Introduction to Diagnostic Accuracy Reviews

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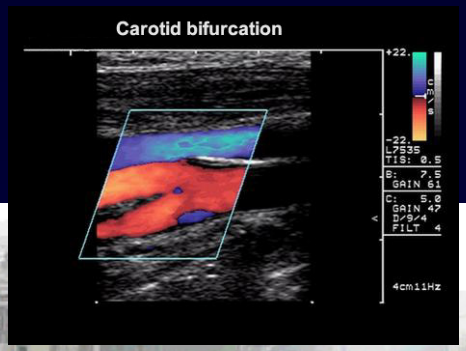
HIV-
HBsAg
hCG
COMBO
SIGNIFY


Carotid bifurcation
+22
-22
LF535
TIS: 0.5
B: 7.5
GAIN 61
C: 5.0
GAIN 47
D/S/4
FILT 4
4cm11Hz


Range/Bettmann/UPI

Overall Goal

To perform high quality and clinical relevant reviews of diagnostic test accuracy

Good Diagnostic Accuracy Reviews

- High quality methodology
  - searching and locating
  - quality assessment
  - statistical analysis

Handbook

- Continental Europe Support Unit
- Editorial process for Cochrane reviews

Relevant Diagnostic Accuracy Reviews

- Clinical useful accuracy reviews:
  - clear and focussed question
  - accuracy helpful in answering the question?

- Selecting and phrasing the right questions for diagnostic reviews is the biggest challenge

Outline

- Inherent complex nature of diagnostic research
- Role of accuracy studies
- Key features of accuracy studies
- Focussed questions for accuracy reviews

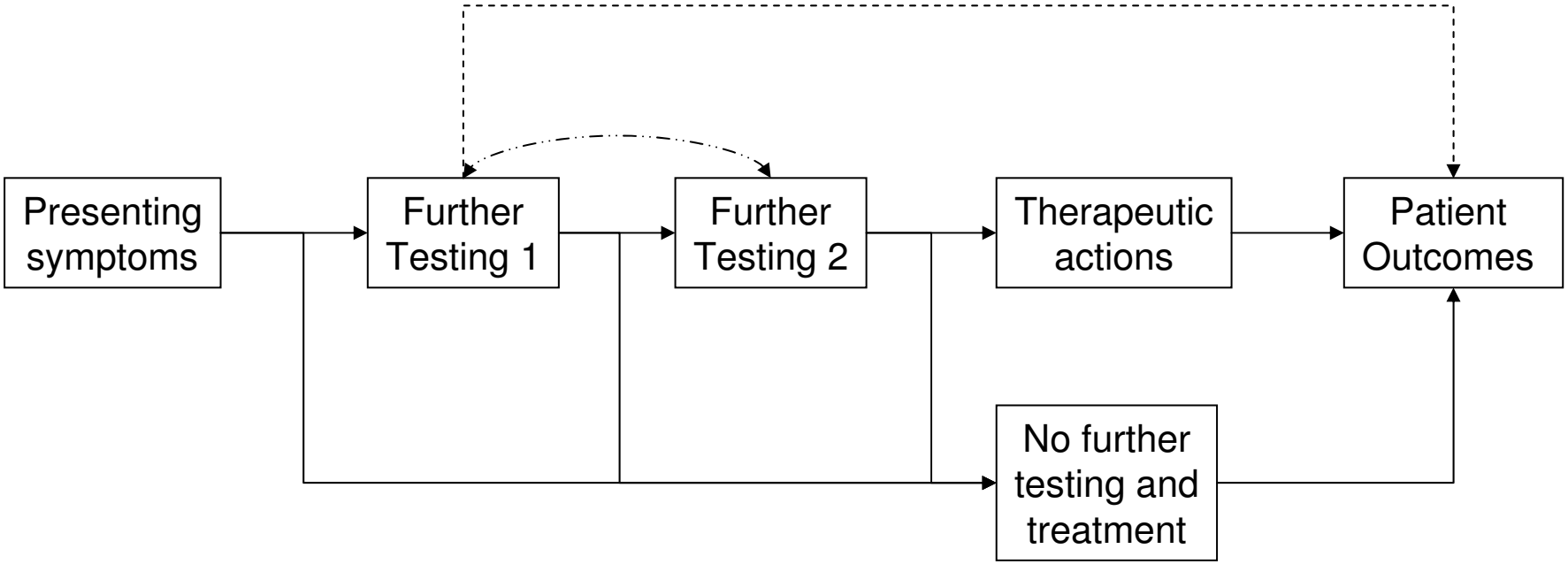
Diversity Diagnostic Research

- "Tests": any method to obtain information on the patient's health status
- Role of tests: making a diagnosis, but also staging, screening, selecting treatment, monitoring health

