RCPS Review
Test Characteristics
Measures of Treatment Effect
Measures of Disease

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5 Major Clinical Questions

- Diagnosis
- Treatment
- Prevention
- Prognosis
- Harm

- Measures of Disease Frequency
  - incidence
  - prevalence

Measures of Disease Frequency

- **Disease Incidence**
  - refers to new cases of disease among a population at risk for that disease over a specified period of time.

Measures of Disease Frequency

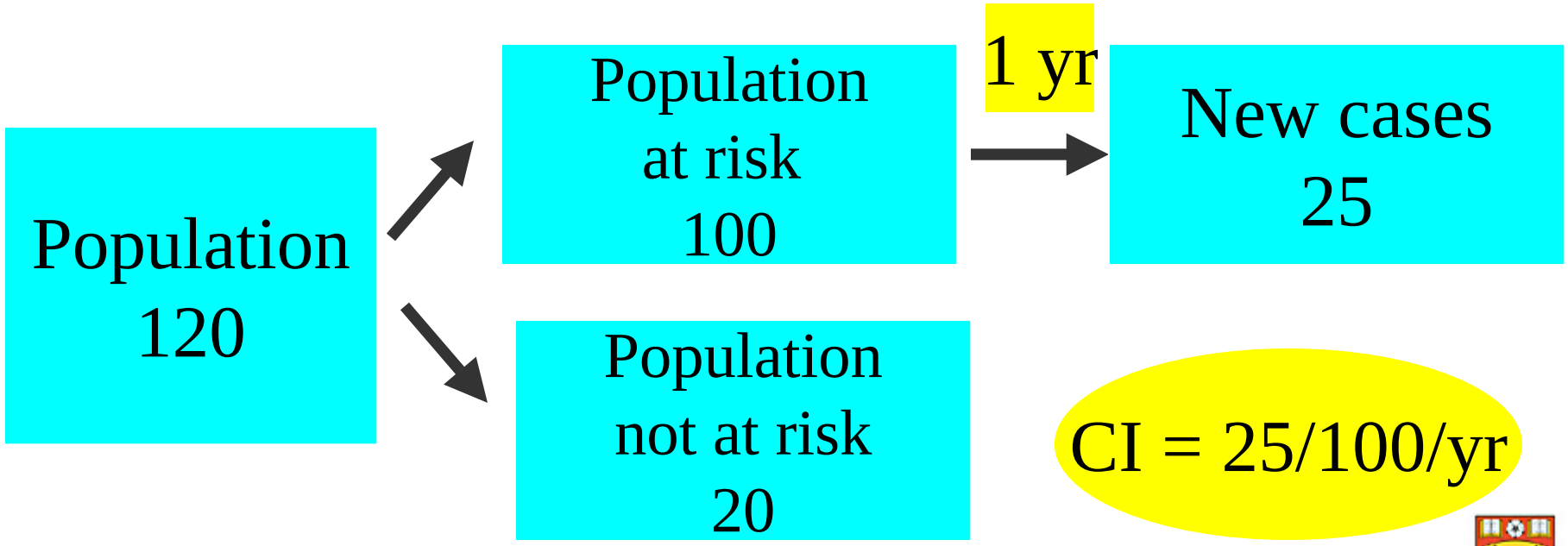
- 120 grade 10 students were followed for 1 year to determine the incidence of hepatitis A infection.
- At the beginning of this study, 20 were known to be immune to hepatitis A.
- There were 25 new cases observed during the year.

- What is the incidence of hepatitis A in this population?

Measures of Disease Frequency

- Cumulative Incidence (CI)

CI = new cases / population at risk / time interval



Measures of Disease Frequency

- Incidence Density

$$ID = \frac{\text{new cases}}{\text{person-time population at risk per time period}}.$$

Useful when there is losses to follow-up among the population under observation

Measures of Disease Frequency

- A study plans to observe 20,000 people at risk for 2 years but 10,000 left town after 6 months.
- 250 cases of disease were observed.

- What is the disease incidence?

Measures of Disease Frequency

- A study plans to observe 20,000 people at risk for 2 years but 10,000 left town after 6 months.
- 250 cases of disease were observed.

```
10,000 observed x 2   yr = 20,000 p-yr
10,000 observed x 0.5 yr =  5,000 p-yr

Total persons years      = 25,000 p-yr
```

Measures of Disease Frequency

- 250 cases of disease were observed among the population.

250 cases / 25,000 person years

100 cases / 10,000 persons / year

Measures of Disease Frequency

- Disease Prevalence
  - refers to the proportion of individuals who have the disease at a specific time among a given population. (not a rate)

$$\text{Prevalence} = \frac{\text{existing cases at a point in time}}{\text{total population}}$$

Measures of Disease Frequency

- Point Prevalence
  - ‘snapshot’ in calendar time or event related time
  - number of cases of diabetes on June 30, 2002 in Calgary
  - number of people with infected incision on post-operative day 3 on General Surgery unit at Foothills Hospital

Measures of Disease Frequency

- Period Prevalence
  - longer duration under consideration
  - number of people with diabetes between Jan 1 and Dec 31, 2002 in Calgary
  - number of people with infected incision between surgery and post-operative day 90 on General Surgery unit at Foothills Hospital

Prevalence of Diabetes in Canada `1996-97

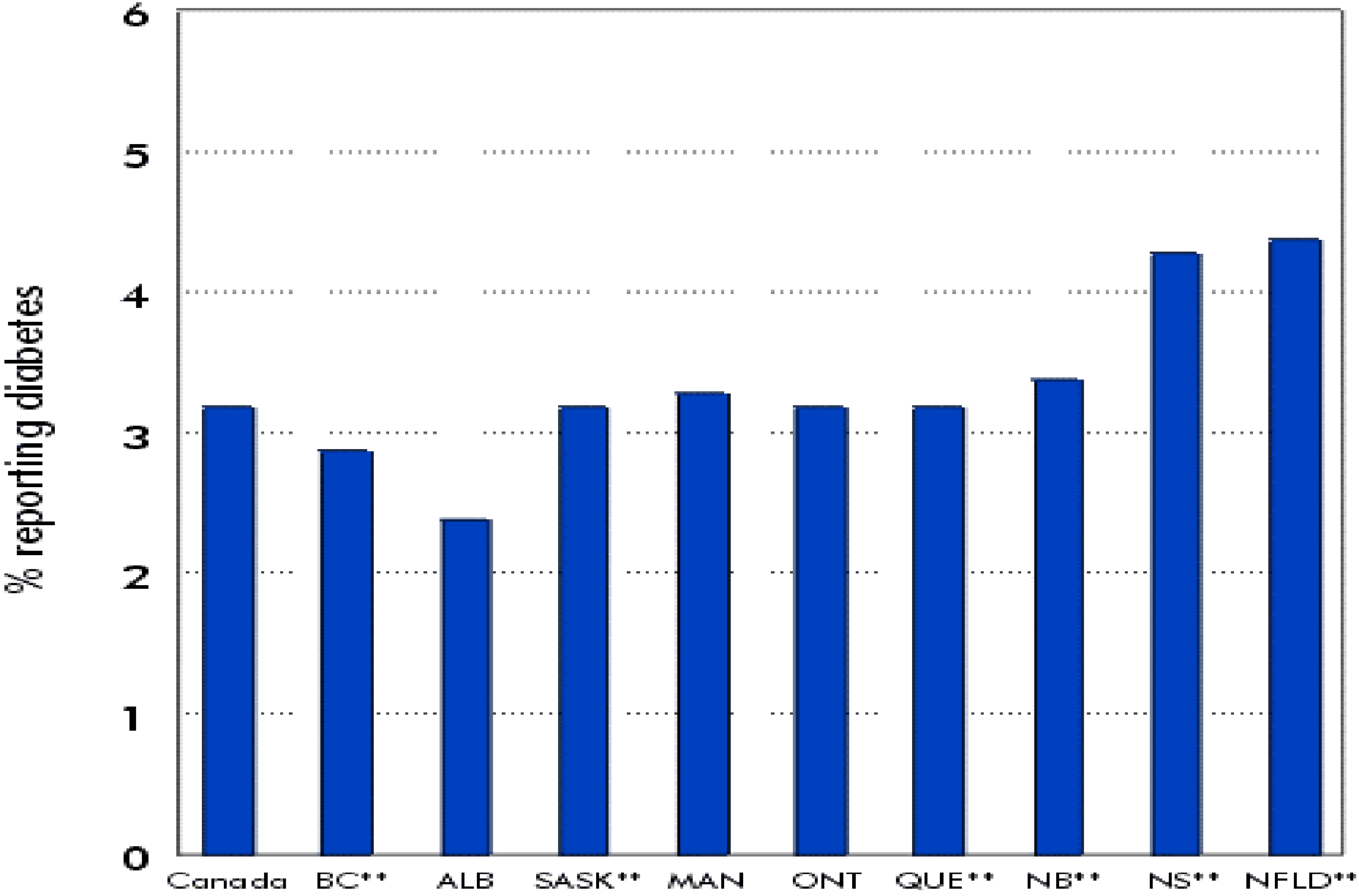
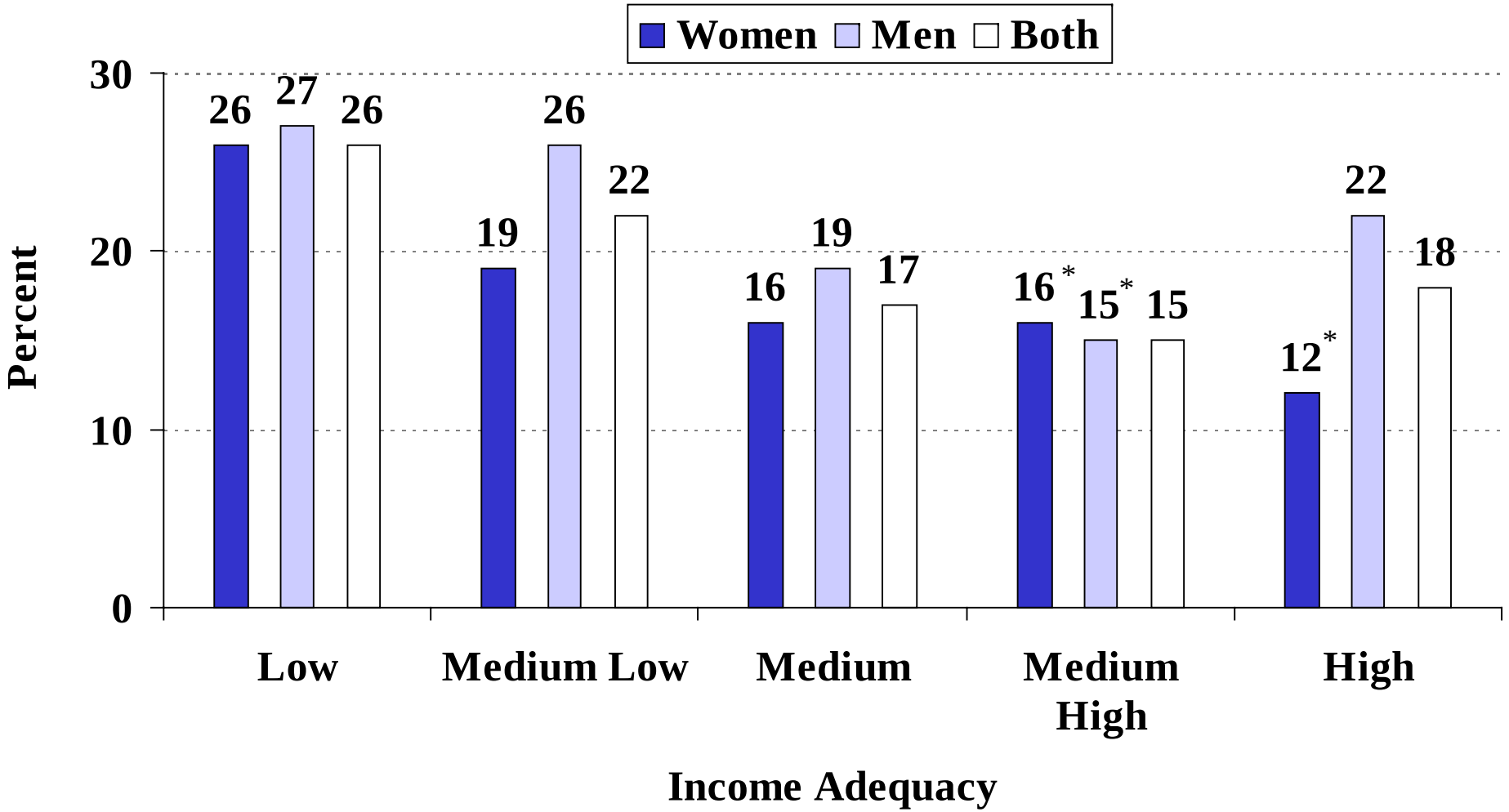


Figure 1-4 **Percentage of the general population aged 15+ years who were daily smokers by income adequacy and sex, Canada, 2001**



*Interpret with caution: based on small sample size

Source: Canadian Tobacco Use Monitoring Survey (CTUMS), Health Canada

- Test Characteristics

What's the best test?

