Evidence-based Chemistry in Critical Care

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Objectives

- Clinical Decision making
- What is EBM
- Why EBM
- EBM Process
- EBLM in Critical care- Hands on

Old Model for Clinical Decisions

- Unsystematic observations/clinical experience
- Pathophysiology plus pharmacology
- Extrapolation from intermediate outcomes
- Authority of local experts
- Practitioners and patients not "equals"

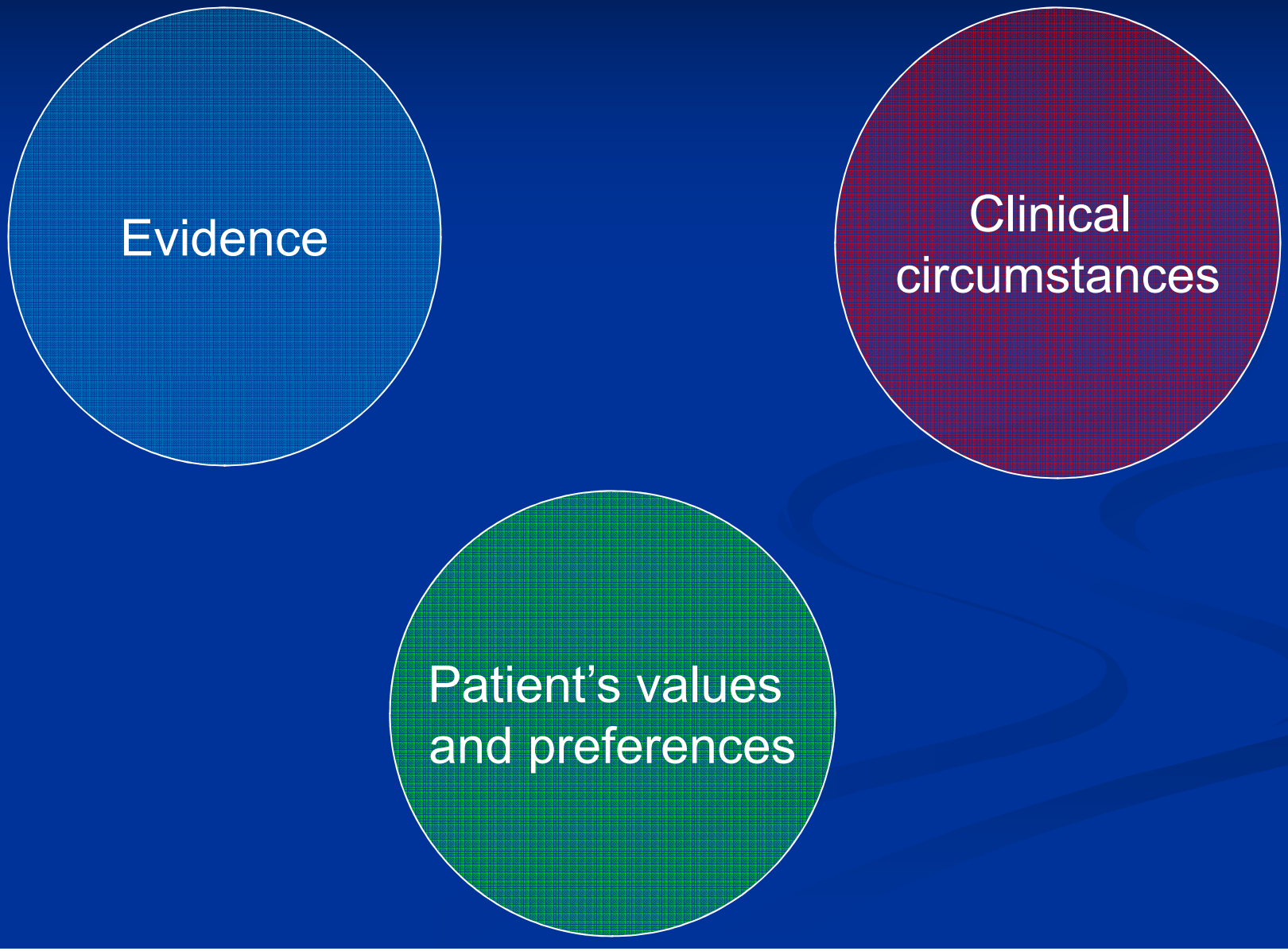
EBM Working Group. JAMA 1992;268:2420-2425

New Model for Clinical Decisions

- Systematic recording of observations - reproducible and unbiased
- Mechanism of disease - necessary but not sufficient
- Critical literature appraisal Vs authority
- Apply rules of evidence
- Full informed participation by patients

EBM Working Group. JAMA 1992;268:2420-2425

What is EBM?


Evidence
Clinical circumstances
Patient's values and preferences

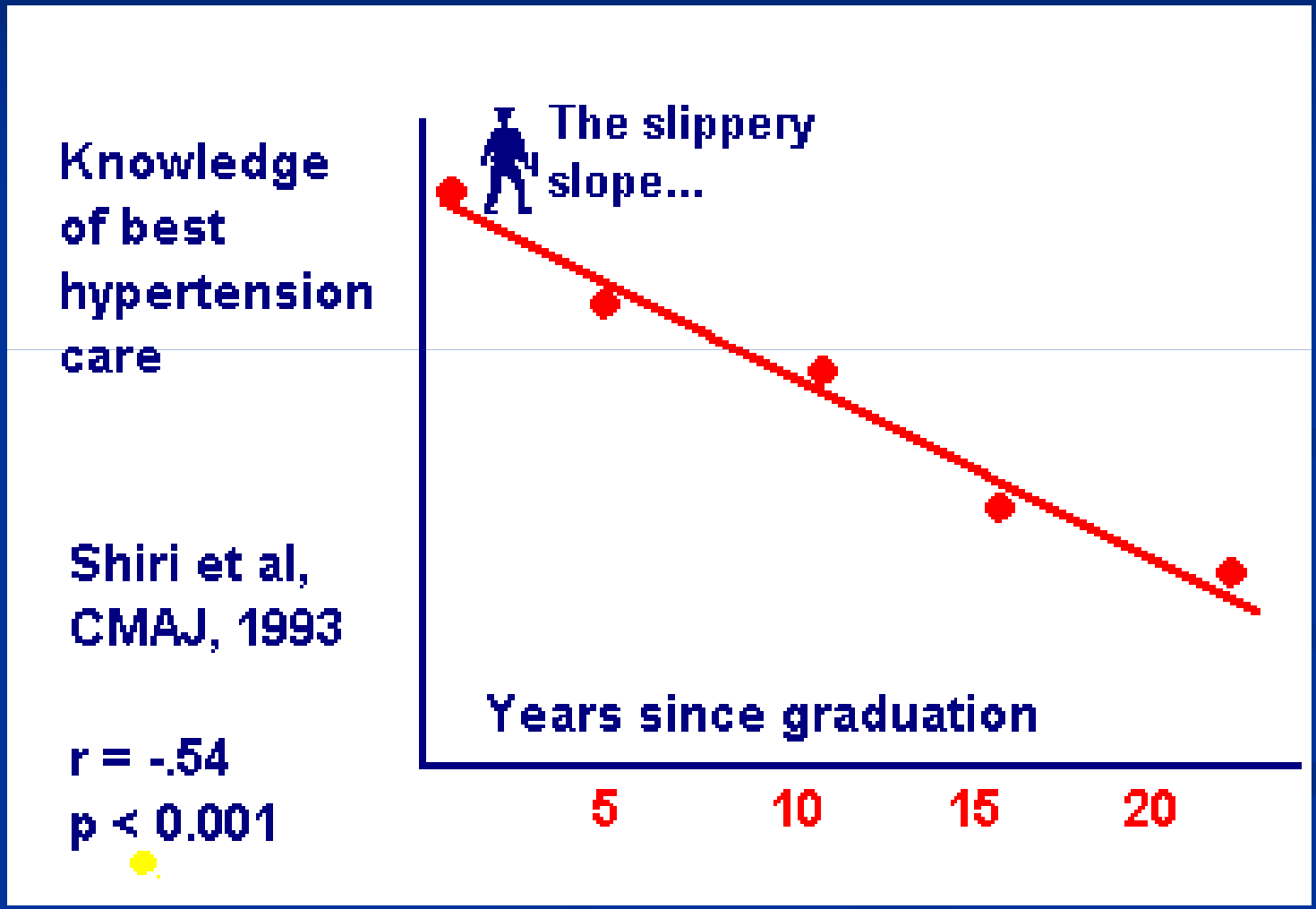
What is EBM?

