Lecture - Day 2 (part 2)
Diagnostic tests

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Outline

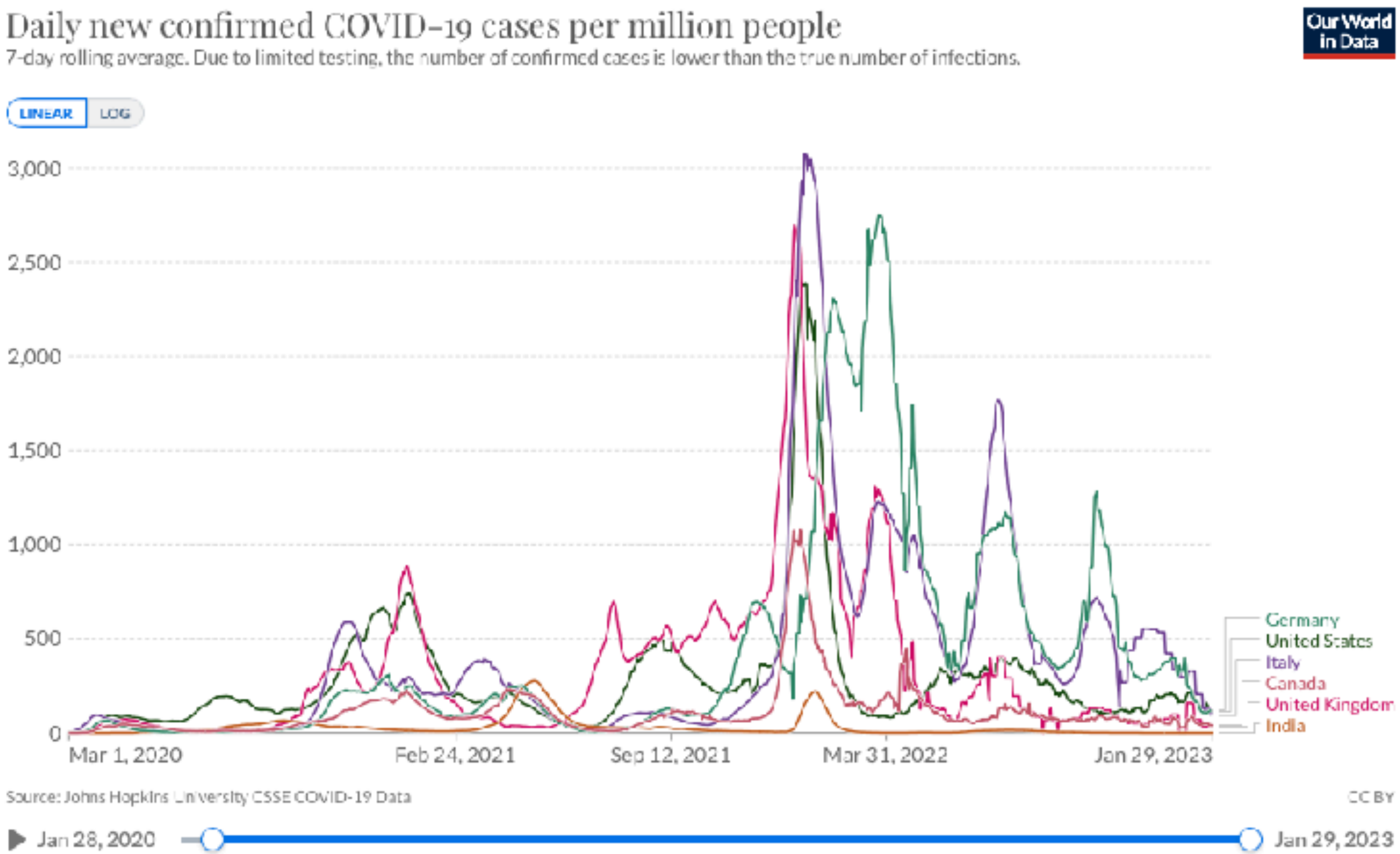
Aalen chapter 3.9-3.10, Kirkwood and Sterne chapter 36.2

- Diagnostic tests
- Sensitivity, specificity and related concepts
- Relation to Bayes Law
- ROC curve