- **Gold Standard**:
  - A method, procedure, measurement that is widely accepted as being the best available.
  - 'reference standard'

Gold Standards

- Defining the gold standard may be difficult…
  - pneumonia
    - chest x-ray versus sputum
  - myocardial infarction
    - CK versus troponin versus nuclear medicine versus ECG versus echocardiogram

Clinical Scenario

- 70 yr old male in emergency
- chest pain, dyspnea for one hour
- + prostate cancer hx
- + recent 10 hour bus trip
- distressed. HR 130, RR 30, BP 110/80

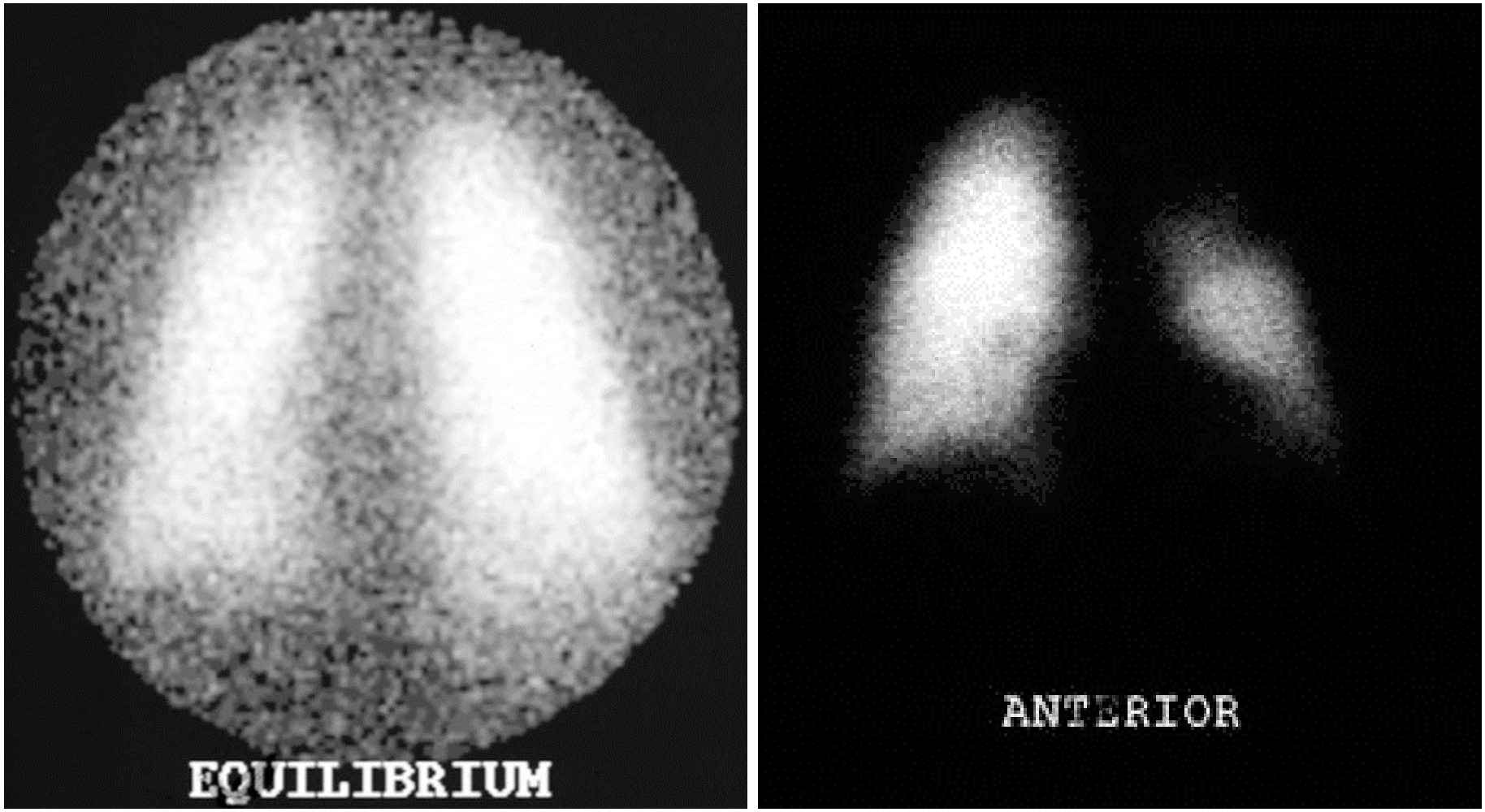
What’s the question?

What's the question?

What's the

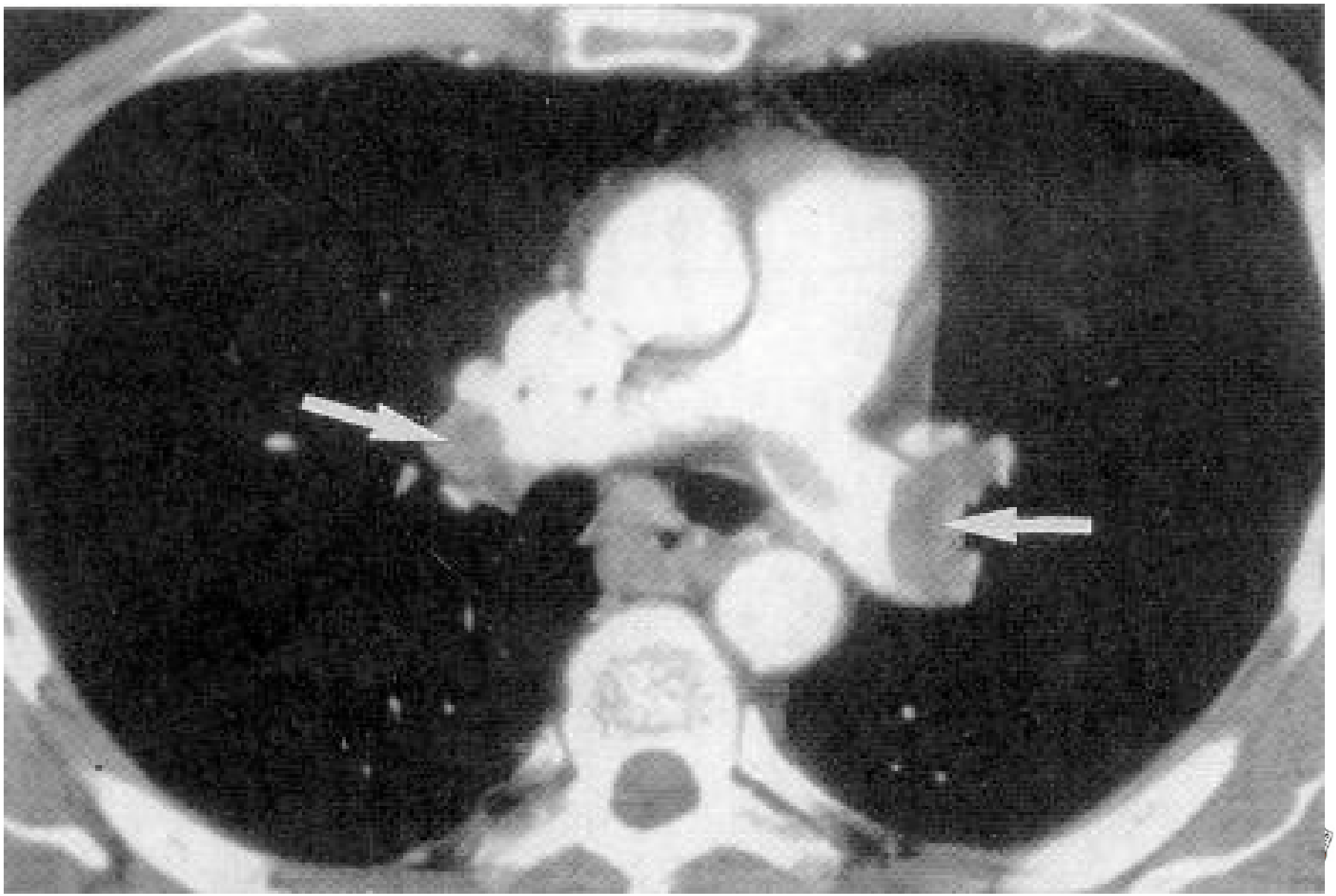
DIAGNOSIS?

PE - diagnosis (V/Q scan)



- high probability V/Q scan (2 defects)

PE - diagnosis (spiral CT scan)



PE - diagnosis

Pulmonary angiogram

- gold standard

PE - diagnosis

Pulmonary angiogram

- gold standard

Pulmonary Thromboembolism

How well does the test perform?

- Welcome to the world of

TEST CHARACTERISTICS

Take a deep breath...

Test Characteristics

- Sensitivity
- Specificity

- Positive predictive value
- Negative predictive value

- Accuracy

- Positive and Negative Likelihood ratios

		DISEASE		
		Present	**Absent**	
TEST	**Positive**	TRUE POSITIVE	FALSE POSITIVE	
	Negative	FALSE NEGATIVE	TRUE NEGATIVE	

Hypothetical Test Results

		DISEASE (PE)		
		Present	**Absent**	
TEST (V/Q scan)	**Positive**	TRUE POSITIVE a = 80	FALSE POSITIVE b = 20	a + b = 100
	Negative	FALSE NEGATIVE c = 10	TRUE NEGATIVE d = 90	c + d = 100
		a + c = 90	b + d = 110	a+b+c+d = 200

Sensitivity

- Probability that test is positive given that disease is present.

$$P\ (T+ \mid D+)$$

Conditional Probability Language
P = probability
T = test
| = given that
D = disease

Sensitivity

		DISEASE (PE)		
		Present	**Absent**	
TEST (V/Q scan)	**Positive**	TRUE POSITIVE a = 80	FALSE POSITIVE b = 20	a + b = 100
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		a + c = 90	b + d = 110	a+b+c+d = 200

80 / (80 + 10) = 88.9%

Specificity

- Probability that test is negative given that disease is absent.

$$P\ (T- \mid D-)$$

Specificity

		DISEASE (PE)		
		Present	**Absent**	
TEST (V/Q scan)	**Positive**	TRUE POSITIVE a = 80	FALSE POSITIVE b = 20	a + b = 100
	Negative	FALSE NEGATIVE c = 10	TRUE NEGATIVE d = 90	c + d = 100
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Specificity