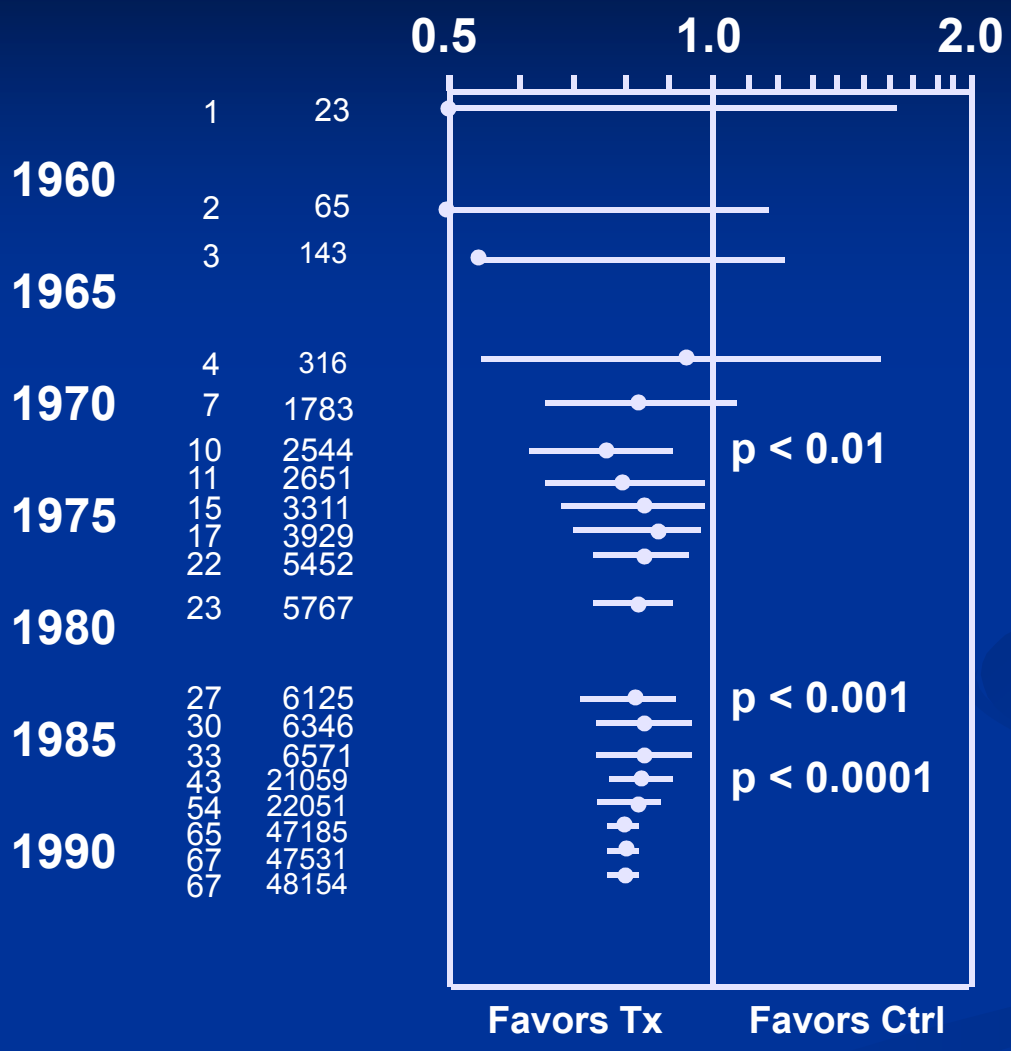
- "Without ***clinical expertise***, practice risks becoming tyrannized by external evidence, for even excellent external evidence may be inapplicable to or inappropriate for an individual patient. Without ***current best external evidence***, practice risks becoming rapidly out of date, to the detriment of patients."

What is EBM?

- Evidence-based practice is "a process of care that takes the patient and his or her preferences and actions, the clinical setting including the resources available, and current and applicable scientific evidence, and knits the three together using the clinical expertise and training of the health-care providers." (Haynes et al., 2002)