Diagnostic testing

Introduction

Covid: RT-PCR, antigen (lateral flow test), antibody

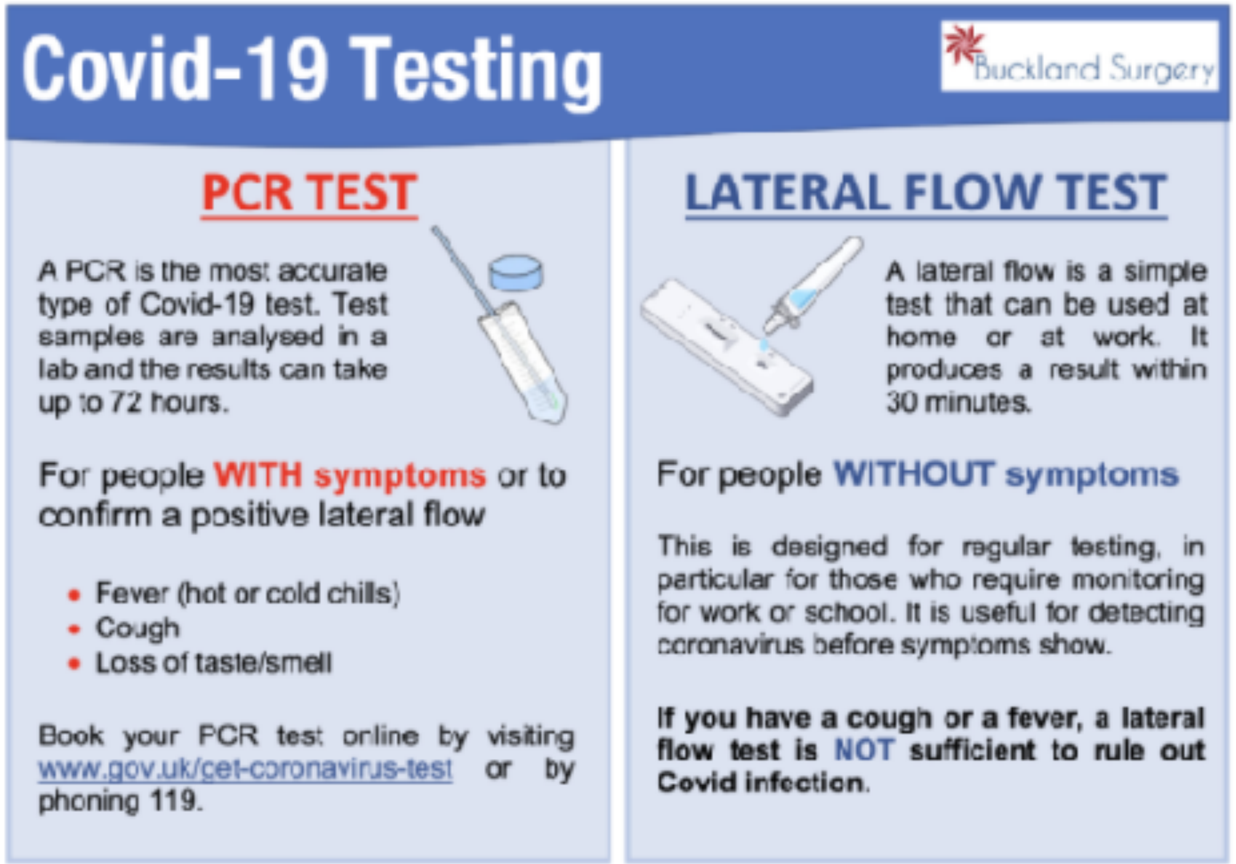


Diagnostic testing

“PCR test is a **highly sensitive** and **accurate** test”
“Antigen test is **less sensitive** than PCR tests”

PCR
sensitivity: around 80%; specificity: 98-99%

Rapid antigen test
overall sensitivity 65.3%; specificity 99.9%
Among asymptomatic individuals, sensitivity 44%



Diagnostic testing

Mammography: an imaging technique used for early detection of breast cancer. Itself is not enough for diagnosis of cancer.

Used together with FNAC (fine needle aspiration biopsy) - more accurate, higher PPV (more on PPV later)

How much do we trust the mammography for diagnosis of breast cancer?

		Mammography	
		Cancer	Not cancer
Final diagnosis	Cancer	22	3
	Not cancer	16	331

Confusion matrix

A 2 by 2 table for test result and true conditions

		Predicted (test result)	
		Positive	Negative
Actual condition	Positive	**True Positive TP**	False Negative FN
	Negative	False Positive FP	**True Negative TN**

		Mammography	
		Malignant	Benign
Final diagnosis	Malignant	22	3
	Benign	16	331

Sensitivity, specificity

		Predicted (test result)	
		Positive	Negative
Actual condition	Positive	**True Positive TP**	False Negative FN
	Negative	False Positive FP	**True Negative TN**

Sensitivity: the ability (expressed as probability) to identify those with disease; i.e. having positive conditions

$$TP/P = TP/(TP+FN)$$

If a test has a sensitivity of 98%:
for 100 people who have the disease, 98 can be detected, 2 are missed by the test

Sensitivity, specificity

		Predicted (test result)	
		Positive	Negative
Actual condition	Positive	**True Positive TP**	False Negative FN
	Negative	False Positive FP	**True Negative TN**

Specificity: the ability to identify those without disease; i.e. having negative conditions

$$TN/N = TN/(TN+FP)$$

If a test has a specificity of 99%:
for 100 people who do not have the disease: 99 can be identified, 1 has a positive result but it is wrong (false postive).

Example: mammography

		Mammography	
		Cancer	Not cancer
Final diagnosis	Cancer	22	3
	Not cancer	16	331

Identify positive and negatives: cancer outcome is positive

Sensitivity: TP/P = TP/(TP+FN) = 22/(22+3) = 0.88
For 100 people who **have** the disease, 88% can be identified

Specificity: TN/N = TN/(TN+FP) = 331/(331+16) = 0.95
For 100 people who **do not have** the disease, 95% can be identified

Positive predictive value

		Predicted (test result)	
		Positive	Negative
Actual condition	Positive	**True Positive TP**	False Negative FN
	Negative	False Positive FP	**True Negative TN**

Positive predictive value (PPV): probability that a positive test result is correct, i.e. identifies the positive actual condition

$$PPV = TP/\text{positive test} = TP/(TP+FP)$$

True and false positive rate

		Predicted (test result)	
		Positive	Negative
Actual condition	Positive	**True Positive TP**	False Negative FN
	Negative	False Positive FP	**True Negative TN**