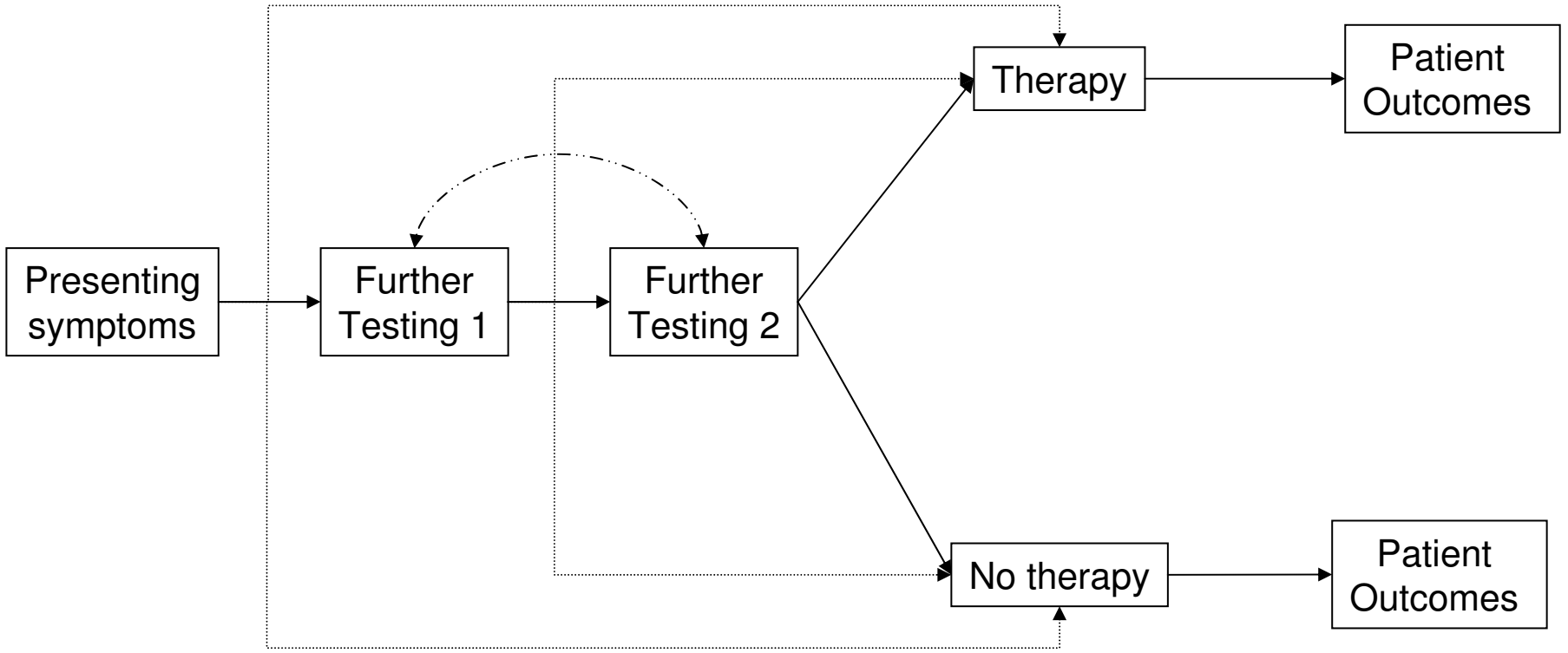
Complexity of Diagnostic Process

- Multiple tests can be performed
- Multiple diseases can be responsible for presenting symptoms
- Dynamic and multistage process