Why EBM?
Slippery Slope

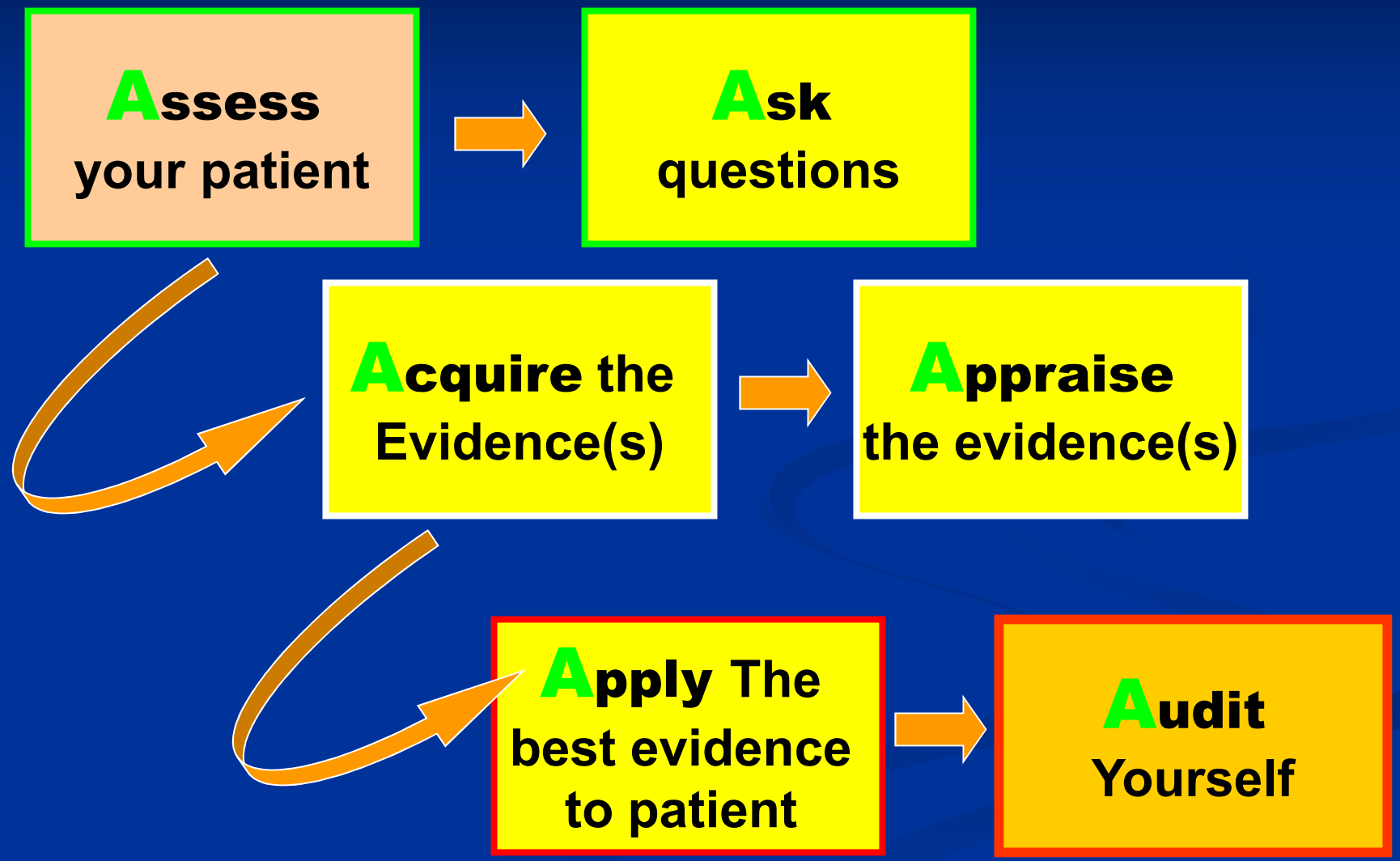




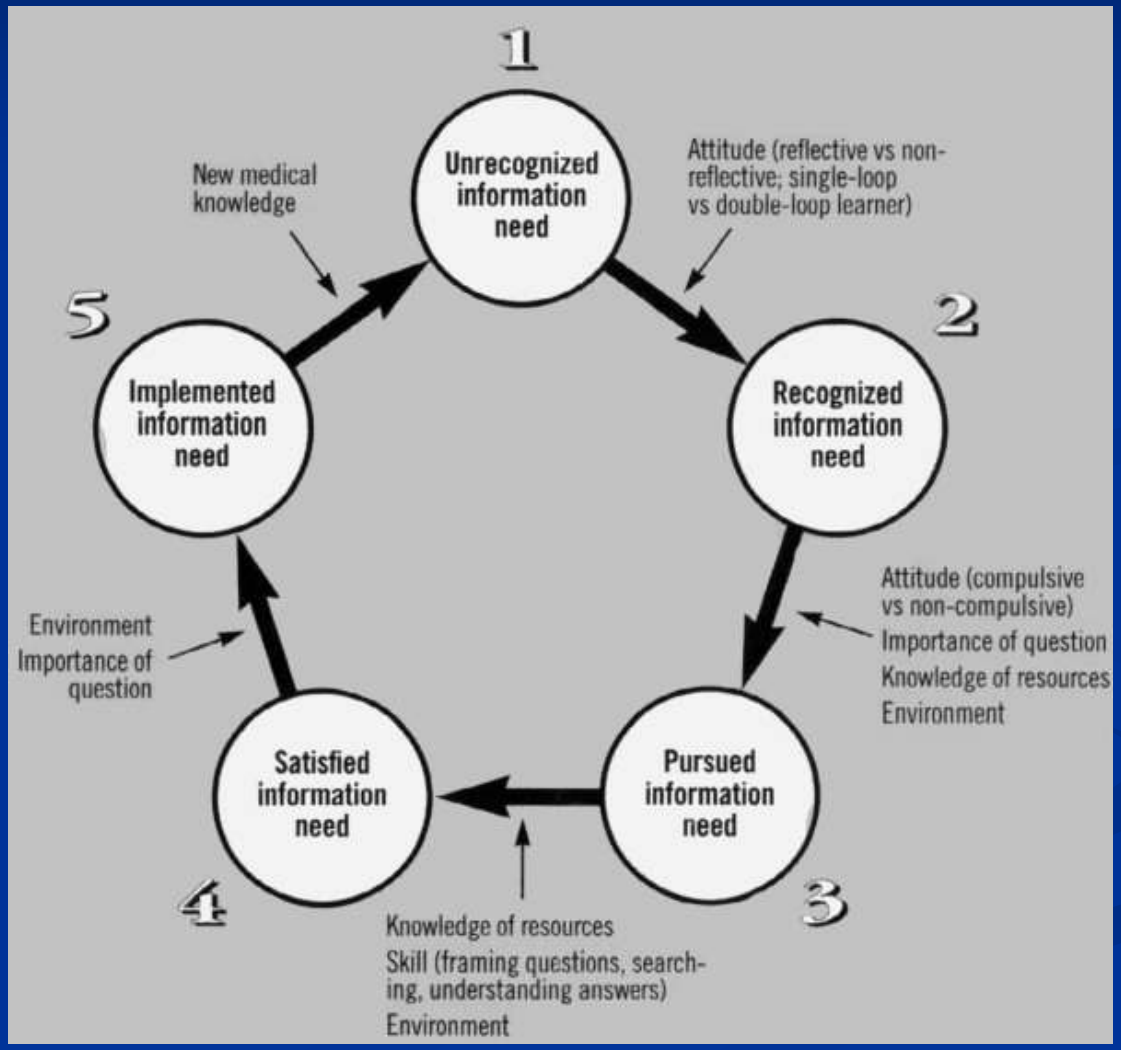
Routine	Specific	Rare/Never	Experimental	Not Mentioned
				21
				5
			1	10
			1	2
			2	8
				7
				8
	1			12
	1		8	4
	1		7	3
5	2		2	1
15	8			6
6	1			

E. M. Antman; J. Lau; B. Kupelnick; et al. ***A comparison of results of meta-analyses of randomized control trials and recommendations of clinical experts.*** *JAMA, Jul 1992; 268: 240 - 248.*