True positive rate (TPR): among the positives (e.g. disease), how many are tested as positive (true positives)

$$TPR = TP/P = \text{sensitivity}$$

False positive rate (**FPR**): among the negatives (e.g. healthy), how many are tested as positive (false positives)

$$FPR = FP/N = FP/(FP+TN) = 1 - \text{specificity}$$

Example: mammography

		Mammography	
		Malignant	Benign
Final diagnosis	Malignant	22	3
	Benign	16	331

Positive predictive value: TP/positive test = TP/(TP+FP) = 22/(22+16) = 0.58

When the **tests are positive** for 100 people, 58% really have the condition

False positive rate: FP/N = FP/(TN+FP) = 16/(331+16) = 0.046

For 100 people who **do not have the condition**, 4.6 (or 5) have a **false positive** test (recall that FPR = 1-specificity, specificity is 95%)

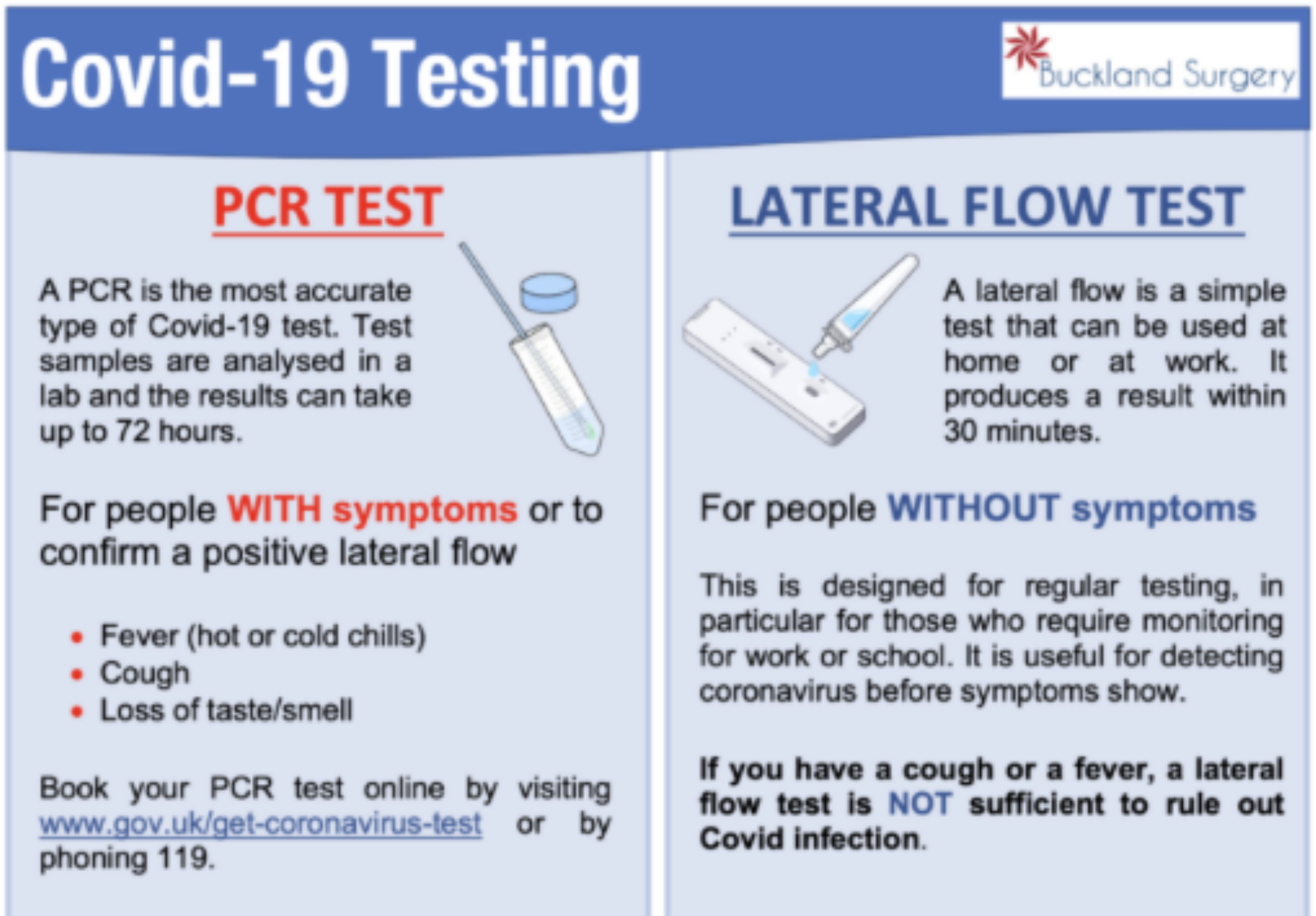
Summary

		Predicted (test result)	
		Positive	Negative
Actual condition	Positive	**TP**	FN
	Negative	FP	**TN**

Sensitivity: TP/P **Specificity**: TN/N
Positive predictive value **PPV**: TP/(TP+FP)

A highly sensitive test: if patient has disease, test makes few false negative

Summary



Both highly **specific** (98% vs 99.8%): if one really doesn't have covid, both tests will give correct result: negative.

For people without symptom (suspect no covid): a negative antigen test is good enough to rule out the disease: and much **faster**!