Multistage, Multidimensional Diagnostic Process



Multistage, Multidimensional Diagnostic Process

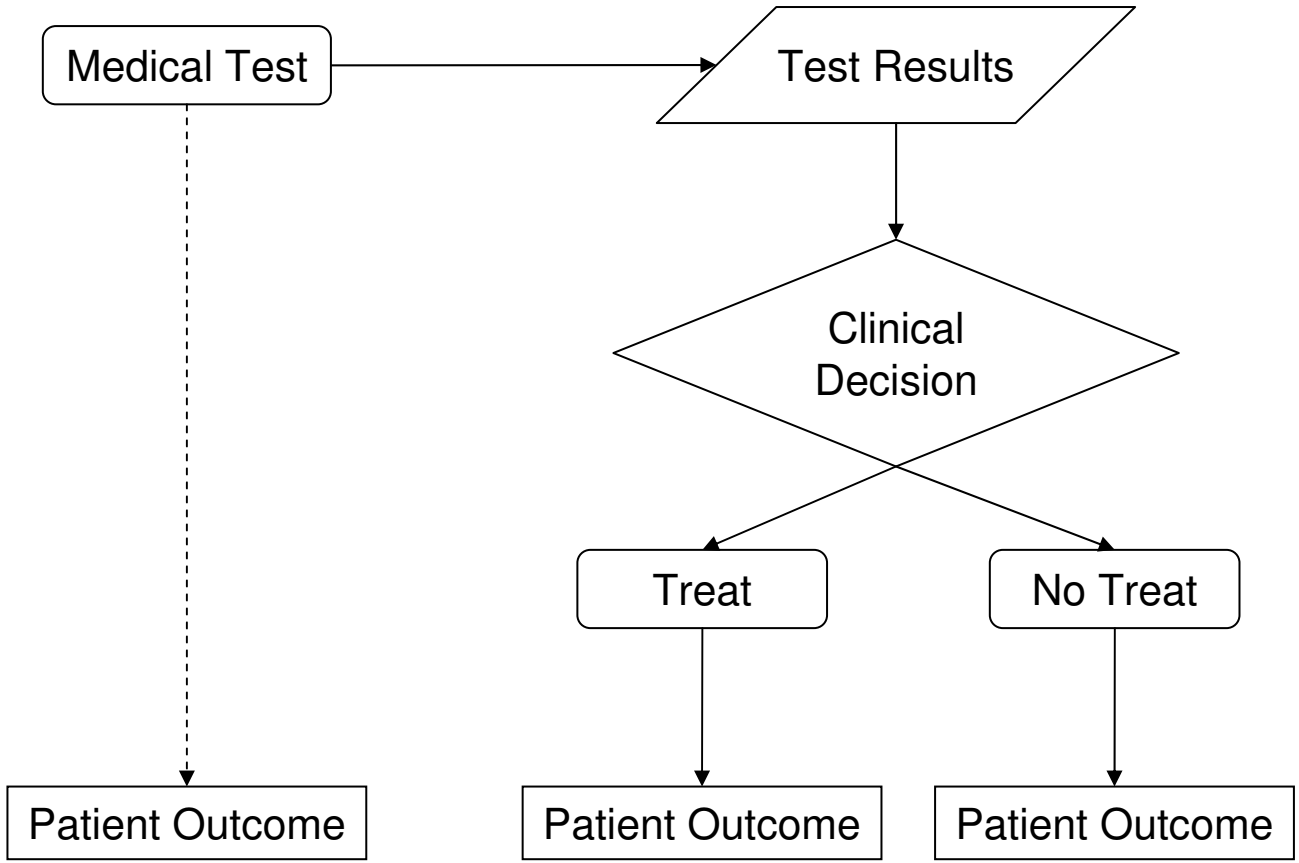


Cave: focus on single disease

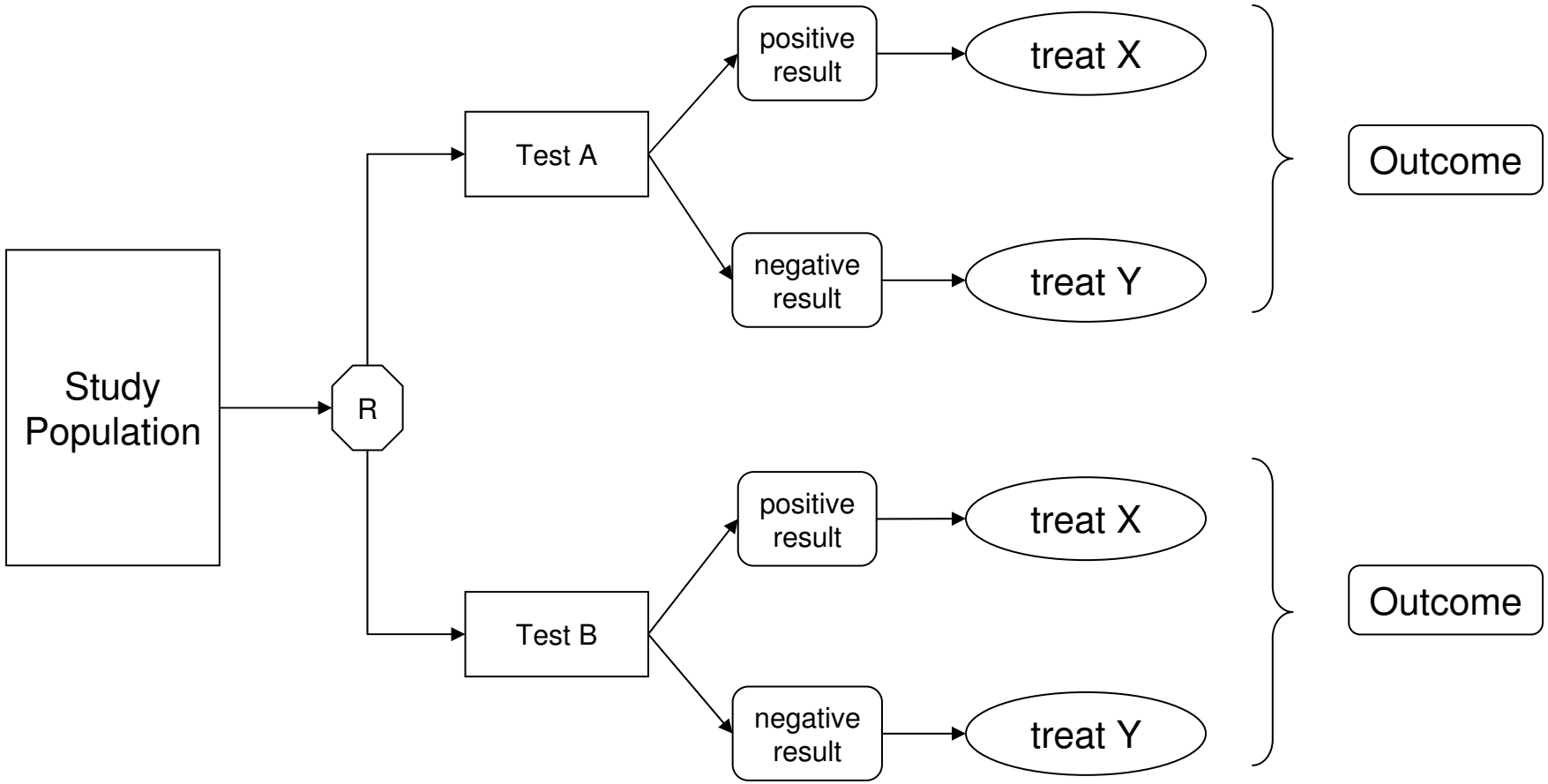
Randomized Trial of Tests

- Specific point in diagnostic work-up (final stage)
- Question: should we do Test A or B?
- Goal: directly observe whether patient outcomes are better with strategy based on test A than on test B

Relation between Tests and Patient Outcomes



RCT of test-treatment combinations



THE LANCET

Randomised controlled trial of faecal-occult-blood screening for colorectal cancer

Jack D Hardcastle, Jocelyn O Chamberlain, Michael H E Robinson, Susan M Moss, Satya S Amar, Tom W Balfour, Peter D James, Christine M Mangham

Summary

Background There is growing evidence that faecal-occult-blood (FOB) screening may reduce colorectal cancer (CRC) mortality, but this reduction in CRC mortality has not been shown in an unselected population-based randomised controlled trial. The aim of this study was to assess the effect of FOB screening on CRC mortality in such a setting.

Methods Between February, 1981, and January, 1991, 152 850 people aged 45–74 years who lived in the Nottingham area of the UK were recruited to our study. Participants were randomly allocated FOB screening (76 466) or no screening (controls; 76 384). Controls were not told about the study and received no intervention. Screening-group participants were sent a Haemoccult FOB test kit with instructions from their family doctor. FOB tests were not rehydrated and dietary restrictions were imposed only for retesting borderline results. Individuals with negative FOB tests at the first screening, together with those who tested positive but in whom no neoplasia was found on colonoscopy, were invited to take part in further screening every 2 years. Screening was stopped in February, 1995, by which time screening-group participants

people died from CRC in the screening group compared with 420 in the control group—a 15% reduction in cumulative CRC mortality in the screening group (odds ratio=0·85 [95% CI 0·74–0·98], p=0·026).

Interpretation Our findings together with evidence from other trials suggest that consideration should be given to a national programme of FOB screening to reduce CRC mortality in the general population.

Lancet 1996; **348:** 1472–77

See Commentary page 1463

Introduction

Colorectal cancer (CRC) is the second commonest cause of death from malignant disease in England and Wales, and resulted in about 16 000 deaths in 1993.[1] Although there have been advances in the management of symptomatic CRC, there has been little overall reduction in CRC mortality during the past 30 years. Tumour stage is an important determinant of outcome; 24–28% of patients have metastatic disease at presentation and the tumour is confined to the bowel wall in only 6–10% (Dukes' stage A).[2–4] Early diagnosis before the