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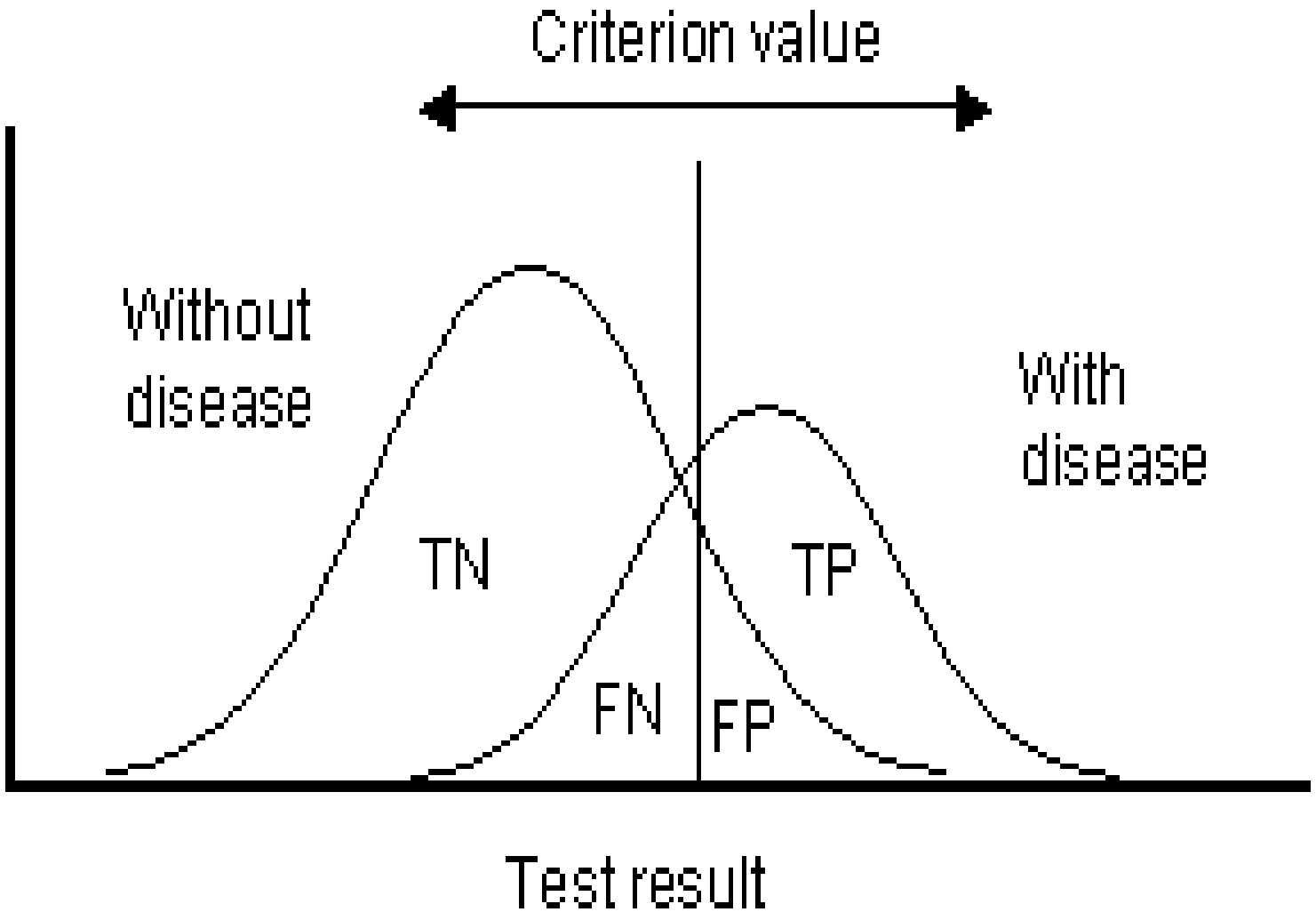
		a + c = 90	b + d = 110	a+b+c+d = 200

90 / (90 + 20) = 81.8%

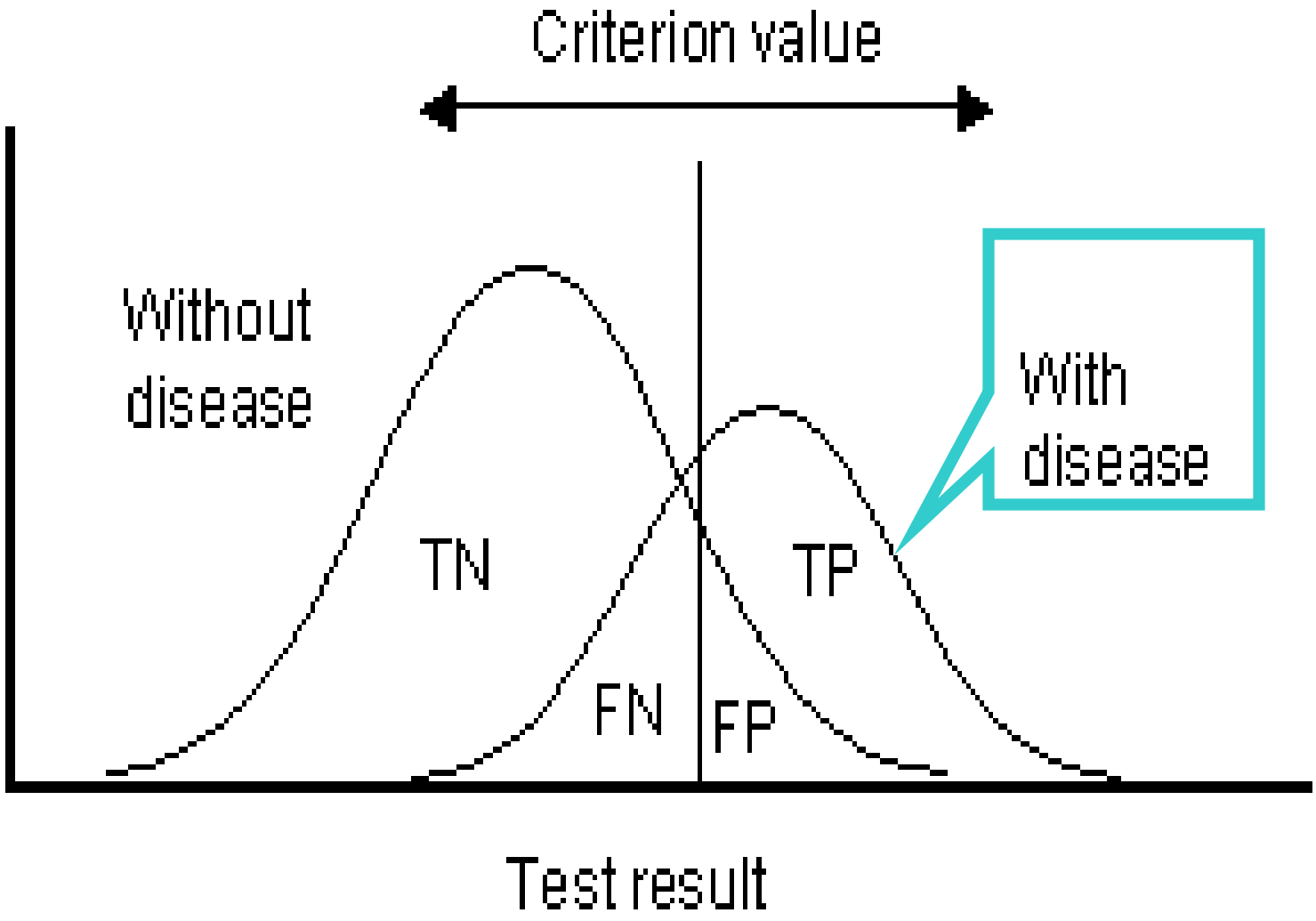
Sensitivity - Specificity Trade-Off

- Most test results are not positive or negative.
- There is often a selected value
  - over which a test is said to be positive
  - under which a test is said to be negative.
- As a result….
  - increasing sensitivity results in loss of specificity
  - increasing specificity results in loss of sensitivity

Sensitivity / Specificity Trade-off



Sensitivity / Specificity Trade-off



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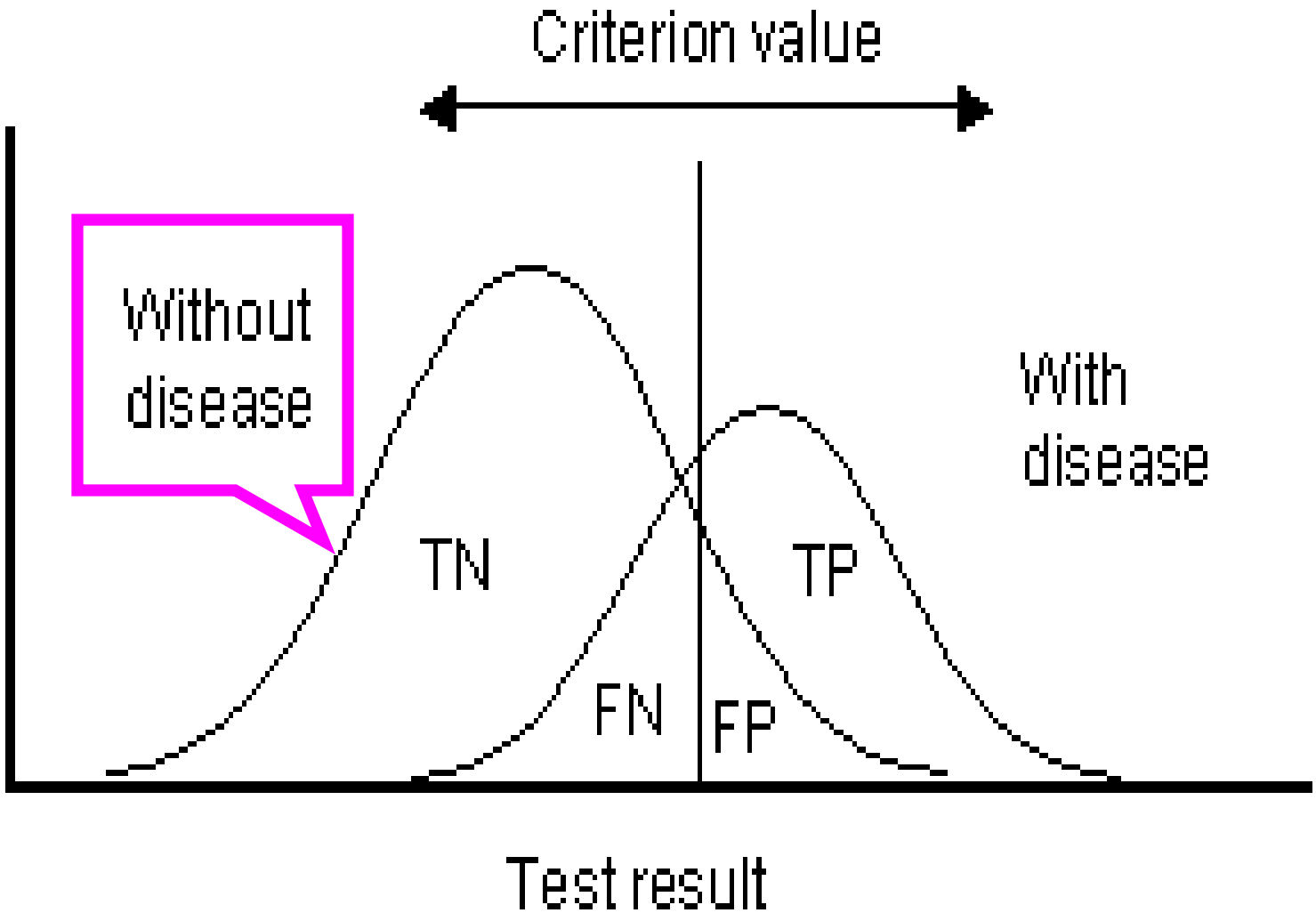