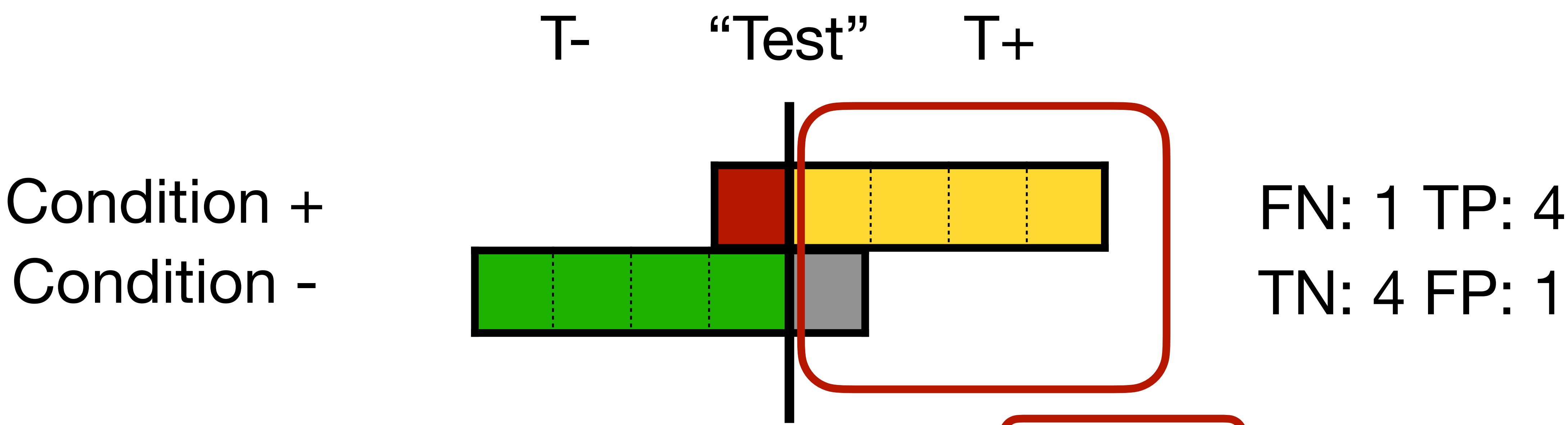
RT-PCR is more **sensitive** than rapid antigen (80% vs 65%): if one has covid, PCR is more likely to give the positive result.

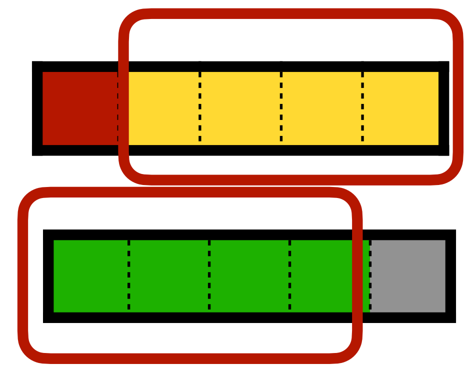
Peopel with symptom (suspecting covid), PCR is better than antigen test to **confirm**.

Visualization

Sensitivity, specificity, PPV

Imagine 10 patients participated in a test.





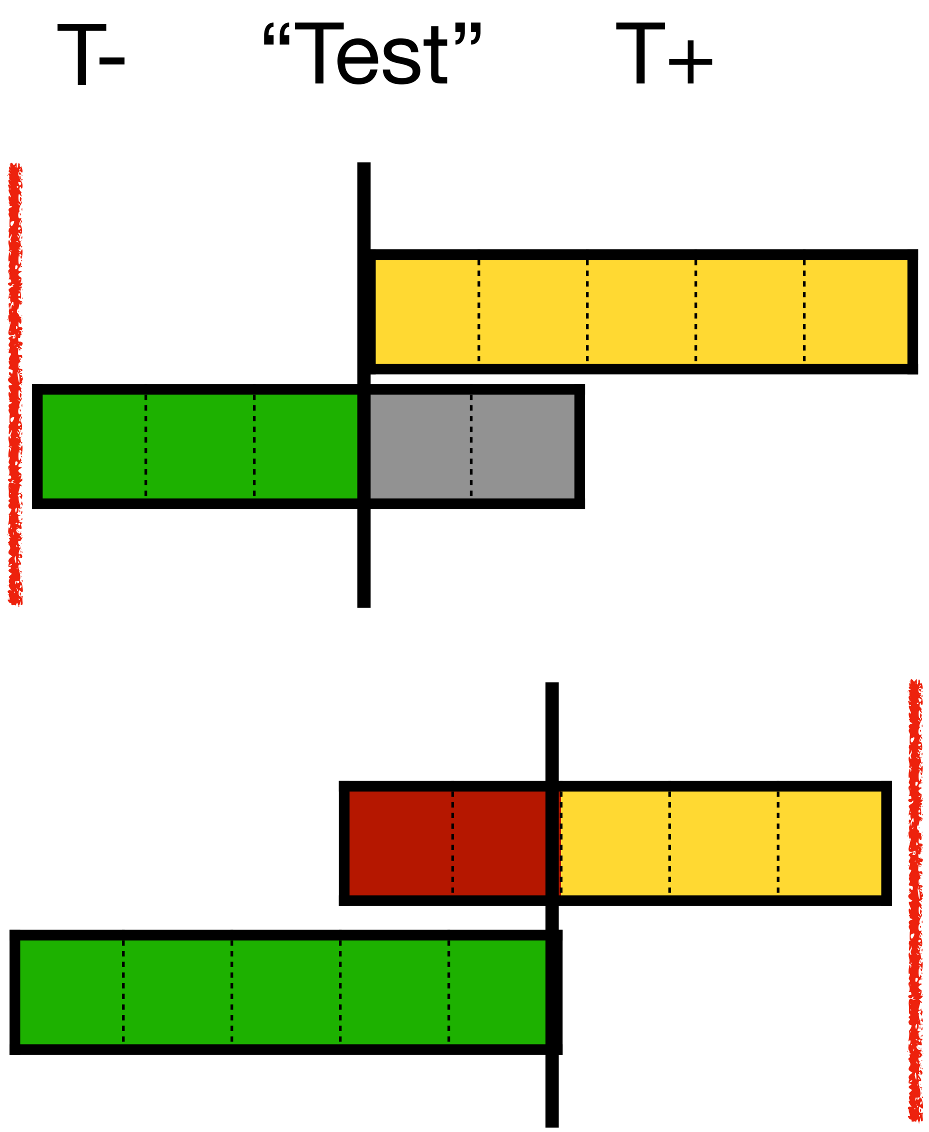
Sensitivity: 4/5 = 0.8
Specificity: 4/5 = 0.8
Positive predictive value: 4/5 = 0.8