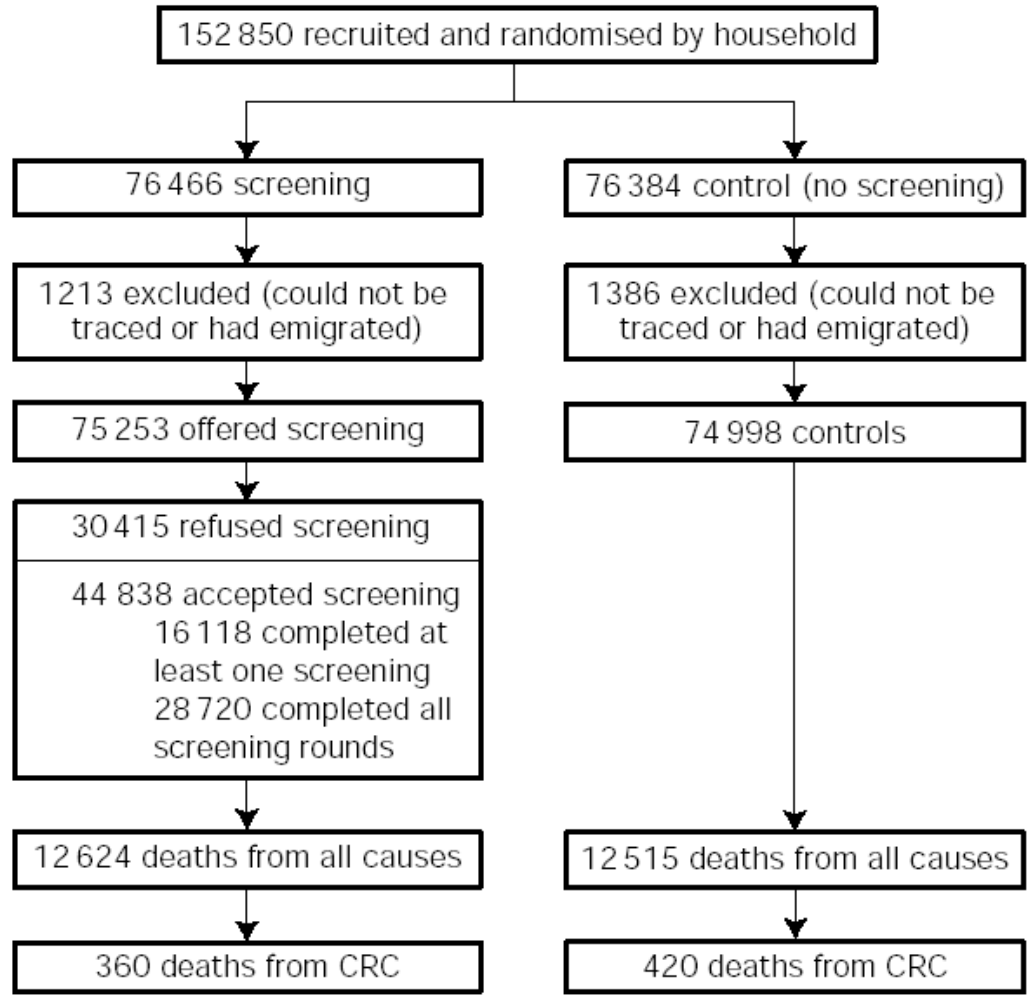


Figure 1: **Trial profile**

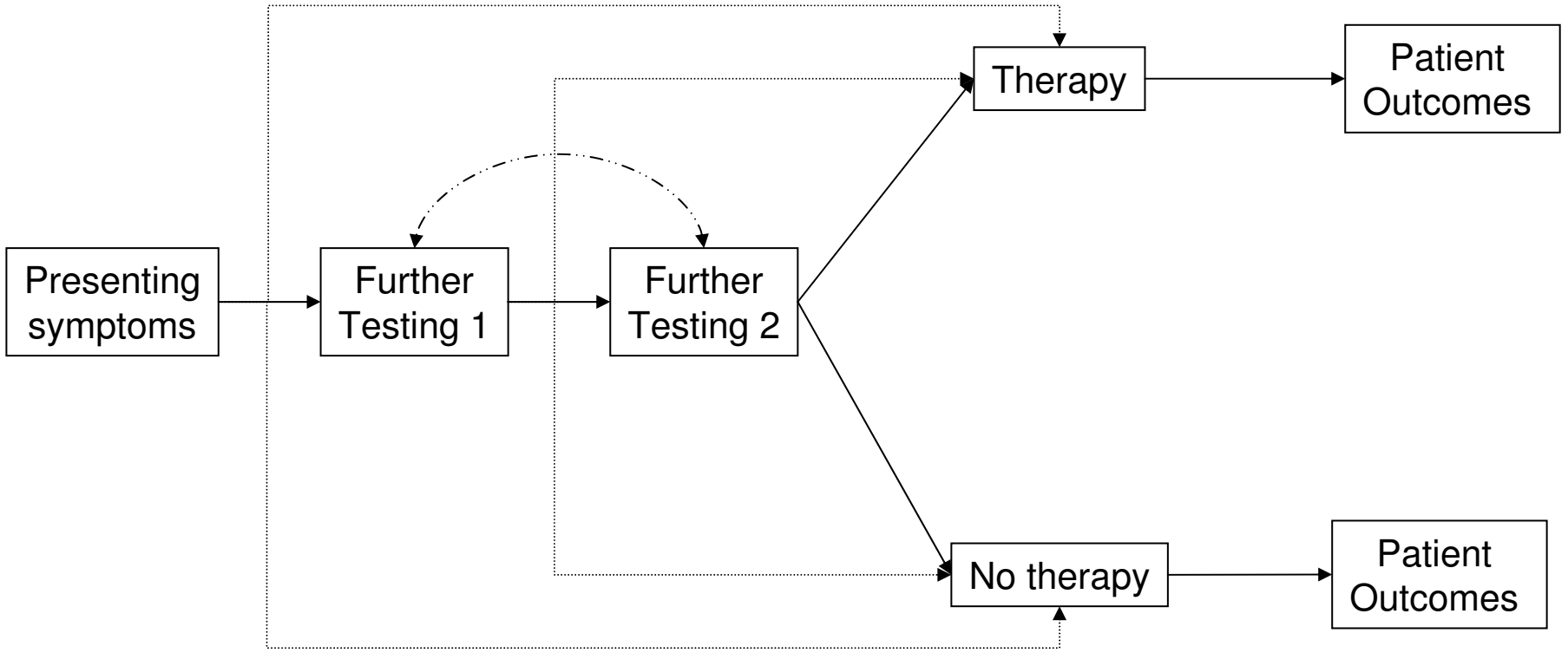
Lancet 1996;348:1473

RCT of Testing

- Best evidence of effectiveness, but rare
- Usually need large sample sizes
- Dynamic, multi-stage nature of diagnostic process leads to infinite number of trials

- Intervention handbook of Cochrane can be used to review such trials

Multistage, Multidimensional Diagnostic Process



Cave: focus on single disease

Classical Diagnostic Thinking

- *Multivariable Approach:*
  - probability disease being present given clinical profile
  - multiple pieces of information
  - estimate independent contribution (weight)
  - multivariable analysis
  - clinical decision rules