Steps in EBM: 6 As of EBM



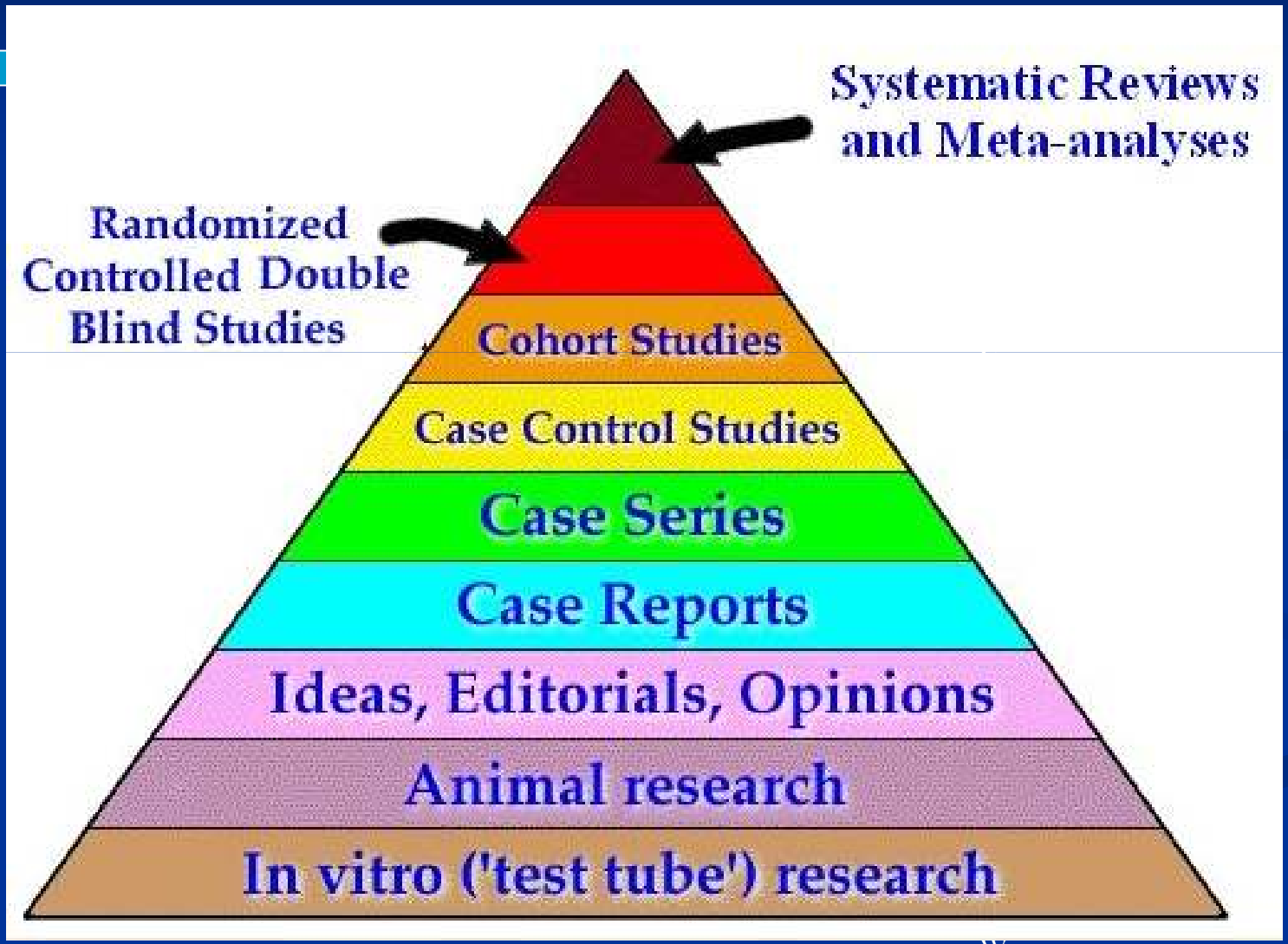
Steps in Practicing EBM



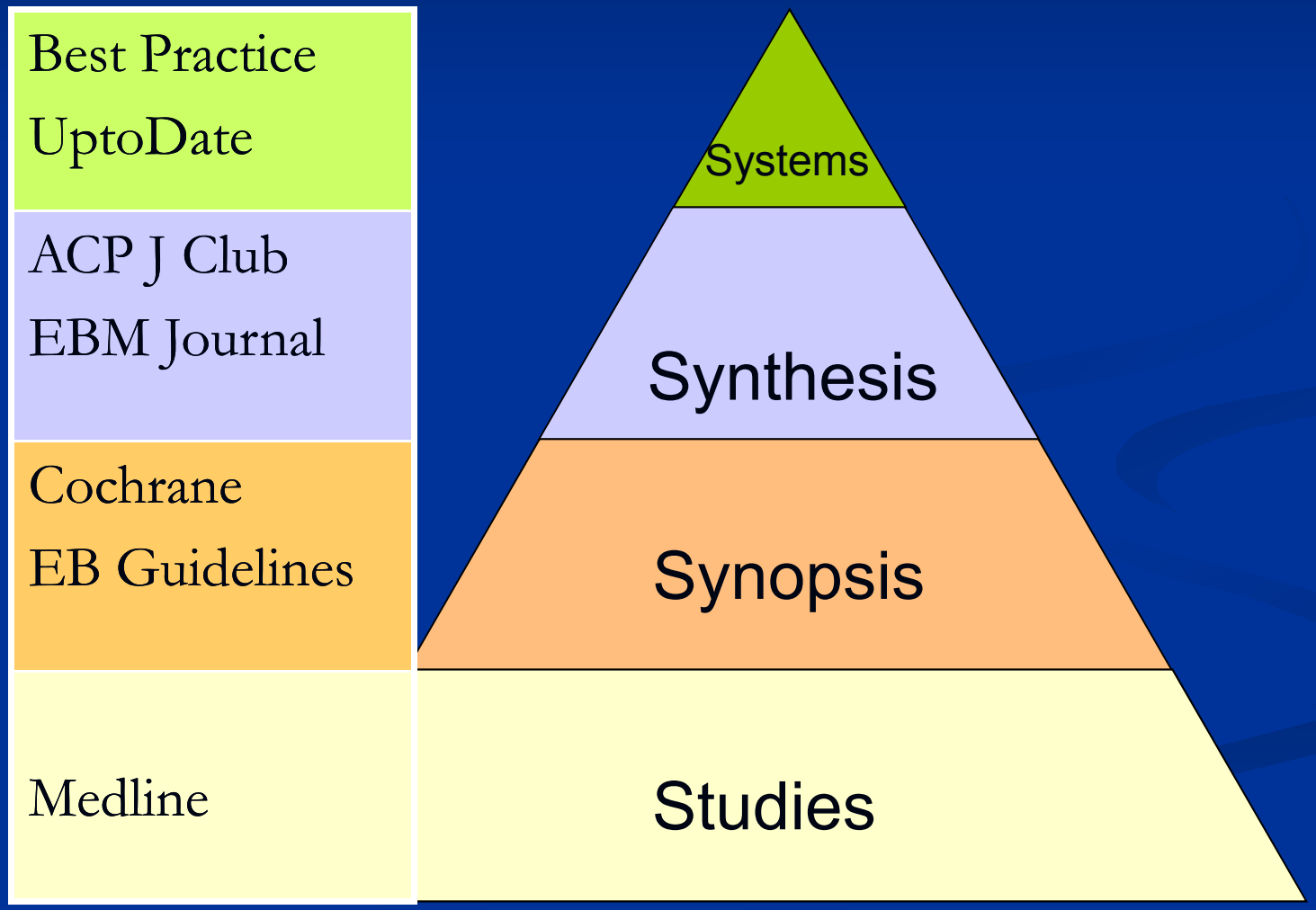
The Clinical Question

- **Population** (patient)
  What are the characteristics of the patients?
- **Intervention** (diagnostic test)
  Which diagnostic test am I considering?
- **Comparison**
  What is the diagnostic gold standard?
- **Outcome**
  How likely is the test to predict/rule out this condition?
- **Study design**
  What study design would provide the best level of evidence for this question?