Different 4 and 5!

Visualization

Sensitivity, specificity

Change the test threshold



A sensitive test

Rarely misses patients with disease;
but can have many false positives

Claim ALL patients test positive: 100% sensitivity!

A specific test

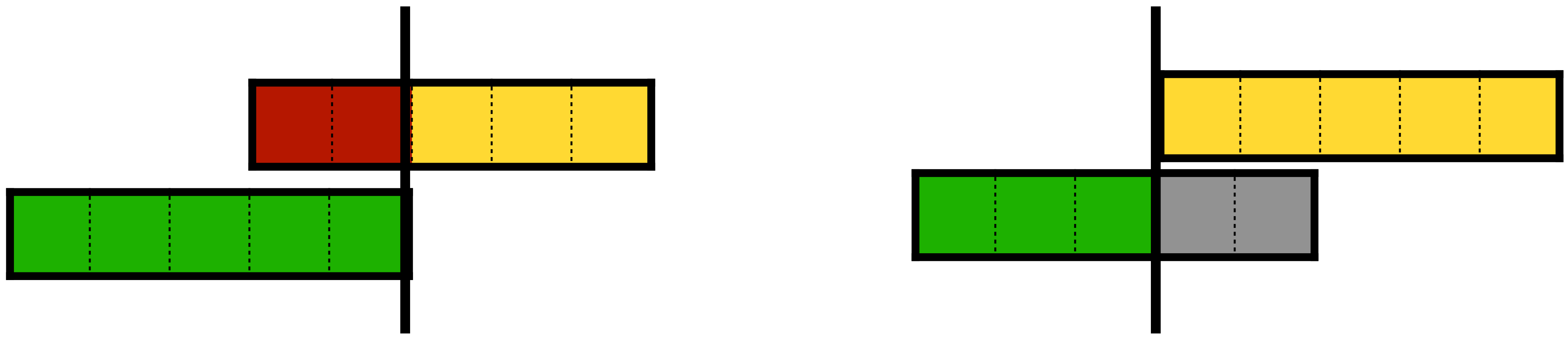
Rarely gives positive results for healthy people; but might miss patients with disease

Claim ALL patients test negative: 100% specificity!

But the test is useless to tell who’s who. Always look at both metrics, and find a balance

ROC Analysis

Receiver Operator Curve



Limitation of sensitivity and specificity: require a single cut—off value (threshold) to determine true positive result

Depending on different cut-off values, sensitivity and specificity would change.