Wells Rule for DVT

Table 1. **The Wells Rule To Estimate the Probability of Deep Venous Thrombosis**

Clinical Feature	Score
Active cancer	1
Paralysis, paresis, or recent plaster immobilization of the lower extremity	1
Recently bedridden for more than 3 days or major surgery within 4 weeks	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling by more than 3 cm when compared with the asymptomatic leg	1
Pitting edema (greater in the symptomatic leg)	1
Collateral superficial veins (nonvaricose)	1
Alternative diagnosis as likely or more possible than that of deep venous thrombosis	−2

Possible Review Questions in Rules

- What is the optimal weight for a specific item?
- Selection of best subset of items
- Focus is on multivariable adjusted weights. Not possible in Cochrane

Landscape of Diagnostic Research

"Multivariable approach"

- probability disease given profile
- multiple pieces of information
- estimate independent contribution
- multivariable analysis
- clinical decision rules

Review:
pooling of regression weights

Cochrane: NO

Other Forms of Test Evaluation

- technical evaluation
- diagnostic accuracy

Randomised Trials of Testing

- randomise between test-treatment combinations
- compare clinical outcomes

Review of RCT's

Cochrane: YES
but use framework of intervention reviews

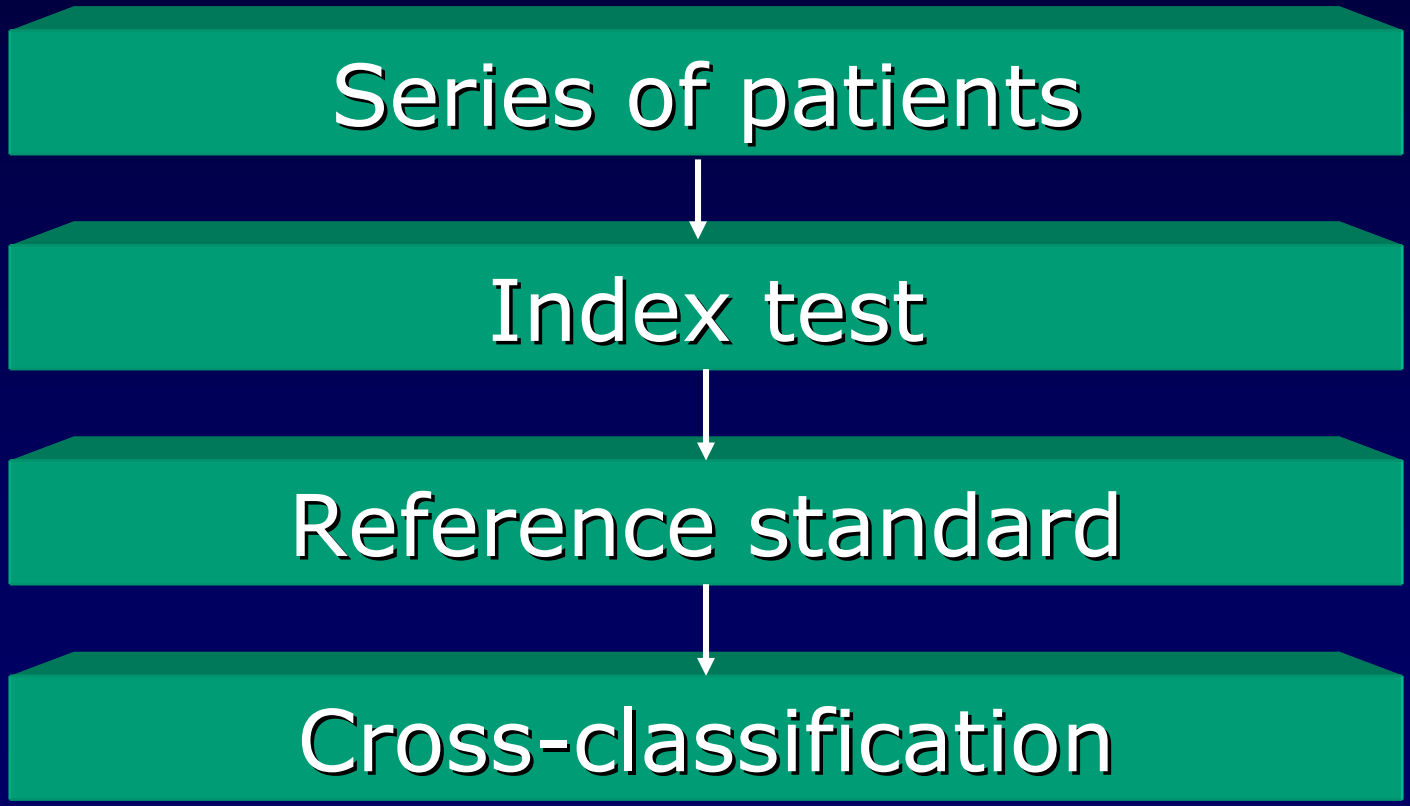
Test Evaluation

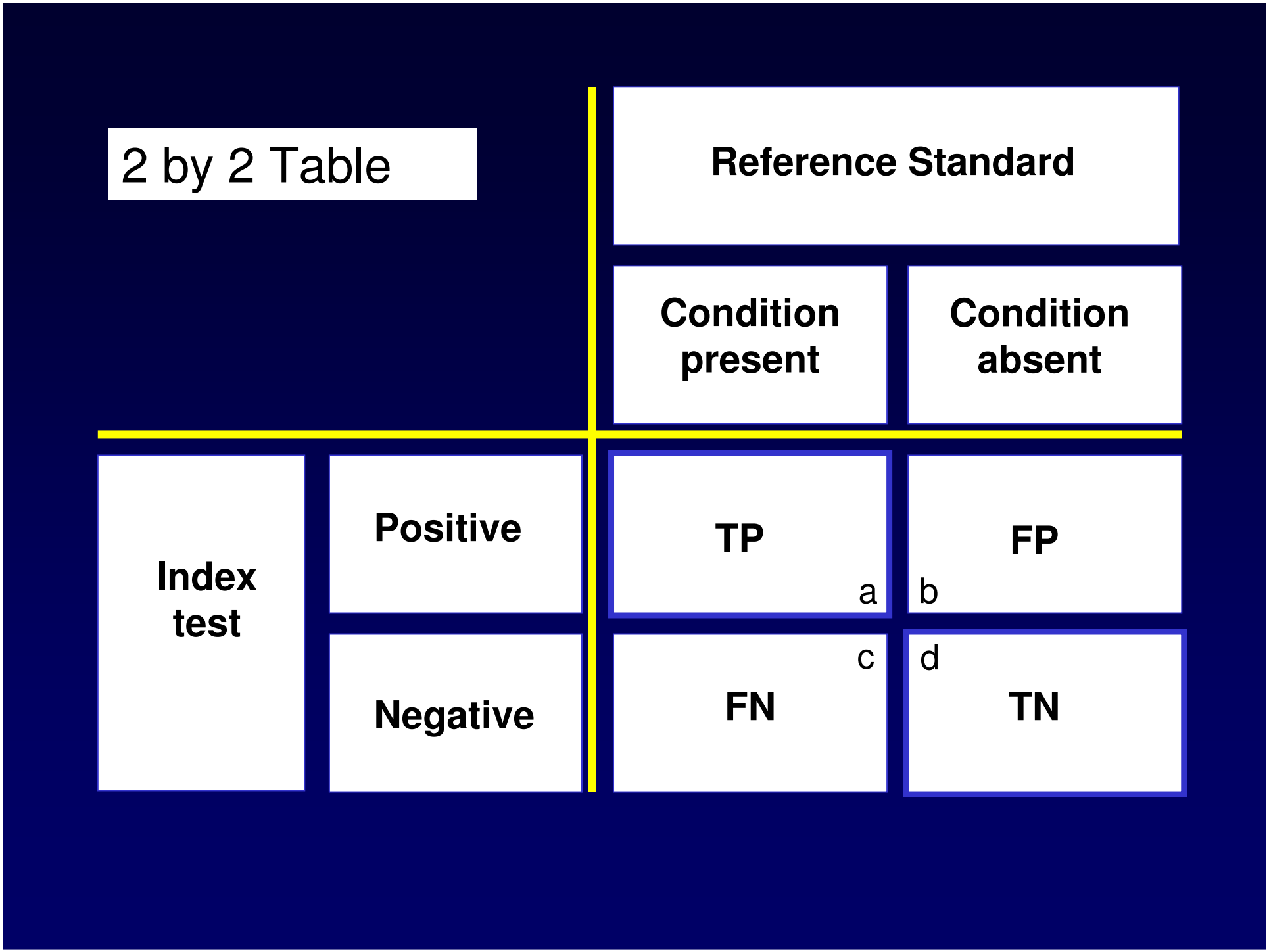
- Early technical evaluation: repeatability & reproducibility, inter-observer variability
- Diagnostic accuracy
- Patient outcome / cost-effectiveness

Diagnostic Accuracy Studies

- Test under evaluation (index test) and reference standard in all patients
- Compare the results of the index test(s) with the results of reference standard: cross sectional relationship
- Accuracy refers to the amount of agreement

Basic Design




2 by 2 Table
Reference Standard
Condition present
Condition absent
Index test
Positive
Negative
TP
a
FP
b
c
FN
d
TN

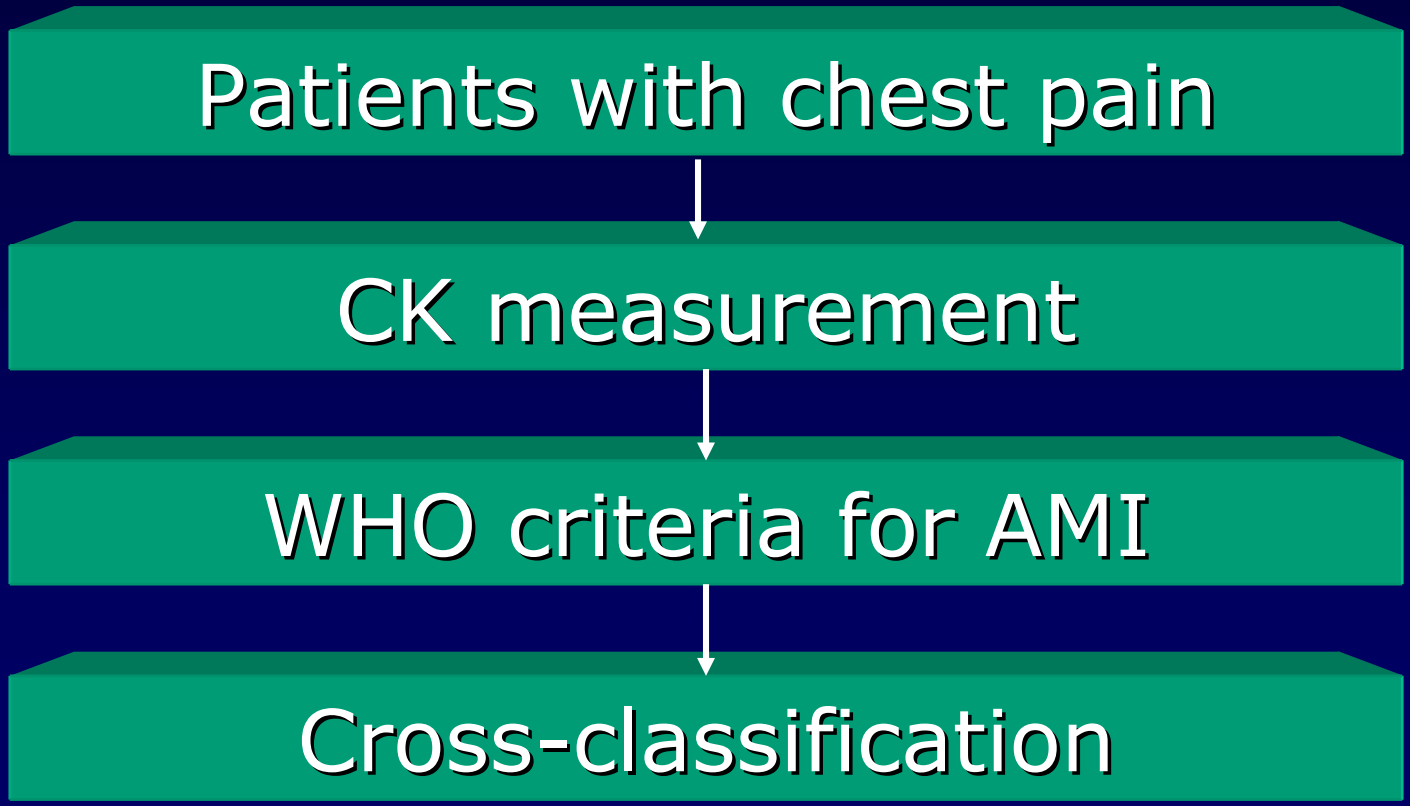
Clinical Problem

- Patient with chest pain suggestive for acute myocardial infarction (AMI)
- Index test: creatine kinase (CK) measurement
- Do low values of CK measurement rule out myocardial infarction (triage)?