All Evidence is not Equal



Hierarchy for EBM Practitioners



Attributes of a Test

- Validity
- Reliability
- Clinical relevance
- Feasibility
- Cost

Concepts pertinent to “the test”

- Sensitivity
- Specificity
- Likelihood ratio of positive test
- Likelihood ratio of negative test
- Pretest probability
- Posttest probability

Sensitivity and Specificity

- **Sensitivity**

  =ability of a test to detect the disease among persons who have it

  =proportion of people with disease who have positive test

- **specificity**

  = ability of a test to confirm normal status among people without disease

  = proportion of people without disease who have negative test result

Relationship between test result and truth

Sensitivity = a/(a+c)
Specificity = d/(b+d)
Positive predictive value = a/(a+b)
Negative predictive value = d/(c+d)
Prevalence = (a+c)/(a+b+c+d)

		Disease	
		Present	Absent
Test result	positive	True-positive (a)	False-positive (b)
	negative	False-negative (c)	True-negative (d)
		a + c	b + d

Sensitivity and specificity do not answer clinical questions:

- If a patient's test result is positive, what is the probability that he or she has the disease being tested?
- If the result is negative, what is the probability that the patient does not have the disease?

Technical issues with Sensitivity and Specificity

- must dichotomize results (2x2 table)
- difficult to apply in clinical practice
  - **Se** applies only to patients with disease
  - **Sp** applies only to healthy patients
  - Clinician does not know disease status, only test result

Making it clinically relevant

$$LR = \frac{\text{Probability of result in diseased people}}{\text{Probability of result in non-dis. people}}$$

In tests measuring dichotomous variables (i.e. yes/no)

LR+ = Sensitivity/(1-Specificity)

LR- = (1-Sensitivity)/Specificity

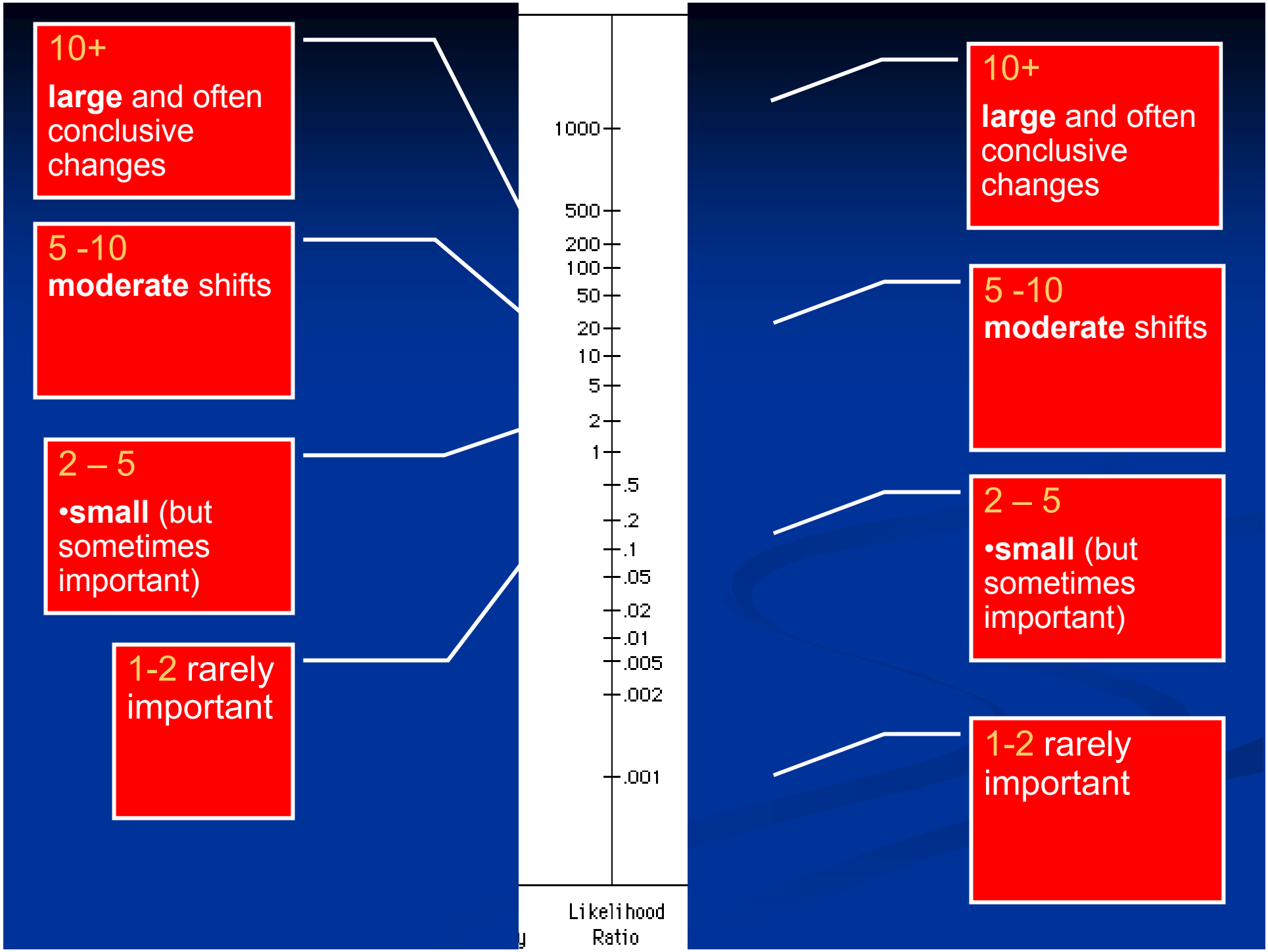
Likelihood ratios

"No effect of prevalence on likelihood ratios"

Likelihood ratios

Sensitivity = a/(a+c)
Specificity = d/(b+d)
LR+ = [a/(a+c)]/[b/(b+d)
LR- = [c/(a+c)/d(b+d)]
Prevalence = (a+c)/(a+b+c+d)

		Disease	
		Present	Absent
Test result	positive	True-positive (a)	False-positive (b)
	negative	False-negative (c)	True-negative (d)
		a + c	b + d