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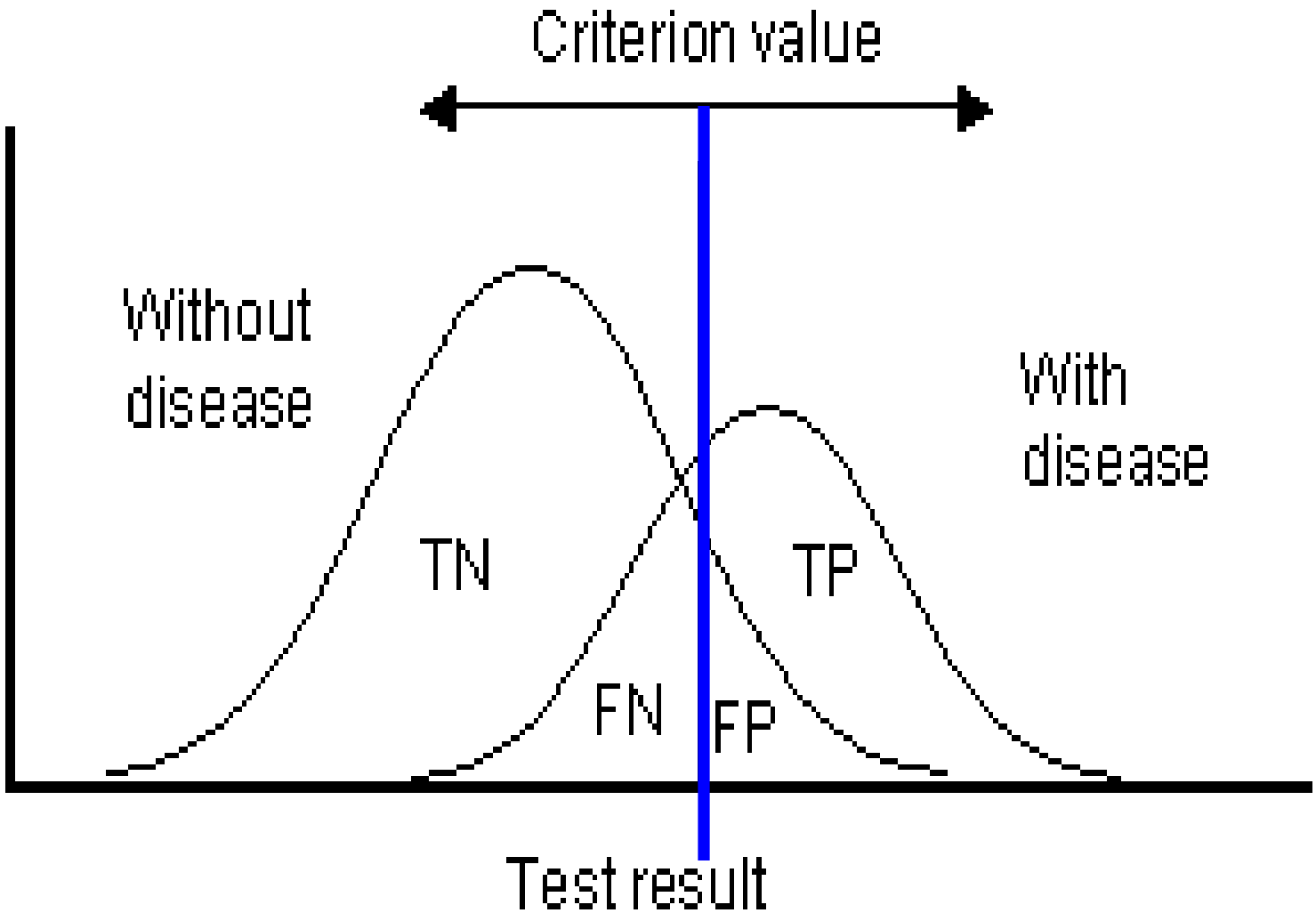

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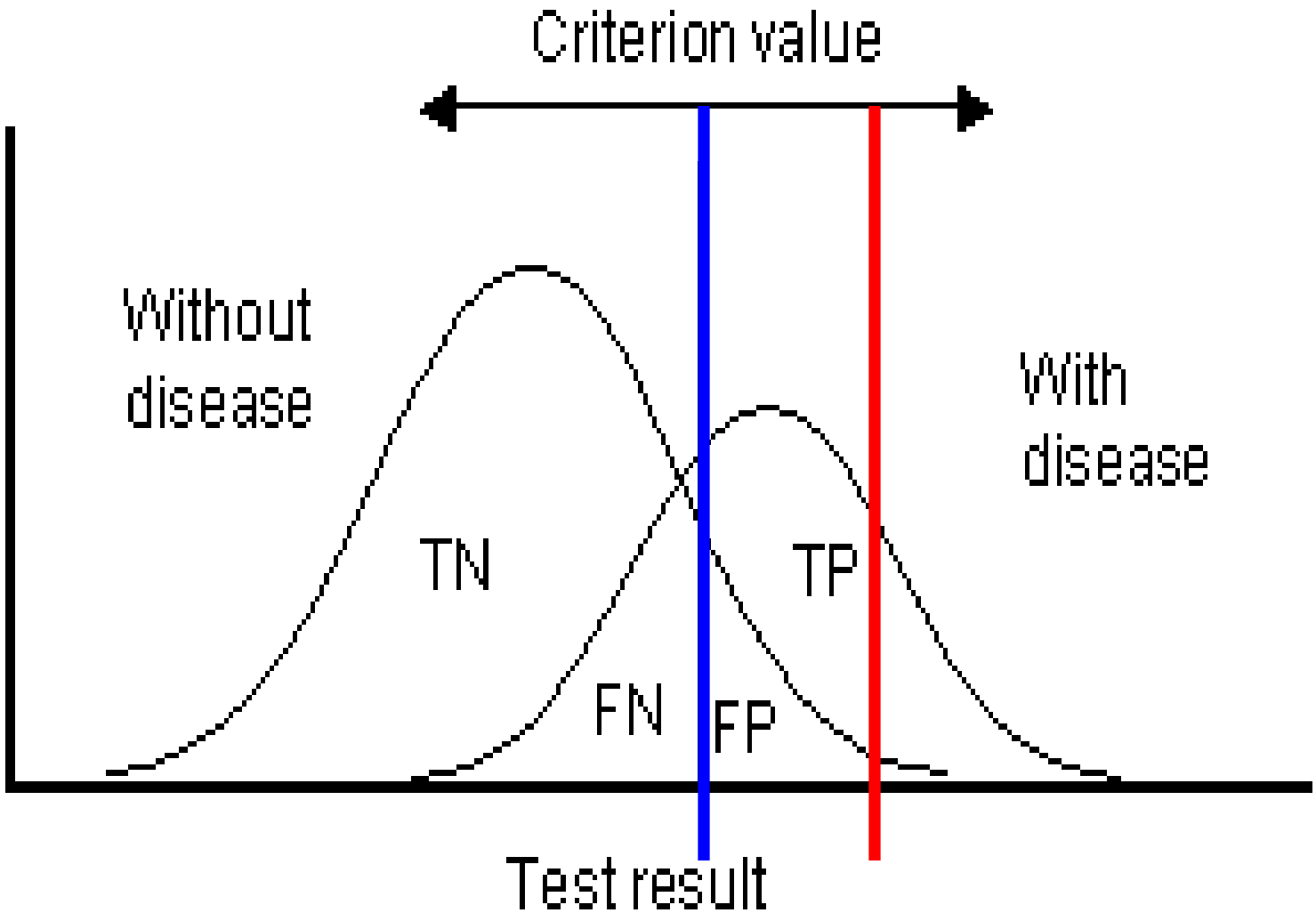

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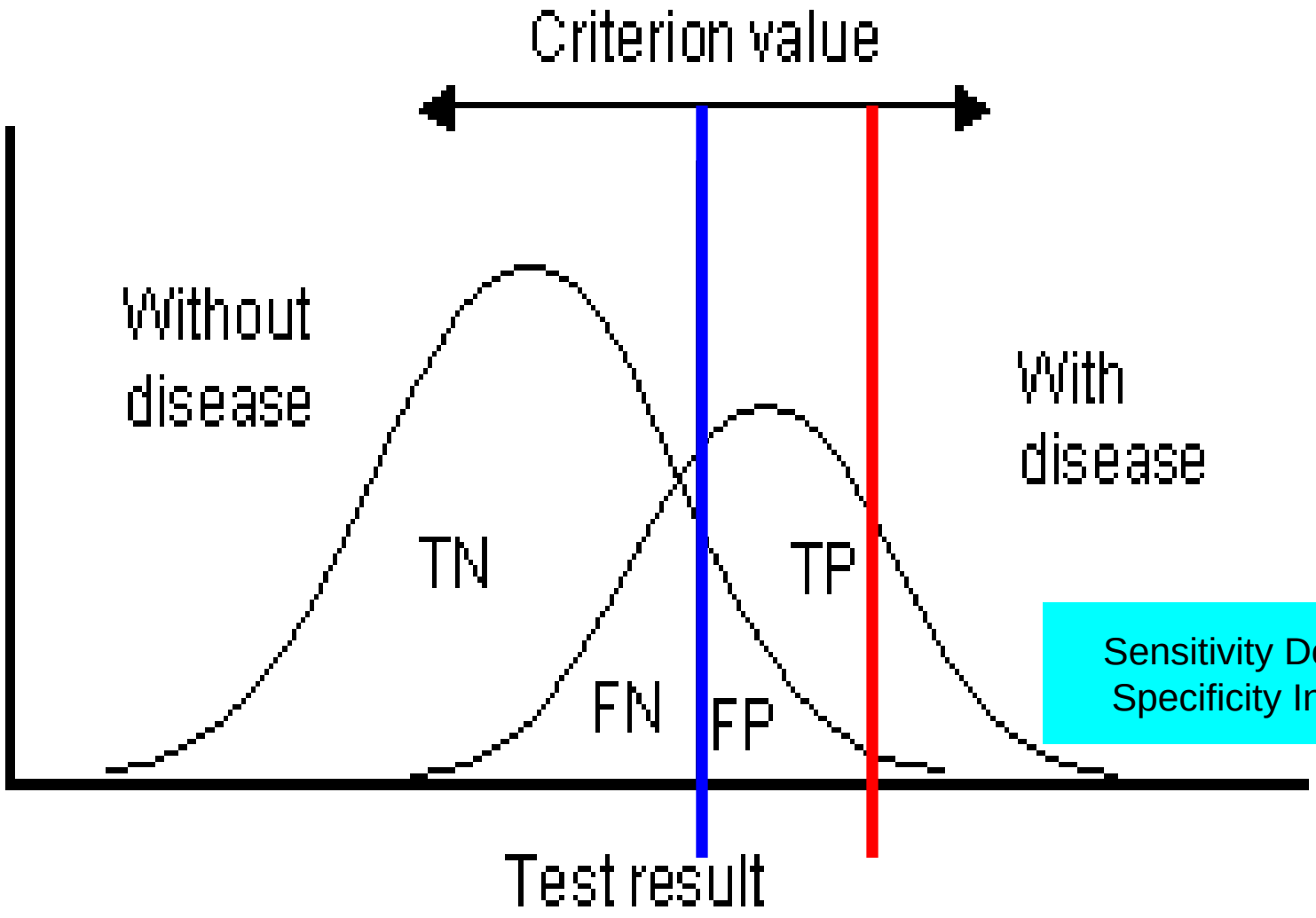