Anatomy of Accuracy Study

- Target population: patients with chest pain
- Index test: CK measurement
- Target condition: acute myocardial infarction
- Final diagnosis based on WHO criteria (reference standard):
  - clinical outcome
  - ECG-changes
  - enzym values
  - autopsy

Example

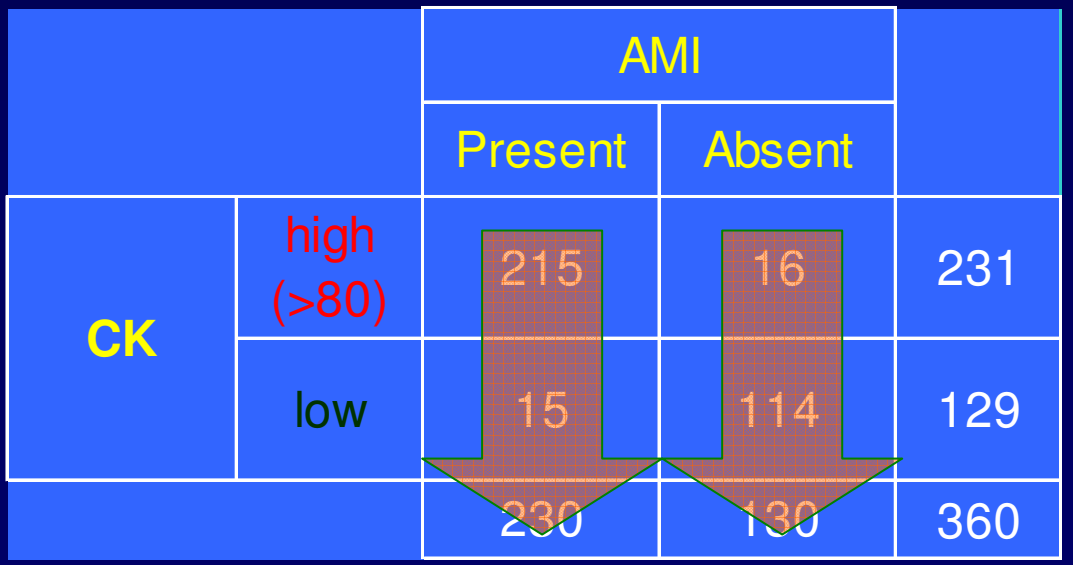

Patients with chest pain
CK measurement
WHO criteria for AMI
Cross-classification

Results of CK Study

		AMI		
		Present	Absent	
CK	high (>80)	215 (a)	16 (b)	231
	low	15 (c)	114 (d)	129
		230	130	360

Test Accuracy Measures

- sensitivity 215 / 230 = 93%
- specificity 114 / 130 = 88%
- odds ratio: (215/15) / (16/114) = 102