10+
large and often conclusive changes
5 -10
moderate shifts
2 – 5
•small (but sometimes important)
1-2 rarely important
1000
500
200
100
50
20
10
5
2
1
.5
.2
.1
.05
.02
.01
.005
.002
.001
Likelihood Ratio
10+
large and often conclusive changes
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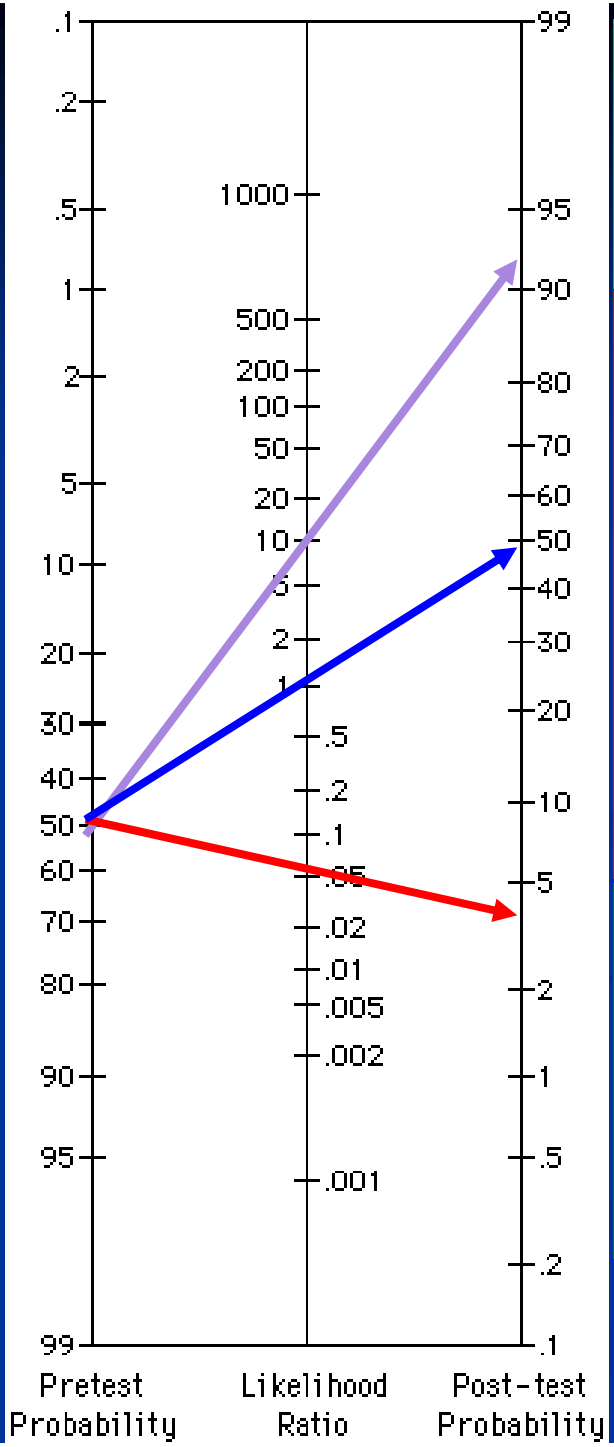


Treatment initiated

Treatment threshold

Further testing required

Test threshold

Diagnosis refuted

Case 1 Presentation

- A 45 years old male with history of diabetes and hypertension presents in ER with acute shortness of breath……..

What is his Probability of acute heart failure?

95%

Case 2 Presentation

- A 45 years old male with history of heavy smoking and hypertension presents in ER with worsening shortness of breath……..

What is his Probability of acute heart failure?

50%

Critical Appraisal

The New England Journal of Medicine

ORIGINAL ARTICLE

◄ Previous Volume 347:161-167 July 18, 2002 Number 3 Next ►

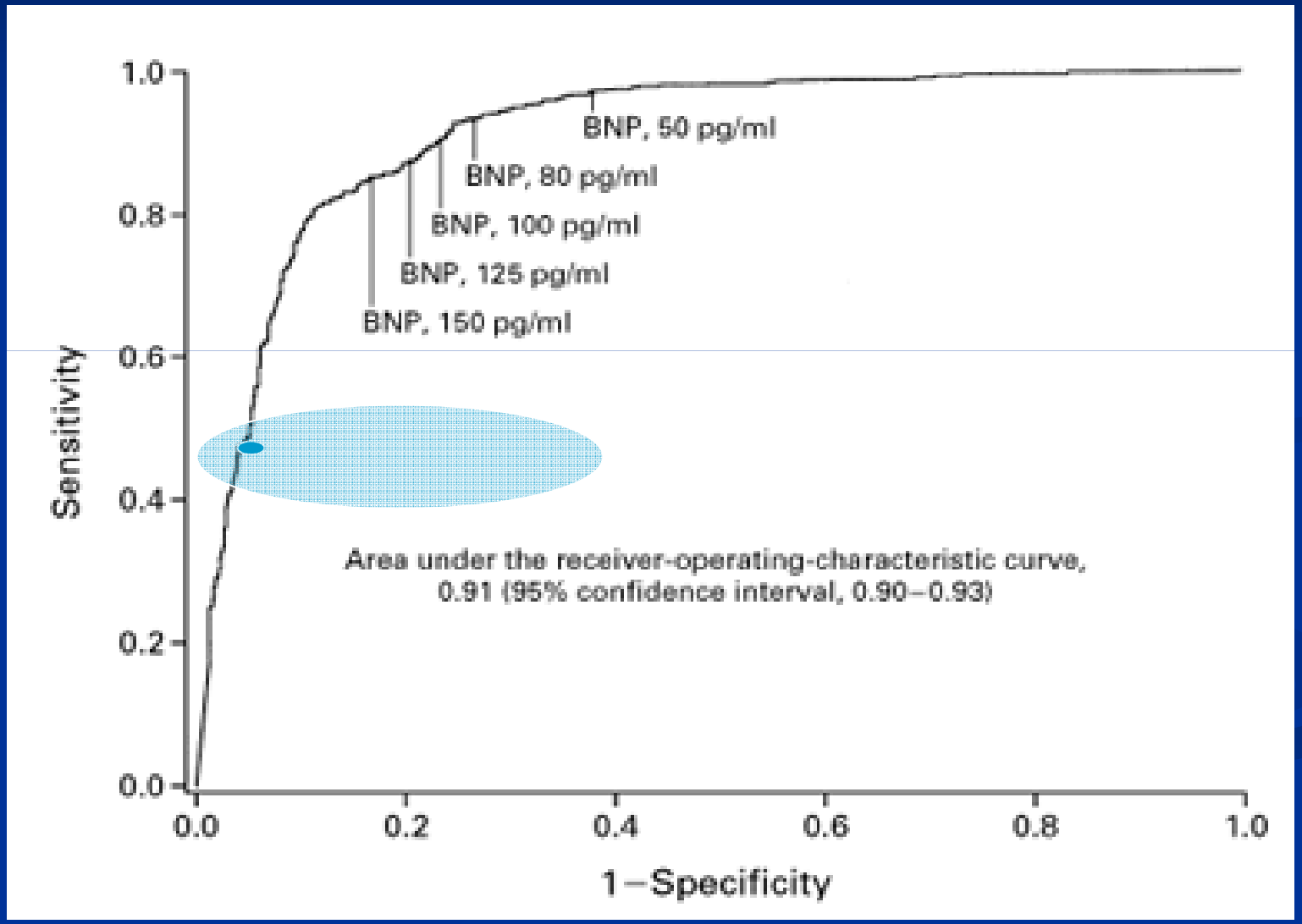
Rapid Measurement of B-Type Natriuretic Peptide in the Emergency Diagnosis of Heart Failure