Sensitivity Decreases
Specificity Increases

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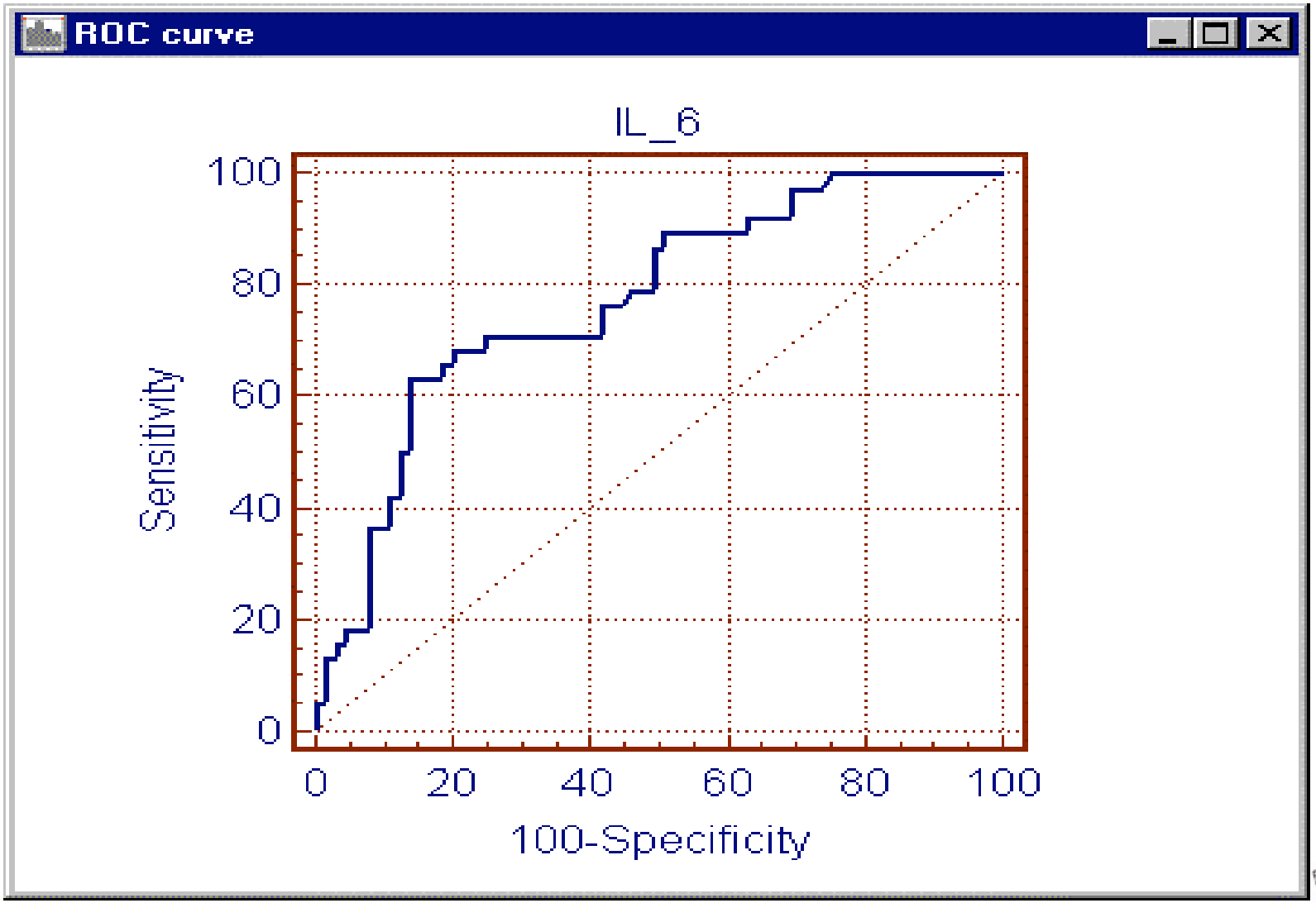
GENERAL CHEMISTRY

POTASSIUM	3.9	3.5-5.0	mmol/L
ALKALINE PHOSPHATASE	70	30-115	U/L
ALT	58 H	1-40	U/L
BILIRUBIN, TOTAL	13	0-20	umol/L
CALCIUM	2.26	2.10-2.55	mmol/L
CREATININE	55	45-100	umol/L
FERRITIN	2934 H	12-200	ug/L
MAGNESIUM	0.85	0.60-1.00	mmol/L
PHOSPHATE	1.00	0.80-1.50	mmol/L
PROTEIN, TOTAL	66	63-80	g/L
ALBUMIN	43	35-50	g/L
URATE	174	140-350	umol/L

Sensitivity / Specificity Trade-off

- Receiver Operating Characteristic (ROC) curve



Test Characteristic Issues

- Highly Sensitive Tests
  - tend to be less invasive, less risky, less costly
  - best for screening programs
  - best for ruling out disease: "SNOUT"

  - E.g. Mammogram for breast carcinoma

Test Characteristic Issues

- Highly Specific Tests
  - tend to be more invasive, more risky, more costly
  - best for confirming (ruling in) disease: “SPIN”

CT guided needle biopsy of lung lesion

Positive Predictive Value

- Probability that disease is present given that the test was positive.

$$P\ (D+ \mid T+)$$

Positive Predictive Value

		DISEASE (PE)		
		Present	**Absent**	
TEST (V/Q scan)	**Positive**	TRUE POSITIVE a = 80	FALSE POSITIVE b = 20	a + b = 100
	Negative	FALSE NEGATIVE c = 10	TRUE NEGATIVE d = 90	c + d = 100
		a + c = 90	b + d = 110	a+b+c+d = 200

Positive Predictive Value

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		a + c = 90	b + d = 110	a+b+c+d = 200

80 / (80 + 20) = 80.0%

Negative Predictive Value

- Probability that disease is absent given that the test was negative.

$$P\ (D- \mid T-)$$

Negative Predictive Value

		DISEASE (PE)		
		Present	**Absent**	
TEST (V/Q scan)	**Positive**	TRUE POSITIVE a = 80	FALSE POSITIVE b = 20	a + b = 100
	Negative	FALSE NEGATIVE c = 10	TRUE NEGATIVE d = 90	c + d = 100
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Negative Predictive Value

		DISEASE (PE)		
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90 / (90 + 10) = 90.0%

Test Characteristic Issues

- Sensitivity and Specificity are conceptually irrelevant
- They assume knowledge of disease status which, if known… the test would not be ordered!

- Positive and Negative Predictive Values has to be the better characteristics….right? (wrong!)

Test Characteristic Issues

- Positive and Negative Predictive Values suffer from depending on disease prevalence
- This is a major drawback.*

(* excellent exam question)

Change Disease Prevalence from 90 to 110 per 200

		DISEASE (PE)		
		Present	**Absent**	
TEST (V/Q scan)	**Positive**	TRUE POSITIVE a = ~~80~~ 97.7	FALSE POSITIVE b = ~~20~~ 16.4	a + b = 114.1
	Negative	FALSE NEGATIVE c = ~~10~~ 12.2	TRUE NEGATIVE d = ~~90~~ 73.6	c + d = 85.8
		a + c = ~~90~~ 110	b + d = ~~110~~ 90	a+b+c+d = 200

Change Disease Prevalence from 90 to 110 per 200

prevalence = 110 / 200 = 0.55 = 55% (was 45%)

sensitivity = 97.7 / 110 = 88.8% (unchanged)
specificity = 73.6 / 90 = 81.7% (unchanged)

positive predictive value = 86.5% (was 80%)
negative predictive value = 85.8% (was 90%)

Accuracy

- Probability that the test is true.

- (not a useful concept as you'll see later)

Accuracy

		DISEASE (PE)		
		Present	**Absent**	
TEST (V/Q scan)	**Positive**	TRUE POSITIVE a = 80	FALSE POSITIVE b = 20	a + b = 100
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(80+90) / (80+ 20 + 10 + 90) = 85.0%

Test Characteristic Issues

- Accuracy:
  - not useful characteristic
  - high sensitivity / low specificity test may have same accuracy as low sensitivity / high specifity test

Positive Likelihood Ratio

- Ratio of:

$$\frac{P(T+|D+)}{P(T+|D-)}$$

Positive Likelihood Ratio

		DISEASE (PE)		
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(80 / 90) / (20 / 110) = 4.89

Utility of Positive Likelihood Ratios

- expresses how many times more likely a test result is to be found in diseased, compared to nondiseased, people.

- can estimate the post-test probability of disease if prevalence is known.

LRs >10 or <0.1 cause large changes in likelihood.

LRs 5-10 or 0.1-0.2 cause moderate changes.

LRs 2-5 or 0.2-0.5 cause small changes.

LRs between <2 and 0.5 cause little or no change.

Negative Likelihood Ratio

- Ratio of:

$$\frac{P(T-|D+)}{P(T-|D-)}$$

Negative Likelihood Ratio

		DISEASE (PE)		
		Present	**Absent**	
TEST (V/Q scan)	**Positive**	TRUE POSITIVE a = 80	FALSE POSITIVE b = 20	a + b = 100
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(10 / 90) / (90 / 110) = 0.14

Pre-test Probability of Disease

- Consider: a female presents for a screening breast mammogram for breast cancer.

- What's her pre-test probability of disease?

Pre-test Probability of Disease

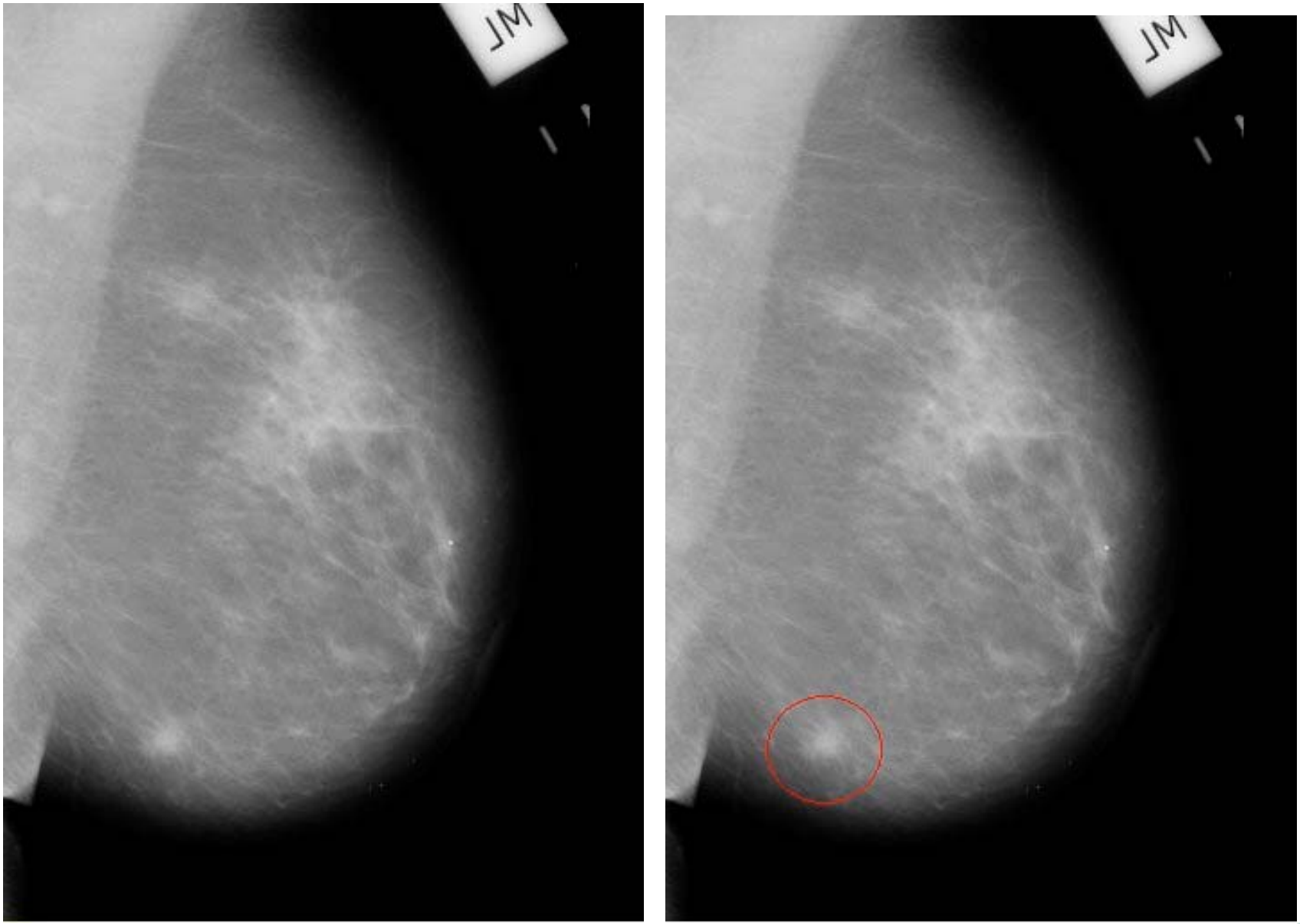
- Consider: a female presents for a screening breast mammogram for breast cancer.

- What's her pre-test probability of disease?

Prevalence of Disease

Positive Test Result

- Say that her mammogram show her to have a 1 cm spiculated calcification
- Say that this finding is associated with a likelihood ratio of 20 (a very suspicious lesion).



Highly suspicious lesion

What is the post-test probability of disease?

Answer:

Pretest odds x Likelihood Ratio = Posttest odds

(the use of odds ratios makes the math convoluted)

What is the post-test probability of disease?

Pretest odds x Likelihood Ratio = Posttest odds

Assume: prevalence = 10 / 1000 = 1% = P(0.01)

Odds = probability of event / (1 - probability of event)

Pre-test Odds = (10/1000) / (1 - (10/1000)) = 0.0101

What is the post-test probability of disease?