Would like to compare different values of cut-off, and compare different tests

ROC Analysis

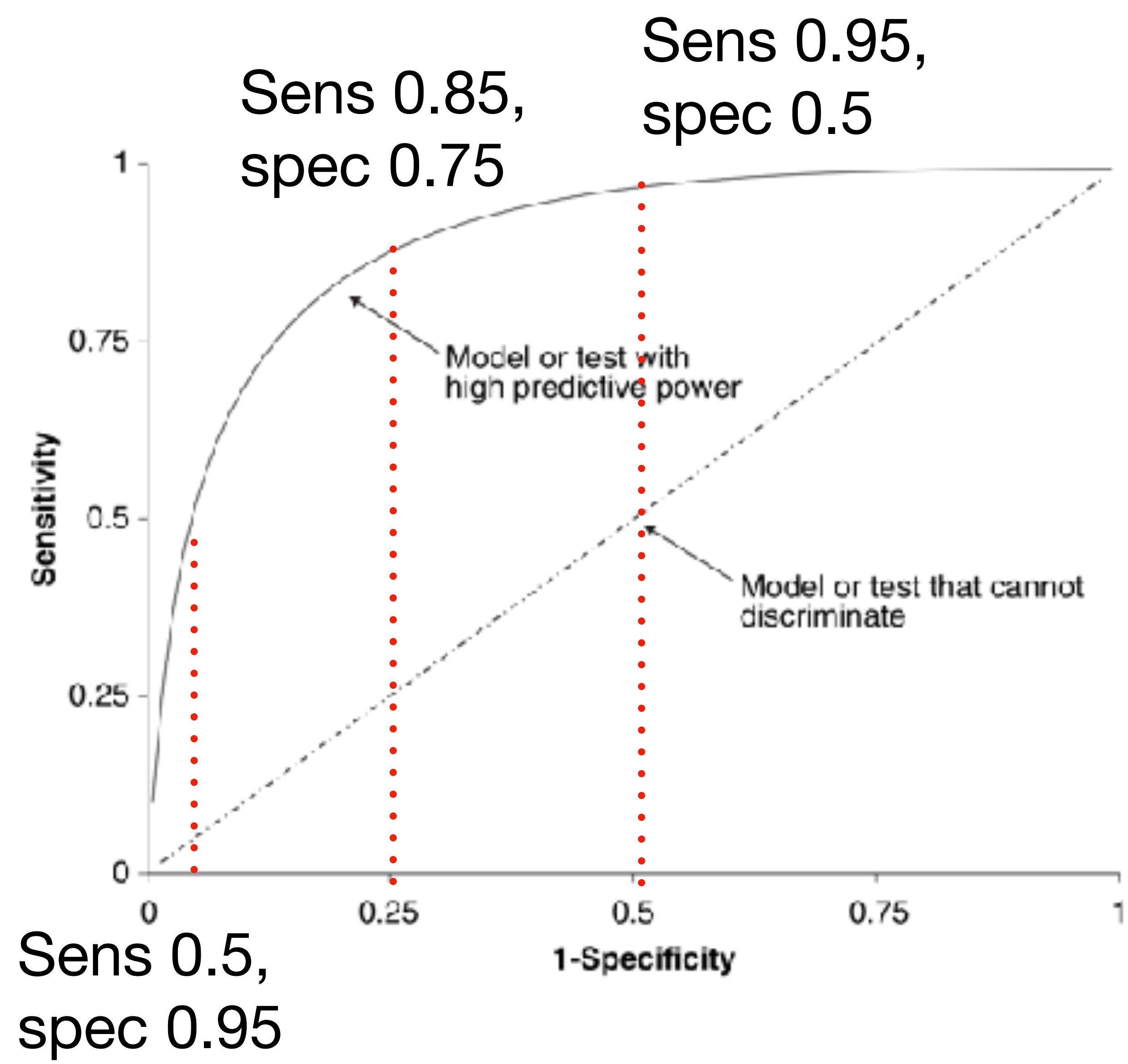
Receiver Operator Curve

ROC curve: plots pairs of sensitivity and (1-specificy) for a range of cut-off values

Equivant to True Positive Rate vs False Positive Rate

Sensitivity: TP / P
Specificity: TN / N

45 degree line: test is no better than random assignment



Linden 2004, doi:10.1111/j.1365-2753.2005.00598.x

ROC Analysis

Receiver Operator Curve

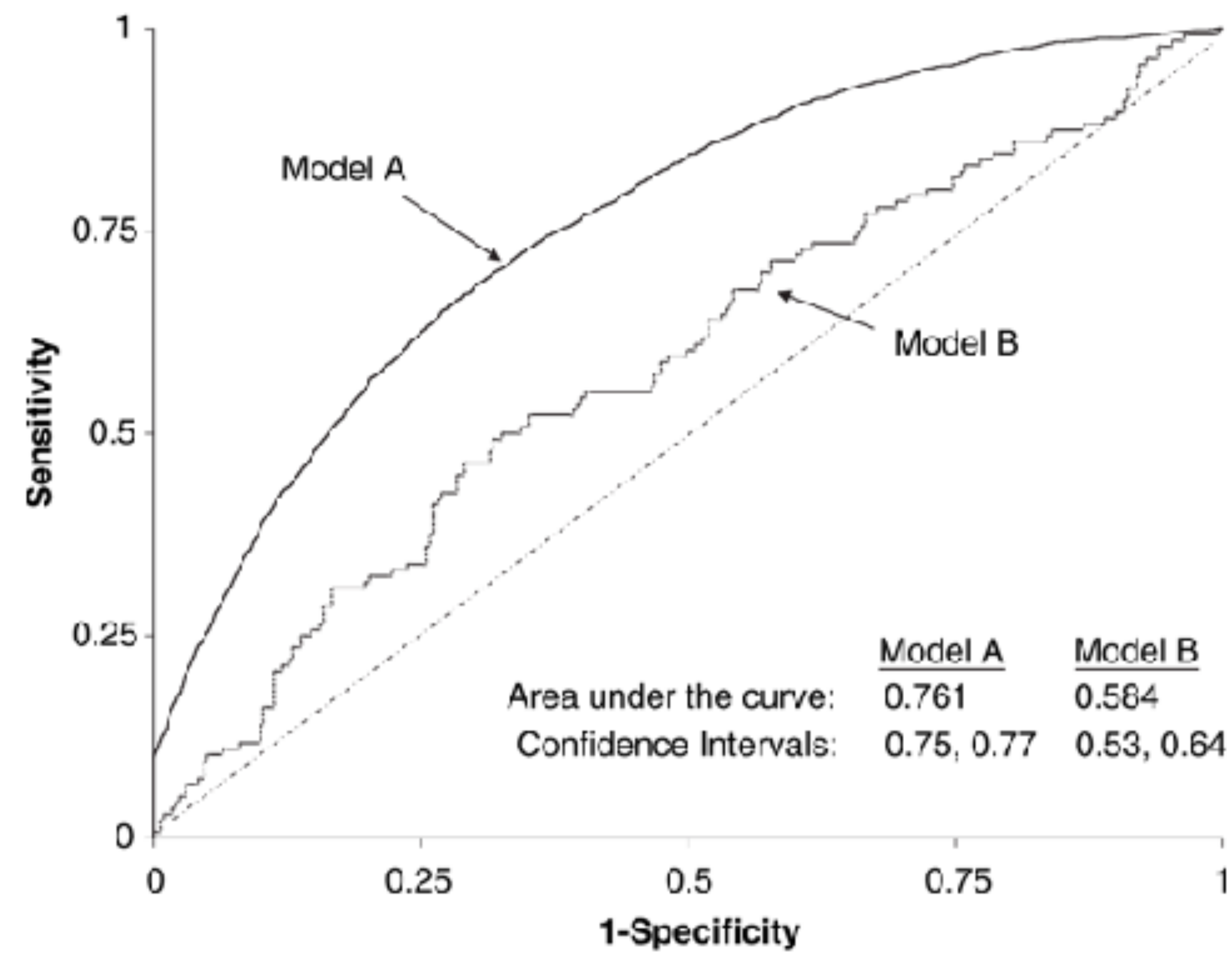
You can compare different tests (or models) using ROC.

