$$

Mr. Bayes & Mr. Price. Phil Trans 1763;53:370

The preclinical rationale...

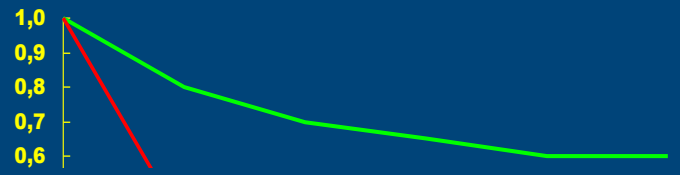


...the prior probability!

The Bayesian probability...

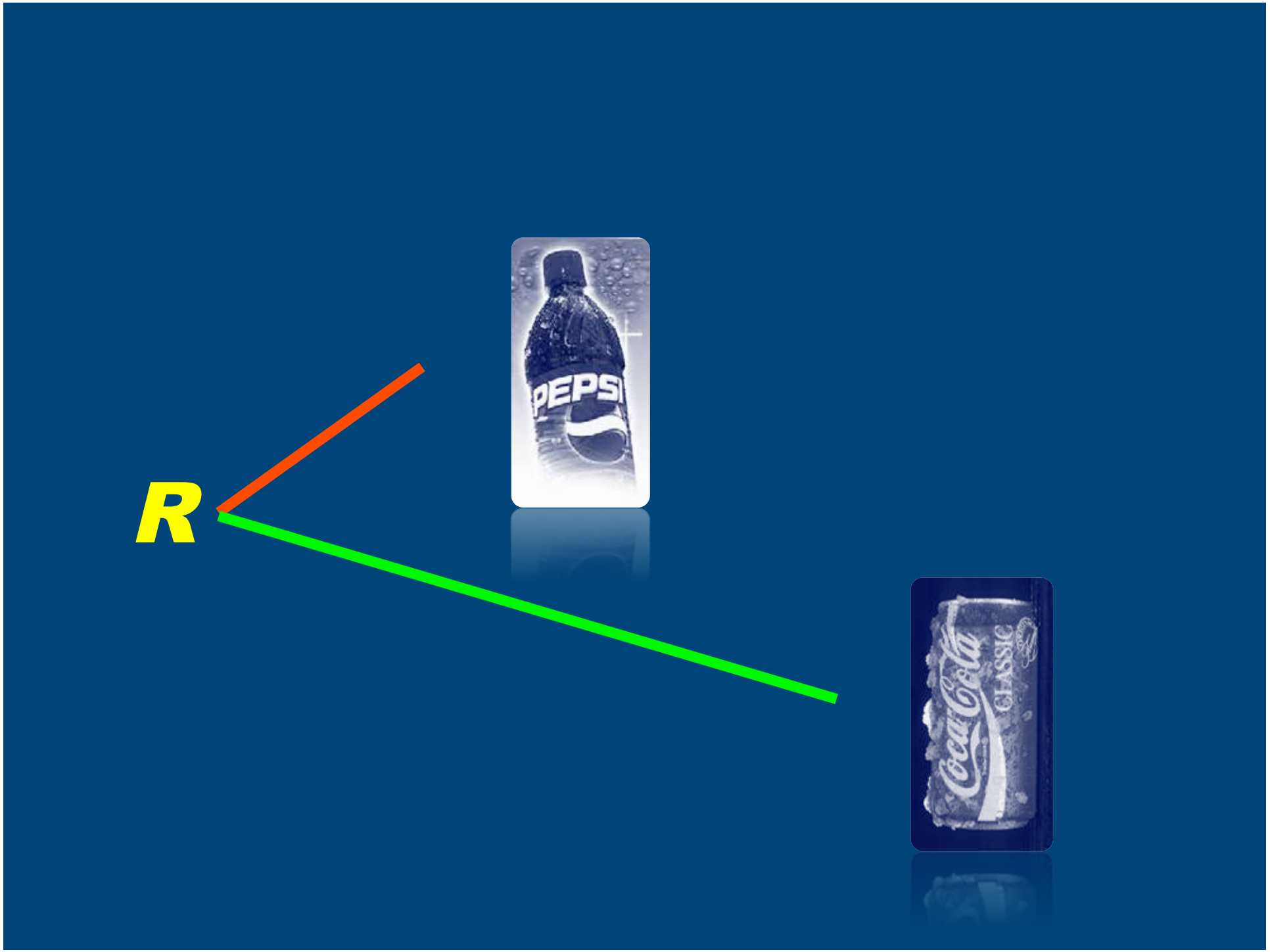
the probability
that the treatment is effective...