Pretest odds x Likelihood Ratio = Posttest odds

0.0101 x 20 = 0.2020

Probability = Odds / (1 + Odds)

Posttest Probability = 0.2020 / (1 + 0.2020)

Posttest Probability = 0.167 = 16.7%

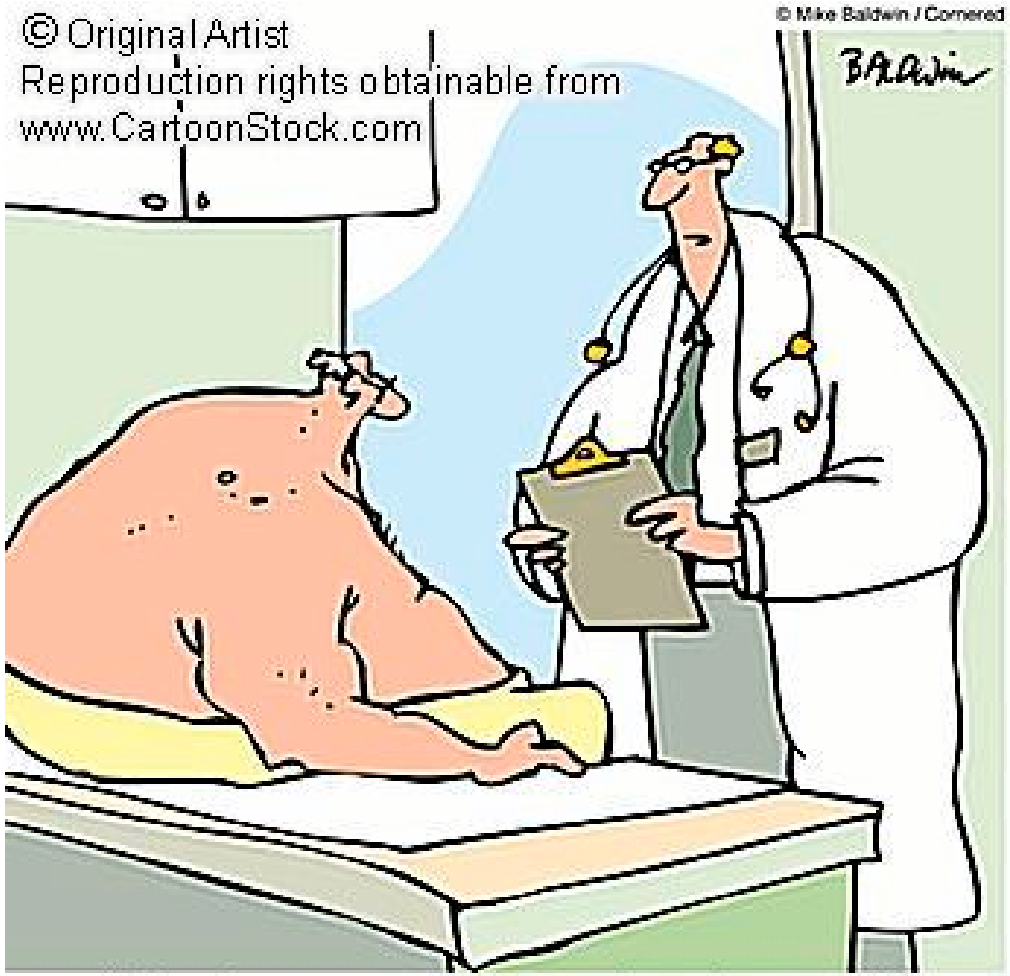
Utility of (Positive) Likelihood Ratio

Pre-test Probability = 1%

Post-test Probability = 16.7%

Prudent Course: move from screening test to confirmatory test!

TREATMENT EFFECT



"You've got six months, but with aggressive treatment we can help make that seem much longer."

Measures of Treatment & Prevention Effect

- Clinical Scenario
  - 75 year old man
  - blood pressure of 210 / 75 mmHg
  - blood pressure readings at future visits same
  - should his blood pressure be treated?

The New England Journal of Medicine

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ORIGINAL ARTICLES

- **Immunoblastic lymphadenopathy. A hyperimmune entity resembling Hodgkin's disease**
- **Immunoblastic lymphadenopathy with mixed cryoglobulinemia. A detailed case study**
- **Vinyl-chloride-induced liver disease. From idiopathic portal hypertension (Banti's syndrome) to Angiosarcomas**
- **Hodgkin's Disease, tonsillectomy and family size**
- **Reduction of ischemic injury by nitroglycerin during acute myocardial infarction (no abstract available)**
- **Frederick Stohlman, Jr., M.D**

Measures of Treatment & Prevention Effect

- VA Trial of HTN therapy
  - two groups identified:
    - those with and without damage

	COMBINED STROKE, MI, DEATH (%)	
	PLACEBO	TREATMENT
DAMAGE	22.2%	8.5%
NO DAMAGE	9.8%	4.0%

Measures of Treatment & Prevention Effect

	Combined End-Point	
	placebo	treatment
damage	22.2%	8.5%
no damage	9.8%	4.0%

Which is better treatment or placebo?

Which group received more benefit?

Measures of Treatment & Prevention Effect

- Absolute Risk Reduction
- Relative Risk
- Relative Risk Reduction
- Odds Ratio
- Number Needed to Treat

Absolute Risk Reduction

Absolute Risk Reduction

- ARR = P(event $_{placebo}$) - P(event $_{treatment}$)

Absolute Risk Reduction

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damage	22.2%	8.5%

Absolute Risk Reduction

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Absolute Risk Reduction

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damage	22.2%	8.5%
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damage 0.222 - 0.085 = 0.137

Absolute Risk Reduction

- ARR = P(event $_{placebo}$) - P(event $_{treatment}$)

damage	22.2%	8.5%
no damage	9.8%	4.0%

damage	0.222 - 0.085 =	0.137
no damage	0.098 - 0.040 =	0.058

Absolute Risk Reduction

- not intuitive
- hard to remember
- groups fared differently in this example

Relative Risk Reduction

Relative Risk Reduction

$$RRR = P(\text{event}_{\text{placebo}}) - P(\text{event}_{\text{treatment}})$$

Relative Risk Reduction

$$RRR = \frac{P(\text{event}_{\text{placebo}}) - P(\text{event}_{\text{treatment}})}{\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad}$$

Relative Risk Reduction

$$RRR = \frac{P(\text{event}_{\text{placebo}}) - P(\text{event}_{\text{treatment}})}{P(\text{event}_{\text{placebo}})}$$

Relative Risk Reduction

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damage	22.2%	8.5%

Relative Risk Reduction

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Relative Risk Reduction

$$RRR = \frac{P(\text{event}_{\text{placebo}}) - P(\text{event}_{\text{treatment}})}{P(\text{event}_{\text{placebo}})}$$

damage	22.2%	8.5%
no damage	9.8%	4.0%

damage (0.222 - 0.085)/ 0.222 = 0.62

Relative Risk Reduction

$$RRR = \frac{P(\text{event}_{\text{placebo}}) - P(\text{event}_{\text{treatment}})}{P(\text{event}_{\text{placebo}})}$$

damage	22.2%	8.5%
no damage	9.8%	4.0%

damage (0.222 - 0.085)/ 0.222 = 0.62

no damage (0.098 - 0.040)/ 0.058 = 0.59

Relative Risk Reduction

- intuitive
- easy to remember
- groups fared similarly

Relative Risk

Relative Risk

$$RR = \frac{P(\text{event}_{\text{treatment}})}{\qquad\qquad}$$

Relative Risk

$$RR = \frac{P(\text{event}_{\text{treatment}})}{P(\text{event}_{\text{placebo}})}$$

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Relative Risk

$$RR = \frac{P(\text{event}_{\text{treatment}})}{P(\text{event}_{\text{placebo}})}$$

damage	22.2%	8.5%
no damage	9.8%	4.0%

damage 0.085 / 0.222 = 0.38

Relative Risk

$$RR = \frac{P(\text{event}_{\text{treatment}})}{P(\text{event}_{\text{placebo}})}$$

damage	22.2%	8.5%
no damage	9.8%	4.0%

damage 0.085 / 0.222 = 0.38

no damage 0.040 / 0.098 = 0.41

Relative Risk

- intuitive
- easier to remember
- groups fared similarly in our example
- smaller is better (unlike RRR)

Odds Ratio

Odds Ratio

Odds (event) = P (event) / (1- P(event))

Odds Ratio

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Think of an Odds Ratio as a ‘ratio of the odds’

Odds Ratio

Odds Ratio

$OR_{treatment}$

Odds Ratio

$$OR = \frac{OR_{treatment}}{\text{---------------}}$$

Odds Ratio

$$OR = \frac{OR_{treatment}}{OR_{placebo}}$$

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damage [0.085 / (1-0.085)] / [0.222 / (1-0.222)]

Odds Ratio

$$OR = \frac{OR_{treatment}}{OR_{placebo}}$$

damage	22.2%	8.5%
no damage	9.8%	4.0%

damage [0.085 / (1-0.085)] / [0.222 / (1-0.222)]

no damage [0.040 / (1-0.040)] / [0.098 / (1-0.098)]

Odds Ratio

$$OR = \frac{OR_{treatment}}{OR_{placebo}}$$

damage	22.2%	8.5%
no damage	9.8%	4.0%

damage [0.085 / (1-0.085)] / [0.222 / (1-0.222)]

no damage [0.040 / (1-0.040)] / [0.098 / (1-0.098)]

damage = 0.33 no damage = 0.38

Odds Ratio

- not intuitive
- easy to remember the results
- groups fared similarly
- math sucks
- smaller number is better (unlike RRR)

Number Needed to Treat

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NNT = 1 / ARR

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damage 1 / (0.222 - 0.085) = 7

Number Needed to Treat

NNT = 1 / ARR

damage	22.2%	8.5%
no damage	9.8%	4.0%

damage	1 / (0.222 - 0.085) = 7
no damage	1 / (0.098 - 0.040) = 17

Number Needed to Treat

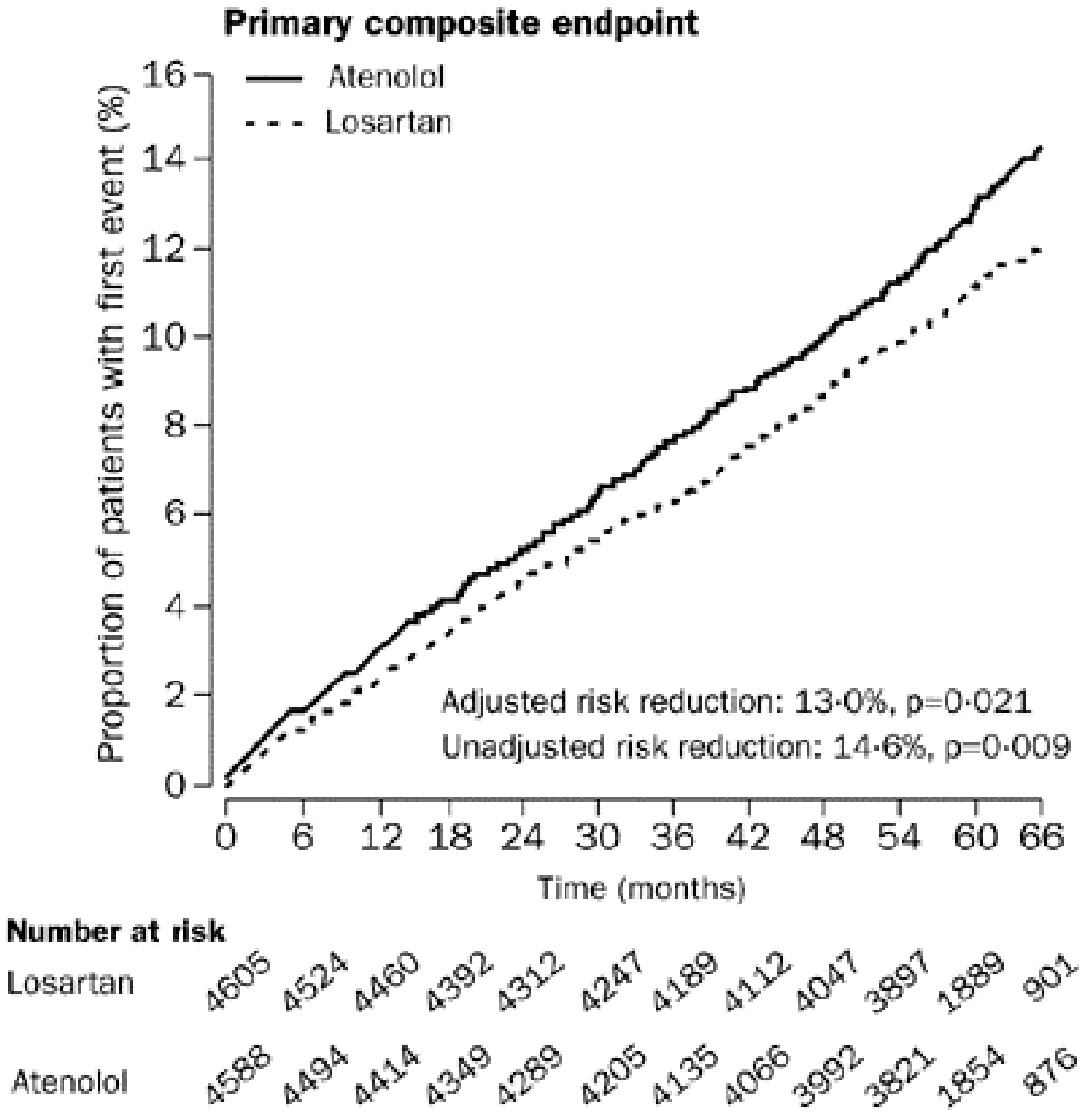
- most intuitive
  - to save an event in the ‘damage’ group, 7 people needed to be treated
  - to save an event in the ‘no damage’ group, 17 people needed to be treated
  - (easier for patients to understand… NOT!)
- easy to remember
- clear distinction between the groups in our example