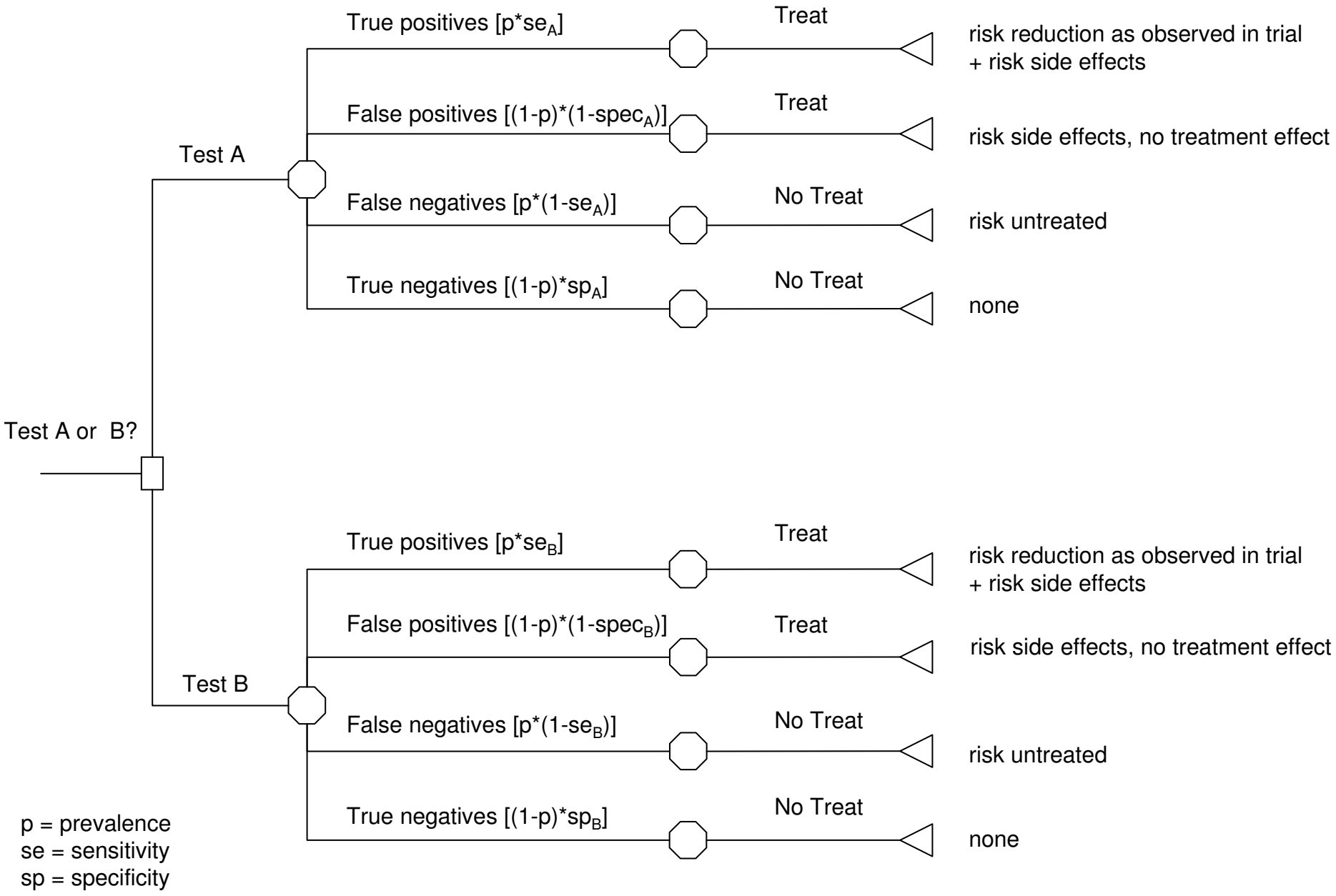


Role of Accuracy Studies

Relevant and focused questions

View on Accuracy

- Accuracy can be seen as a surrogate for clinical outcomes
- Evidence from accuracy studies combined with existing data about effectiveness can predict the outcome of hypothetical trial

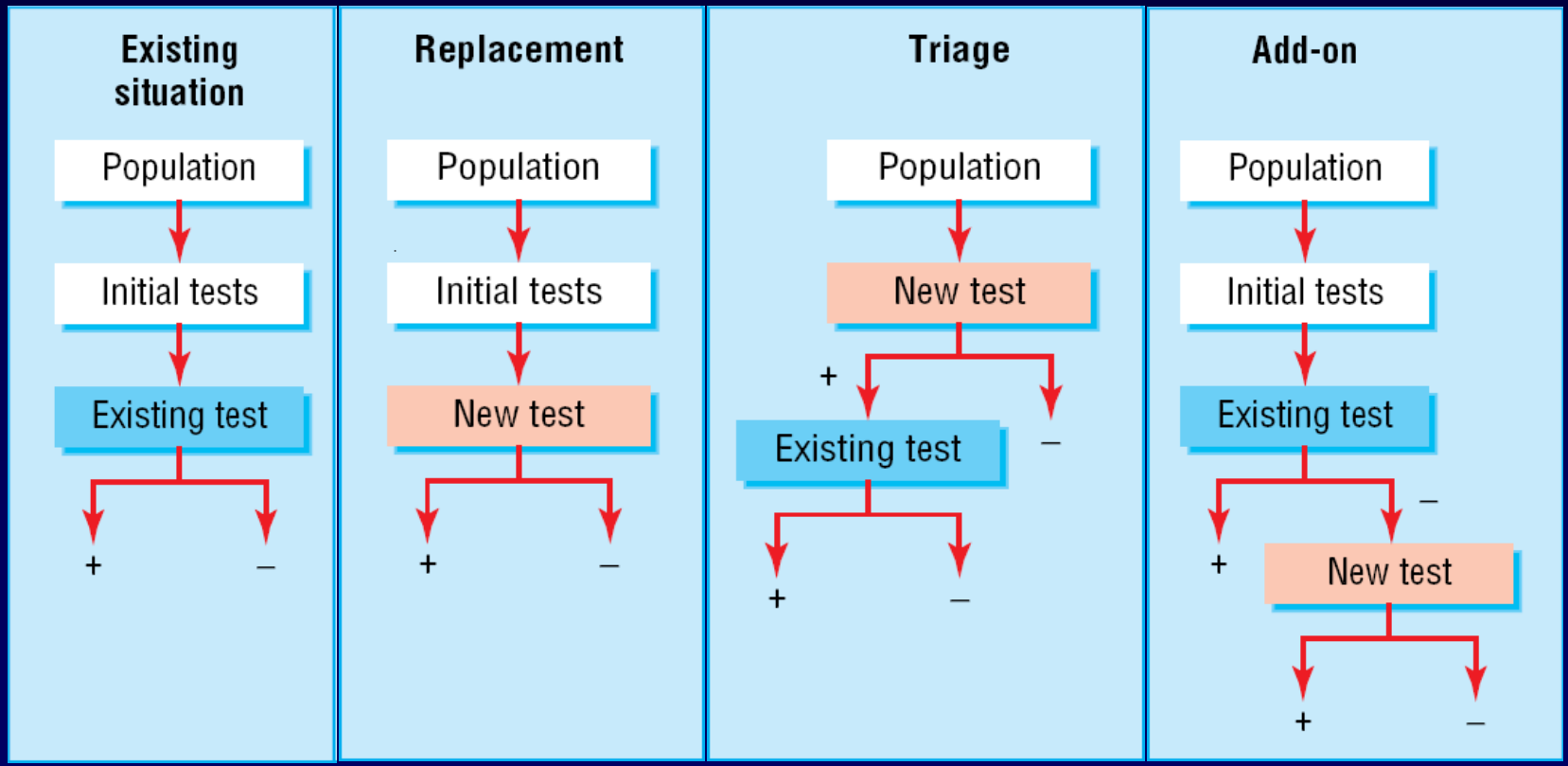


Sutton et al. Integration of meta-analysis and economic decision modelling for evaluating tests. MDM 2008

Relevant Accuracy Questions

- Describe existing diagnostic pathway
- Formulate the intended role of the index test (triage, replacement, add-on)

Roles of Test



Bossuyt et al. BMJ 2005;332:1089-92

Intended Role of Test

- Describing the change in the diagnostic pathway is helpful for:
  - patient selection
  - selecting the right comparator test
  - choice and interpretation of accuracy measures

Landscape of Diagnostic Research

"Multivariable approach"

- multiple pieces of information
- estimate independent contribution
- multivariable analysis
- probability disease given profile
- clinical decision rules

Review:
pooling of regression weights

Cochrane: NO

Other Forms of Test Evaluation

Phased approach

- technical evaluation
- diagnostic accuracy
- clinical outcomes

Key question:
Is accuracy sufficient?

Review of accuracy studies

Cochrane: YES

Randomised Trials of Testing

- randomise between test-treatment combinations
- compare clinical outcomes

Review of RCT's

Cochrane: YES
but use framework of intervention reviews

Take Home Messages

- Focus of accuracy reviews is on test evaluation
- The ultimate goal is to determine whether change in testing improves patient outcomes
- Randomized trials of test-treatment combinations provide the best direct evidence
- Accuracy studies meaningful if their design match the intended role