The frequentist probability in clinical trials...



the probability
you had to find this difference
if there were no difference
(null effect)...

p<0.05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Generalizability of Cancer Clinical Trial Results

Prognostic Differences between Participants and Nonparticipants

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BACKGROUND. The generalizability of clinical trial results is questionable, because fewer than 5% of cancer patients participate. The authors examined the comparability of clinical trial participants and nonparticipants and the potential impact of differences.

METHODS. A retrospective cohort of 19,340 cancer patients who were diagnosed between January 1990 and December 1997 was characterized by trial participation. The distributions of prognostically important factors among trial participants were compared with the distributions among nonparticipants and the population of patients diagnosed during the same period in the Surveillance, Epidemiology, and End Results population. The impact of these factors on survival was examined by using a Cox proportional hazards analysis.

RESULTS. Trial participants were younger and had better performance status and fewer comorbid conditions compared with nonparticipants. However, participants were more likely to have locally advanced disease, positive lymph node status, poorly differentiated tumors, liver metastases, and multiple metastatic sites. The former factors were associated with significantly longer survival, whereas the later factors were associated with significantly shorter survival.

CONCLUSIONS. The lack of comparability between trial participants and nonparticipants called into question the generalizability of clinical trial results. Although selective recruitment for clinical trials is justified, the authors encourage the use of population-based trials of effectiveness in "all comers." ***Cancer*** **2006;106:2452–8.**

Generalizability of Cancer Clinical Trial Results

Elting et al.[1] have demonstrated that a number of characteristics differ between patients with cancer who do and do not participate in randomized controlled trials. Many of these characteristics are associated with the likelihood of survival, leading the authors to conclude that the lack of comparability between trial participants and nonparticipants calls into question the generalizability of clinical trial results. They go on to assert that, after initial evaluation of selected patients in randomized trials, large, population-based effectiveness trials of all comers will be needed to provide realistic benefits of treatment in general oncology practice. I disagree with both conclusions.

1. Just because trial participants and nonparticipants differ in certain ways does not mean that the impact of cancer treatment or prevention activities will differ between them. What would call into question the generalizability of the results of a given trial would be either: a) a suggestion that, in 1 or more subgroup(s) of the trial participants, the overall result did not apply (recognizing that many such suggestions turn out to be false positive[2]); or b) specific reasons (eg, genetic, hormonal, metabolic) to believe that some groups of patients ought to be atypical in their response to the therapy. Although exceptions do occur (eg, the apparently greater efficacy of epidermal growth factor receptor tyrosine-kinase inhibitors among Asian patients with lung cancer[3]), generally, the influence of treatment does not differ enough across patient subgroups to bear on the decision whether or not to use that therapy.

2. Once results of initial trials are available in selected patients, equipoise often no longer exists. In such a circumstance, a similar trial based on all comers would not be ethical to undertake.

Elting et al. argue that, because fewer than 5% of patients with cancer participate in randomized controlled trials, the generalizability of the results of those trials is questionable. I suggest that, if the quality of these trials is high, then we should not hesitate to generalize from them—that's how science works!—barring some *specific* reasons to believe that the study participants and patients in question ought to differ in their response to the particular therapy.

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How to generalize efficacy results of randomized trials: recommendations based on a systematic review of possible approaches

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Keywords
applicability, external validity, generalizability, guidelines, randomized controlled trials

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Abstract

Rationale, aims and objectives Randomized controlled trials (RCTs) are the preferred source for evidence for the effect of treatment. However, patients participating in RCTs often manifest important differences from patients seen in practice. Therefore, guideline developers have to decide whether the results are generalizable to the target population not represented in RCTs.

Method A systematic review of the literature was undertaken to identify methods to decide whether to generalize the results from RCTs to patients who were not represented in these trials.

Results One approach is to examine the in- and exclusion criteria of trials and infer from these whether the trial population was sufficiently representative. Other authors suggest, because of the inclusion of a broader range of patients, reliance on observational studies if no direct evidence for the target population is available.Another approach is to apply the relative effect of treatment found in trials to patients in practice unless there is a compelling reason to believe the results would differ substantially as a function of particular characteristics of those patients. Although there are exceptions, this approach is supported by empirical evidence that, in general, relative effect of treatment on benefit outcomes seldom differs to an important extent across subgroups of patients.