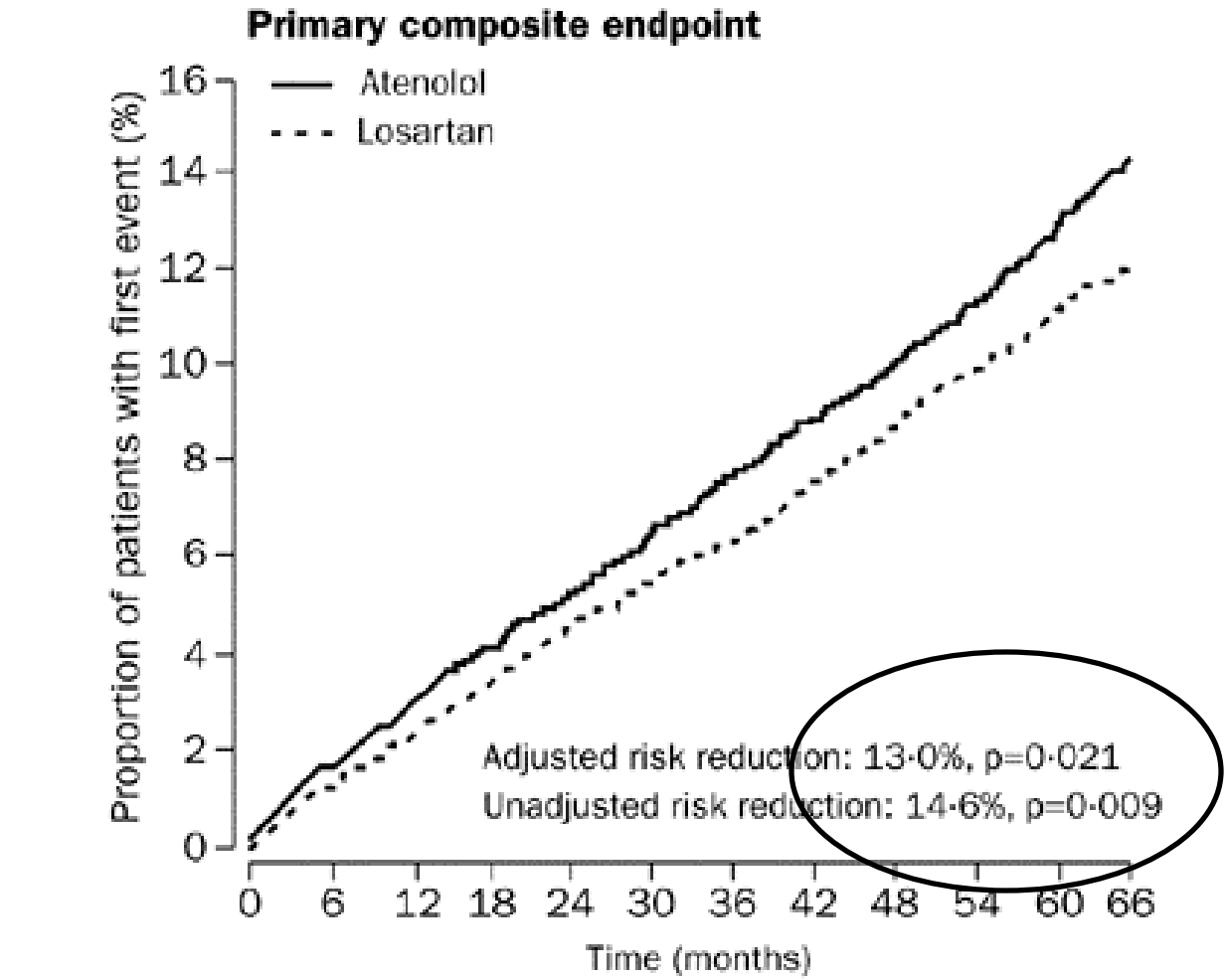
Measures of Treatment & Prevention Effect

- What's the fuss?
  - Can't compare treatments using apples and oranges.
  - E.g.
  - Study A reports NNT and Study B reports RRR

Measures of Treatment & Prevention Effect

- What's the fuss?
  - Absolute risk graphs may not convey the whole story.
  - see data from a recent large trial...


Primary composite endpoint
Atenolol
Losartan
Proportion of patients with first event (%)
16
14
12
10
8
6
4
2
0
Adjusted risk reduction: 13·0%, p=0·021
Unadjusted risk reduction: 14·6%, p=0·009
0 6 12 18 24 30 36 42 48 54 60 66
Time (months)
Number at risk
Losartan 4605 4524 4460 4392 4312 4247 4189 4112 4047 3897 1889 901
Atenolol 4588 4494 4414 4349 4289 4205 4135 4066 3992 3821 1854 876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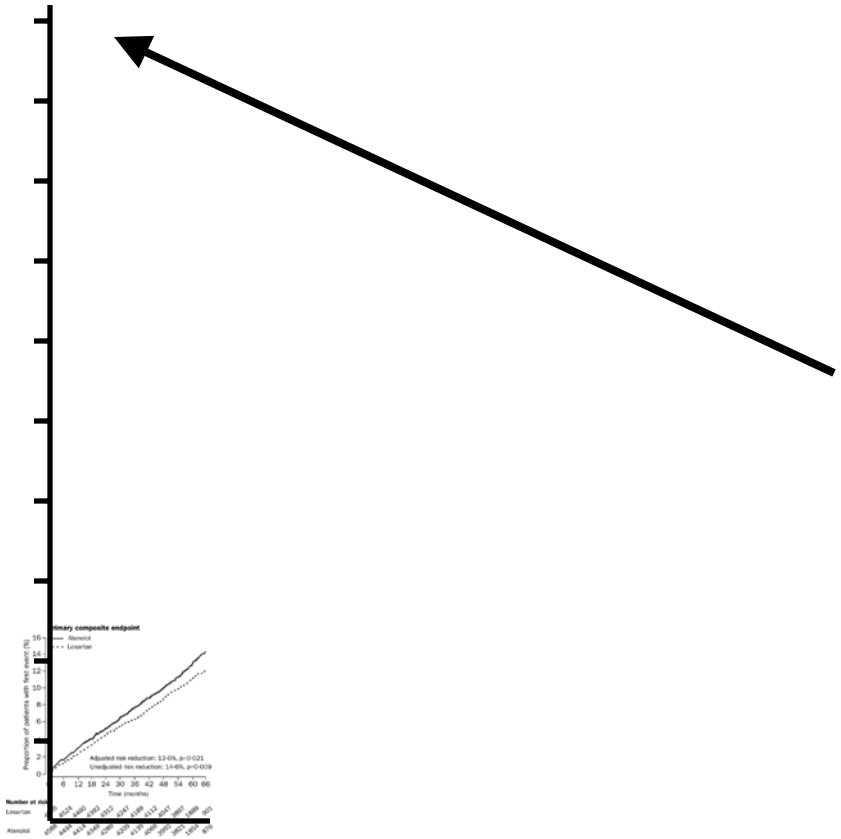
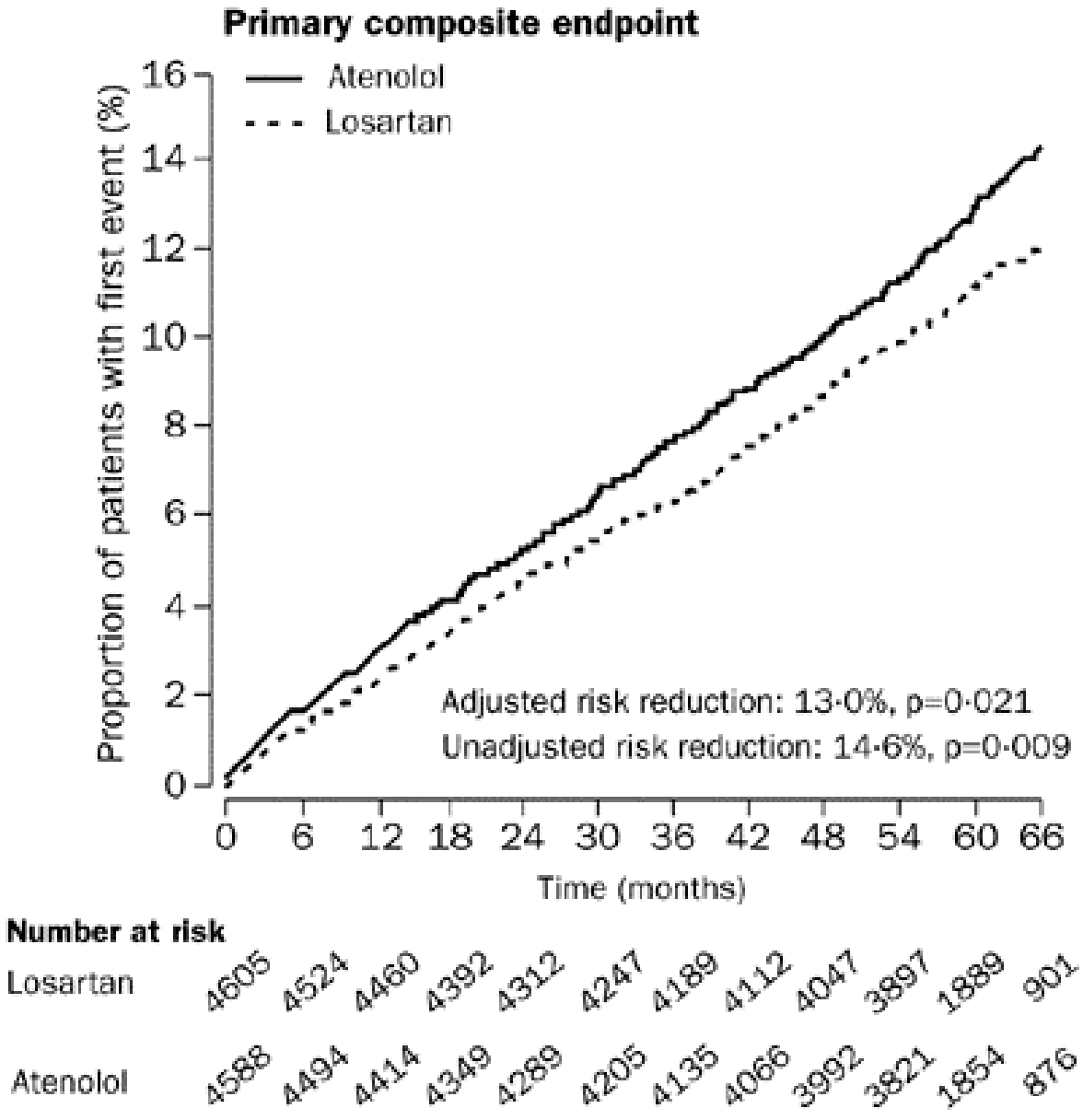
Measures of Treatment & Prevention Effect