Alan S. Maisel, M.D., Padma Krishnaswamy, M.D., Richard M. Nowak, M.D., M.B.A., James McCord, M.D., Judd E. Hollander, M.D., Philippe Duc, M.D., Torbjørn Omland, M.D., Ph.D., Alan B. Storrow, M.D., William T. Abraham, M.D., Alan H.B. Wu, Ph.D., Paul Clopton, M.S., Philippe G. Steg, M.D., Arne Westheim, M.D., Ph.D., M.P.H., Catherine Wold Knudsen, M.D., Alberto Perez, M.D., Radmila Kazanegra, M.D., Howard C. Herrmann, M.D., Peter A. McCullough, M.D., M.P.H., for the Breathing Not Properly Multinational Study Investigators

BNP Results

BNP	Sensitivity	Specificity	LR +	LR-
50	97	62	2.55	0.05
80	93	74	3.58	0.09
100	90	76	3.75	0.13
125	87	79	4.14	0.16
150	85	83	5.00	0.18

BNP ROC Curve



BNP vs NT-proBNP

BNP AUC = 0.916 (95% CI: 0.874, 0.947)
NT-proBNP AUC = 0.903 (95% CI: 0.859, 0.939)

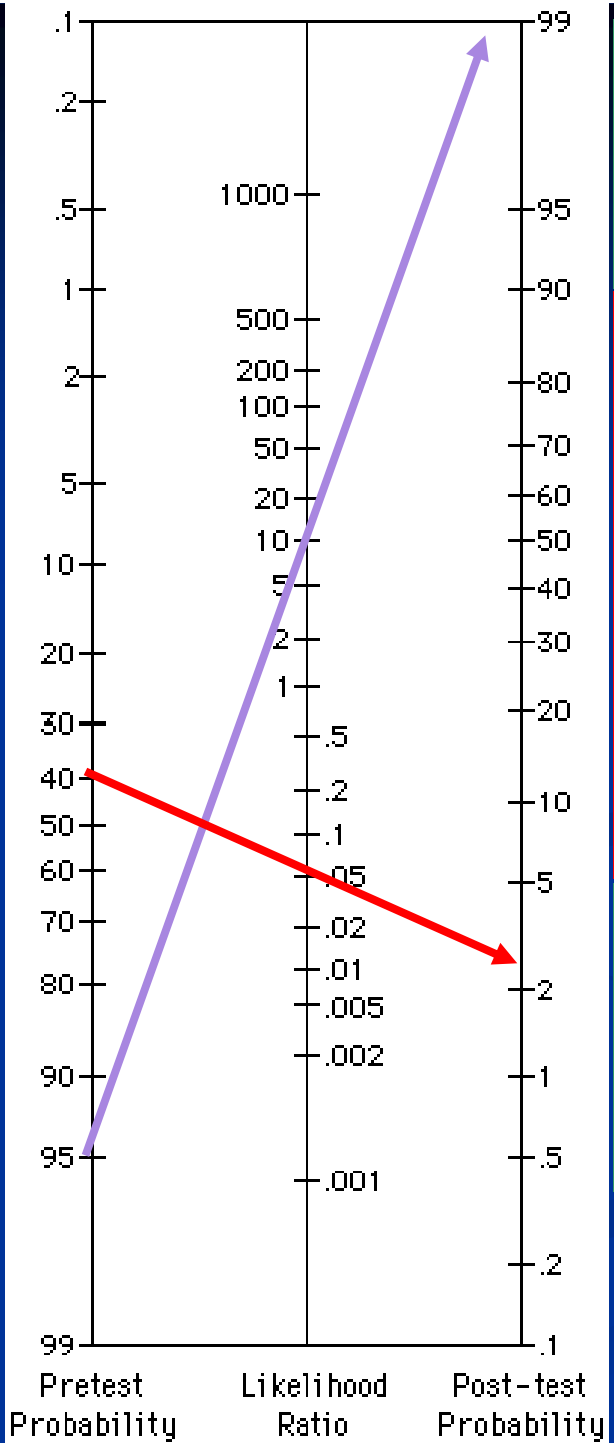
Nearly identical ROC curves

Mueller T, et al. Diagnostic accuracy of B type natriuretic peptide and amino terminal proBNP in the emergency diagnosis of heart failure. Heart. 2005 May;91(5):606-12.

Case 2
BNP of 50

Case 1

BNP of 500



Treatment initiated

Treatment threshold

Further testing required

Test threshold

Diagnosis refuted

Case 3

- A 4 month infant was brought to ER with history of fever and vomiting. She looked tachypneic. There was no obvious source of infection. The resident on call decided to admit the baby in ICU.

Clinical Question

- Would procalcitonin help in identifying serious bacterial infection in a 4 month old infant with fever without a source?

Procalcitonin in Young Febrile Infants for the Detection of Serious Bacterial Infections

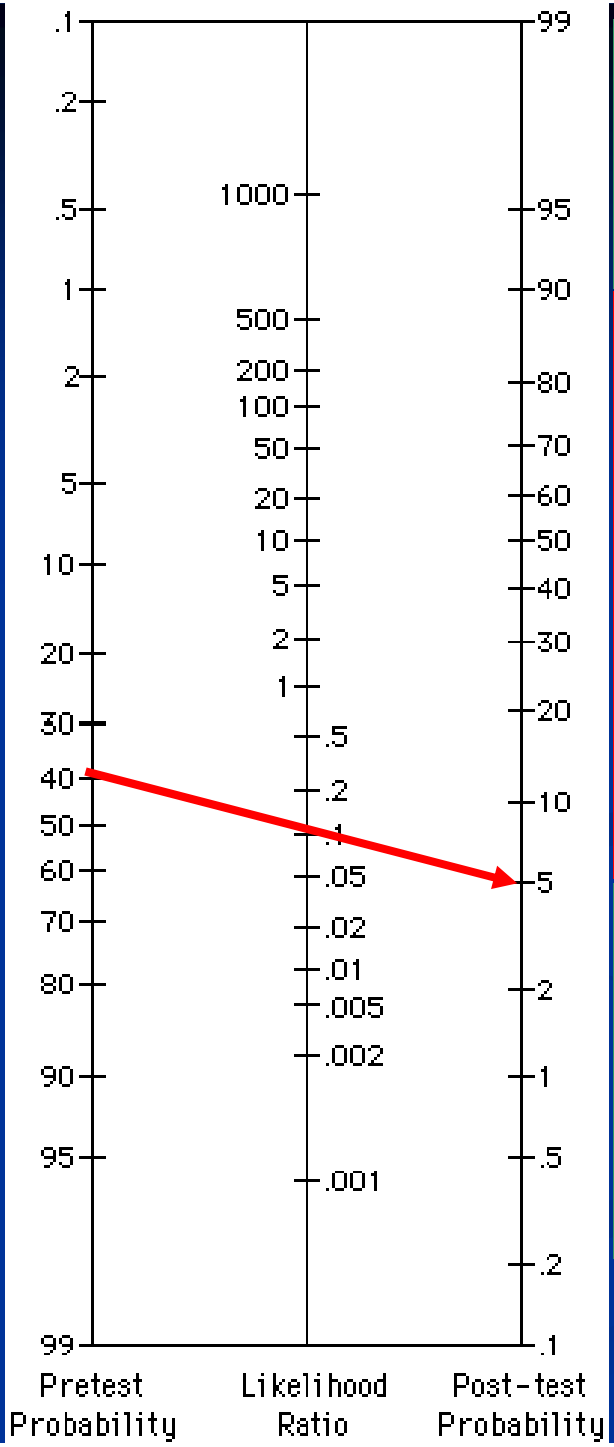
Maniaci V et al. Pediatrics 2008;122:701-710.