Conclusion We propose this last approach: focusing on RCTs unless there is a compelling reason not to do so. Compelling reasons will most often be found with respect to issues of rare adverse effects, for which observational studies are likely to provide the best estimates.

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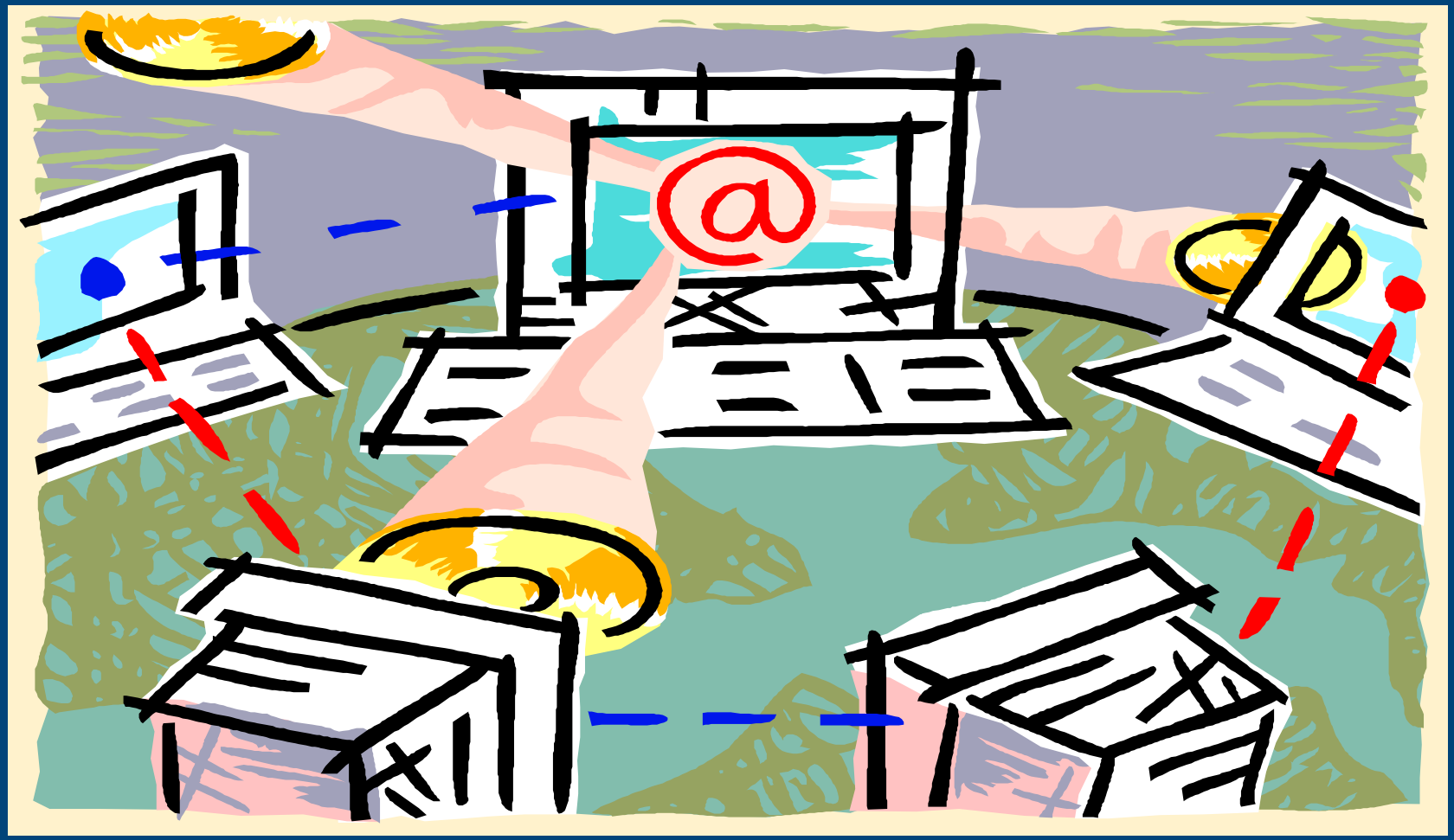
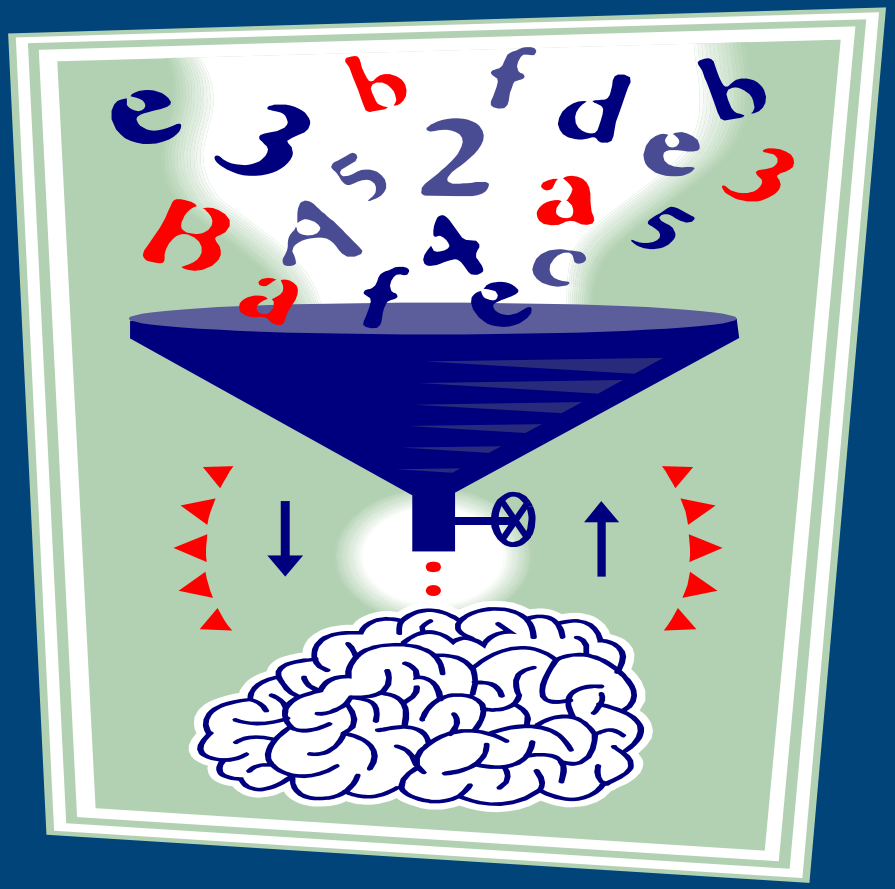
Box 1 Process of evaluation of compelling reasons that might limit generalizability, adapted from Dans *et al.* [15])