Use AUC: Area Under the Curve (a value between 0 and 1) as an overall metric for the test

The higher AUC is, the better

For example, Model A has AUC 0.761 and model B has AUC 0.584

Model A is better



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Prevalence

Application of Bayes Law

Sensitivity and specificity are not affected by disease prevalence.

Prevalence: positive cases among the total population

Positive predictive value PPV (TP/TP+FP) is affected by prevalence.

Why do we care about PPV?
You as a doctor have 100 positive test results. You want to know how many are actually really having cancer; how many are just false positives.

Low PPV means **#false positive >> #true positive**

Tests with the same <u>high sensitivity and specificity</u> can have very different PPV, depending on how common the disease is.

Example: HIV testing

We want to test for antibodies of the HIV virus.
A positive test: shows antibodies
A negative test: does not show antibodies

We know that the false positive rate (FPR) is 0.2%, and false negative rate (FNR) is 2%. Assume that the **prevalence** of HIV in the population is 0.1%.

FPR = FP/N= FP/(FP+TN) = 1- specificity
FNR = FN/P = FN/(FN + TP) = 1 - sensitivity

What is the probability of a person really having HIV, when he is tested positive?

Translate: find PPV: TP/(TP + FP)

Example: HIV testing
Method I

Probability of a person really having HIV, when he is tested positive: **PPV**

Prevalence = 0.1% i.e. for 100000 persons, 100 are HIV infected (both TP and FN), 99900 are not.

False positive rate (FPR) = 0.2%, i.e.
specificity = 99.8%

In 99900 negatives, TN = 99700, FP = 200

False negative rate (FNR) = 2%, i.e.
sensitivity = 98%

In 100 positives, TP = 98, FN = 2

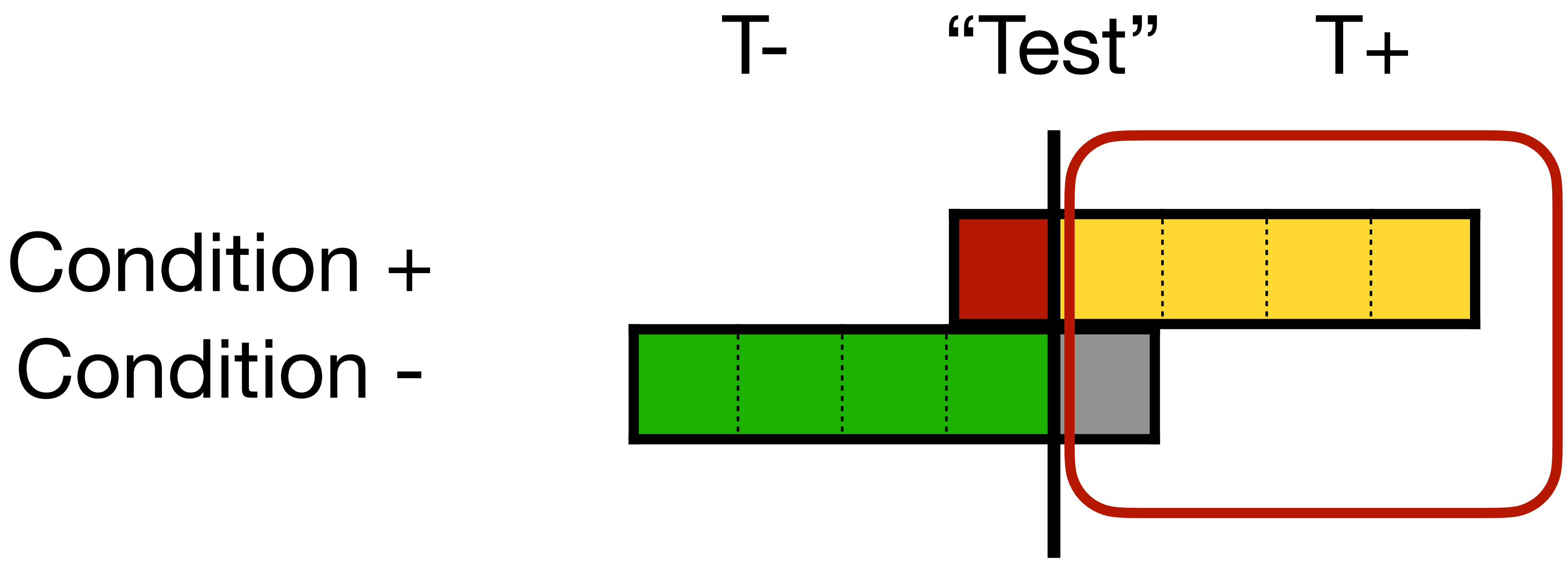
For 100,000 people		Test result: P	Test result: N	
Have HIV?	P	98	2	100
	N	200	99700	99900