- 100% scale on y - axis

Measures of Treatment & Prevention Effect

- What's the fuss?
  - Relative risk and relative risk reduction may also overstate differences between groups
  - see data again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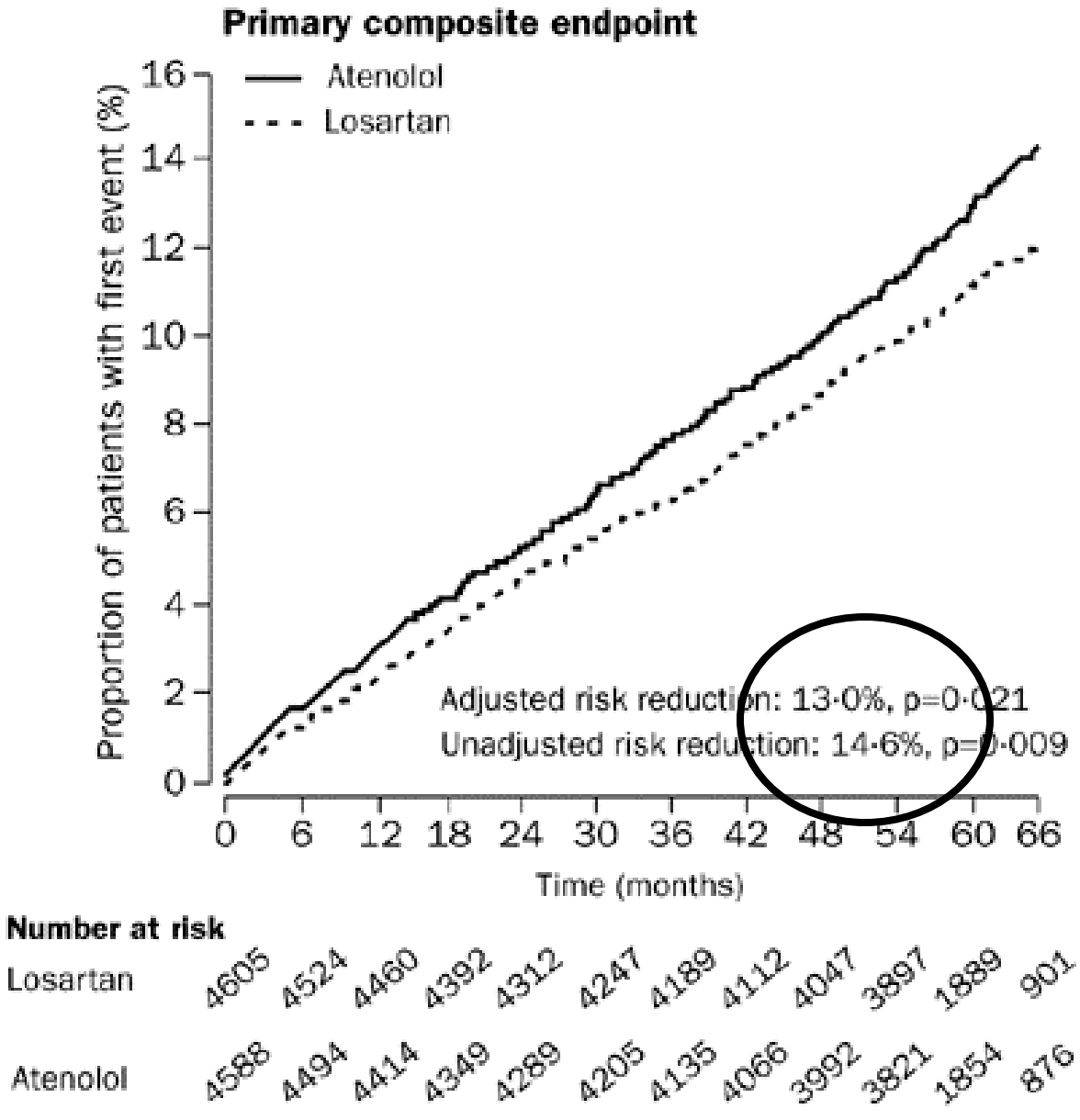
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Measures of Treatment & Prevention Effect

- Raw data:
  - losartan: 508 events / 4605 subjects = 11.0%
  - atenolol: 588 events / 4588 subjects = 12.8%

  - ARR: 0.018 1.8%
  - RRR: 0.14 14.0%
  - RR: 0.86 86.0%

Measures of Treatment & Prevention Effect

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Which number would you like?

Measures of Treatment & Prevention Effect

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  - RRR: 0.14 14.0%
  - RR: 0.86 86.0%

Which number would you like?

NNT = 55.5

Measures of Treatment & Prevention Effect (examples)

Therapy	Endpoint	NNT (5yr)
stepped care for diastolic BP of 115 - 129	death, stroke, myocardial infarction	3
coronary artery bypass grafting for left main disease	death	6
ASA for transient ischemic attack	death, stroke	6
cholestyramine for hypercholesterolemia	death, myocardial infarction	89
INH for inactive tuberculosis	active tuberculosis	96
stepped care for diastolic BP 90 - 109	death, stroke, myocardial infarction	141

Efficacy versus Effectiveness

- Clinical Trials (treatment efficacy):
  - ideal setting

- Everyday Practice (treatment effectiveness)
  - subjects not excluded owing to artificial criteria
  - less monitoring by health care workers
  - patients will be less adherent on average
  - less rigor in measurement

Prevention

- Primary
- Secondary
- Tertiary

- Be mindful of what is risk factor, disease, and complication of disease.

Prevention

- Primary Prevention
  - removing risk factors prior to onset of disease
  - e.g. smoking cessation prior to onset of emphysema, lung cancer, coronary disease, or stroke.
  - e.g. folate to prevent neural tube defects in utero

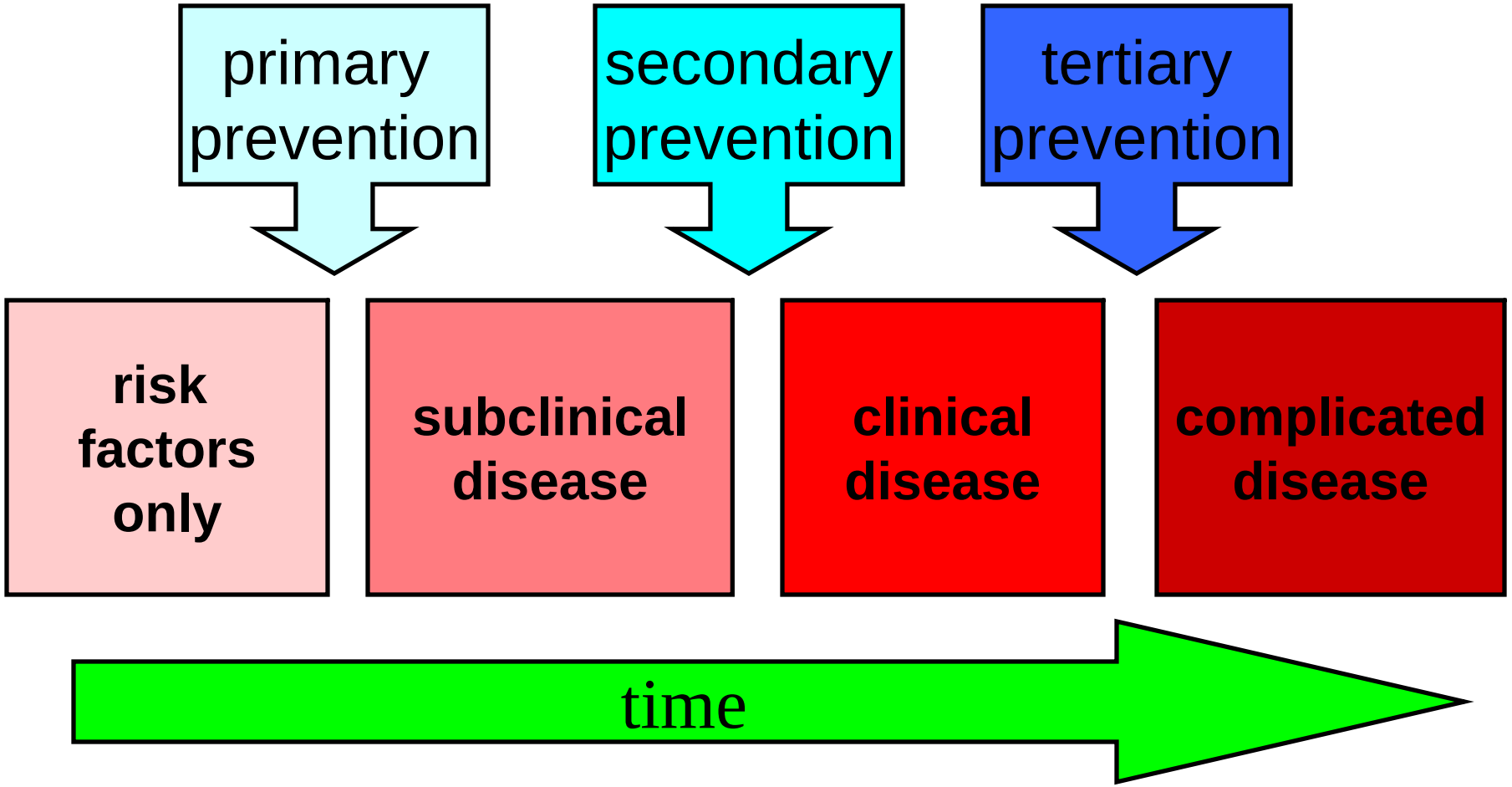
Prevention

- Secondary Prevention
  - detecting disease while it is asymptomatic and when early treatment can stop it from progressing
  - e.g. screening for cervical cancer with Pap smear, digital rectal examination for prostate cancer

Prevention

- Tertiary Prevention
  - prevent clinical deterioration or complications once disease has declared itself
  - e.g. scheduled retinal examinations for patients with known diabetes mellitus, use of an ACE-inhibitor to reduce risk heart failure among those with known coronary disease, consideration of feeding strategies to prevent pneumonia among patients with amytrophic lateral sclerosis (terminal neurological disease)

Prevention


primary prevention
secondary prevention
tertiary prevention
risk factors only
subclinical disease
clinical disease
complicated disease
time

Prevention versus Therapy

- depending on perspective, a ‘disease’ may really be a ‘risk factor’ for disease
- distinction between therapy and prevention may blur
- e.g. is osteoporosis is a risk factor or disease? (ask an endocrinologist, ask an orthopedic surgeon)

Prognosis

- natural history of disease
  - disease course without intervention
- clinical course of disease
  - disease course with intervention

Prognosis

- Common outcomes of disease
  - 5-year survival: percent of patients surviving for 5 years from some point in their disease
  - Case Fatality Rate: percent of patients with a disease who die of it
  - Disease-specific Mortality: number of people per 10,000 (or 100,000) population dying of a specific disease
  - Response: percent of patients showing some evidence of improvement following an intervention
  - Remission: percent of patients entering a phase in which disease is no longer detectable
  - Recurrence: percent of patients who have return of disease after a disease-free interval

Prognosis

- Common outcomes of disease
  - not all outcomes are as definite (or bleak) as those just shown
  - health related quality of life
    - more qualitative (than quantitative)
    - may be more important to patients than mortality outcomes
    - is likely to become increasingly important

Prognostic Factor versus Risk Factor

- A good example:
  - low blood pressure is protective against a myocardial infarction
  - low blood pressure is predicts a poor prognosis among those having a myocardial infarction
  - Why?

Prognosis versus Risk Factor

- High BP is associated with atherosclerosis and thickening of the heart muscle which both increase risk of heart attack (MI)

- Low BP at an MI is consistent with sufficient muscle damage that it cannot generate a satisfactory blood pressure.

**"The red blobs are your red blood cells.
The white blobs are your white blood cells.
The brown blobs are coffee. We need to talk."**