Issues	Questions
Biologic	**1** Are there pathophysiologic differences in the illness under study that may lead to a diminished treatment response?
	2 Are there patient differences that may diminish the treatment response?
Social and economic	**3** Are there important differences in patient compliance that may diminish the treatment response?
	4 Are there important differences in provider compliance that may diminish the treatment response?
Epidemiologic	**5** Do my patients have co-morbid conditions that significantly alter the potential benefits and risks of the treatment?
	6 Are there important differences in untreated patients' risk of adverse outcomes that might alter the efficiency of treatment?

Collaborative networks / EPR



«Big data»...



Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Gordon C S Smith, Jill P Pell

Parachutes reduce the risk of injury after gravitational challenge, but their effectiveness has not been proved with randomised controlled trials

topic

Parachutes are widely used to prevent death and major injury after gravitational challenge

Parachute use is associated with adverse effects due to failure of the intervention and iatrogenic injury

Studies of free fall do not show 100% mortality

What this study adds

No randomised controlled trials of parachute use have been undertaken

The basis for parachute use is purely observational, and its apparent efficacy could potentially be explained by a "healthy cohort" effect

Individuals who insist that all interventions need to be validated by a randomised controlled trial need to come down to earth with a bump

BMJ 2003;327:1459

The Rational Clinical Examination

Evidence-Based Medicine

A New Approach to Teaching the Practice of Medicine

Evidence-Based Medicine Working Group

JAMA 1992;268:2420

The Pandora Box, J.W. Waterhouse - 1896

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