Results

- A cutoff value of 0.12 ng/ml
  - sensitivity of 95.2%
  - specificity of 25.5%
  - LR + = 1.26
  - LR - = 0.1

Maniaci V et al. Pediatrics 2008;122:701-710

Case 3
Procalcitonin
of 0.14



Treatment initiated

Treatment threshold

Further testing required

Test threshold

Diagnosis refuted

LRs in Cushing's syndrome

Test	Se	Sp	LR+	LR-
Cushing's syndrome				
Plasma cortisol 8.00 am >13-20 ug/100ml	83.0	67.0	2.5	0.16
Plasma cortisol midnight > 6-15 ug/ml	96.0	96.0	24.0	0.04
24-hr urine free cortisol >20-181 ug/day	94.0	91.0	10.0	0.07
Low-dose dexamethasone suppression: urine free cortisol > 0.019-0.025mg/day	95.0	97.0	32.0	0.05
Cushing's disease				
High-dose dexa- suppression test Urine free cortisol suppressed > 50%	90.0	79.0	4.3	0.13
High-dose dexa- suppression test Urine free cortisol suppressed > 80%	81.0	92.0	10.1	0.21

LRs in thyroid disorders

test	Se	Sp	LR+	LR-
hyperthyroidism				
Total T_4	90.0	90.0	9.0	0.11
T_3 RIA	96.0	96.0	24.0	0.04
TSH	99.0	99.0	99.0	0.01
Primary hypothyroidism				
Total T_4	90.0	85.0	6.0	0.12
T_3 RIA	95.0	95.0	19.0	0.05
TSH	99.0	99.0	99.0	0.01

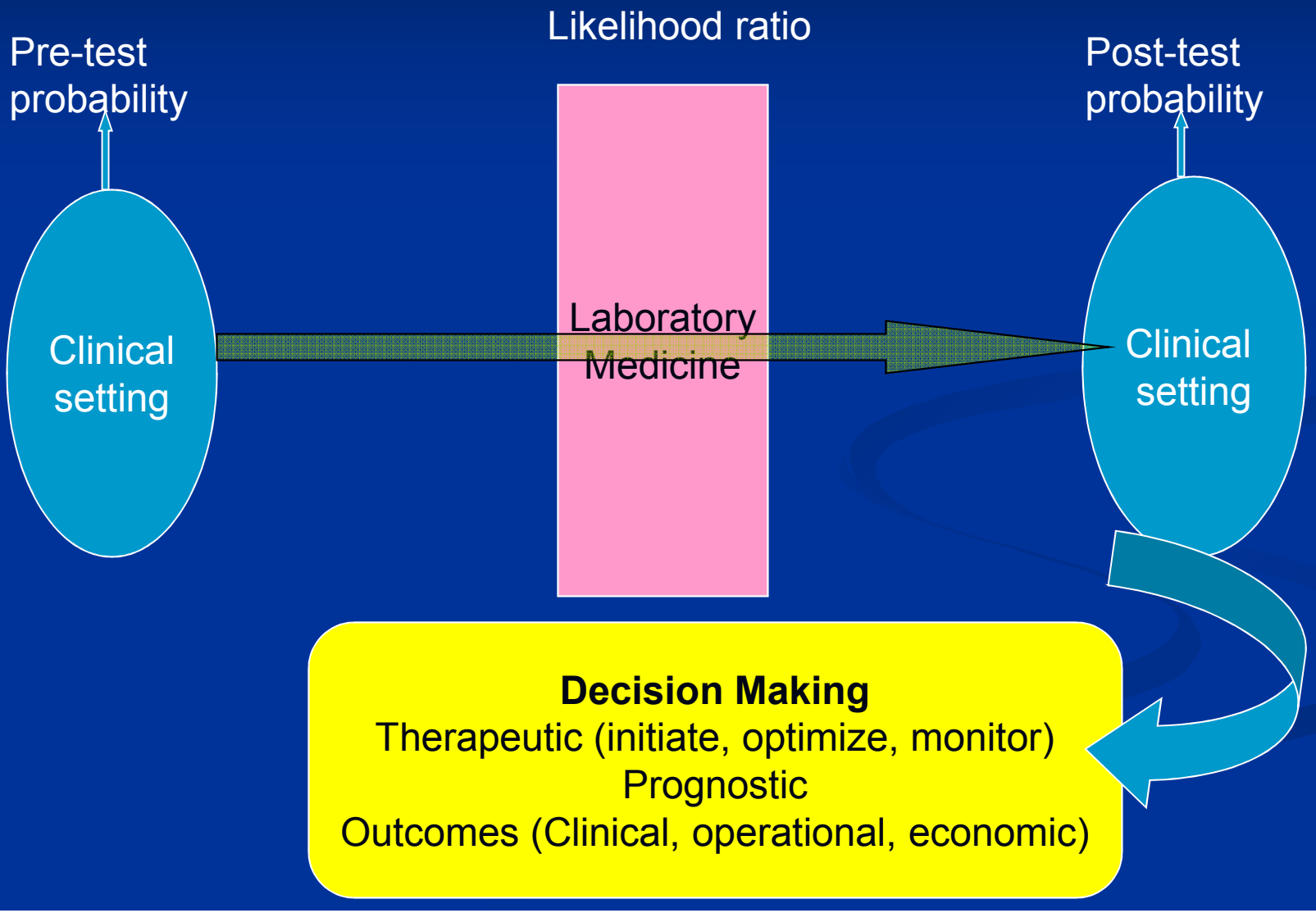
LRs in Iron Deficiency

Test	Likelihood ratio (LR)
MCV <70	12.5
70-74	3.3
75-79	1.0
Trans sat < 5	10.5
5-9	2.5
10-19	.81

Test	LR
Ferritin < 15	51.8
15-24	8.8
25-34	2.5
35-44	1.8
45-100	.54
> 100	0.08

Killip et al. Iron deficiency anemia. AFP 2007;75:671-8

Evidence-based Laboratory Medicine



Ending with Hope