PPV = 98/(98+200) = 32.9%

FPR = FP/N = 1- TN/N = 1 - specificity
FNR = FN/P = 1-TP/P = 1 - sensitivity

Prevalence and PPV

Visualization



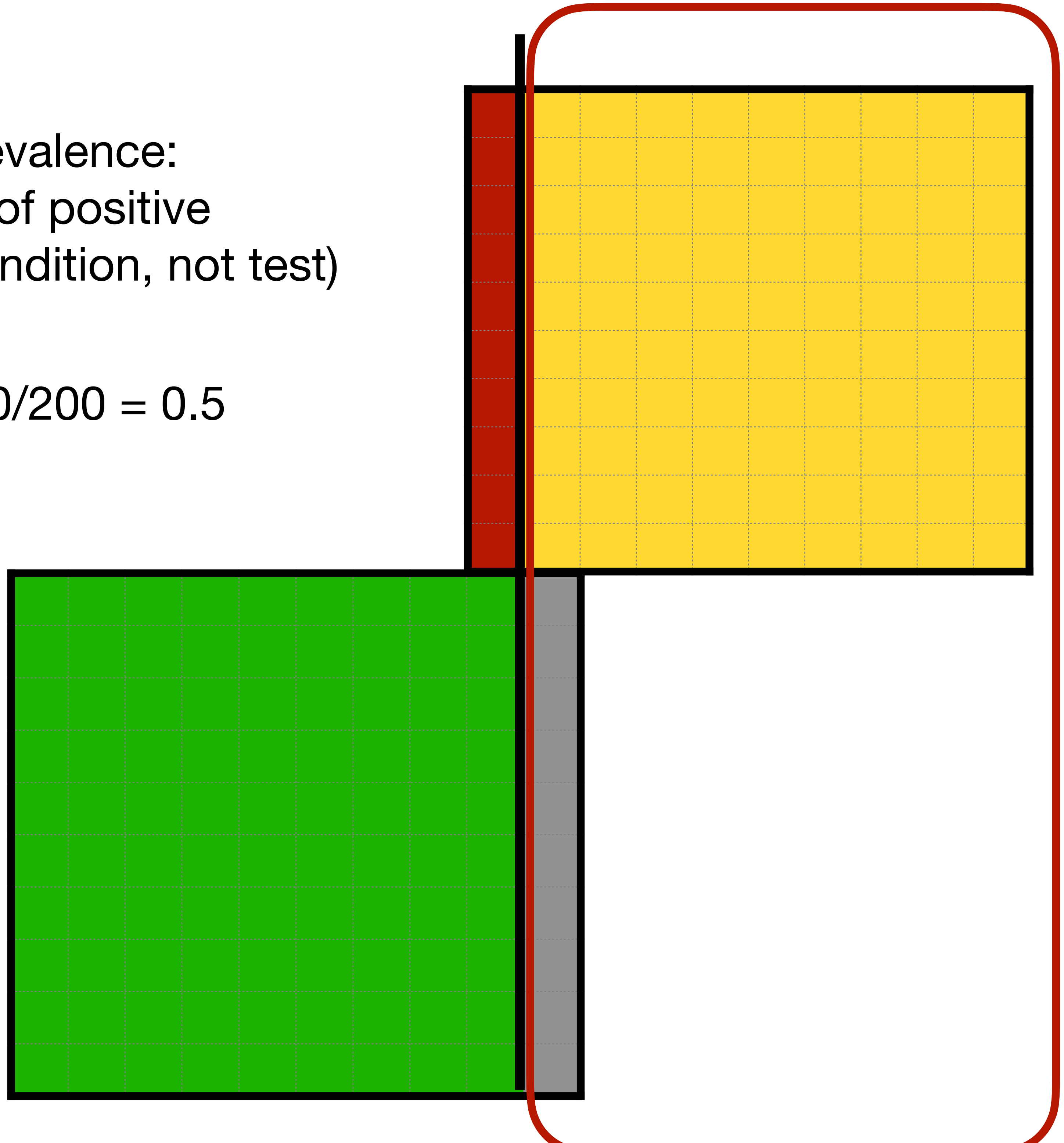
Sensitivity: 4/5 = 0.8
Specificity: 4/5 = 0.8
Positive predictive value: 4/5 = 0.8

Prevalence and PPV

A “good” test

Prevalence:
% of positive
(condition, not test)

100/200 = 0.5



High sensitivity:
90/100 = 90%

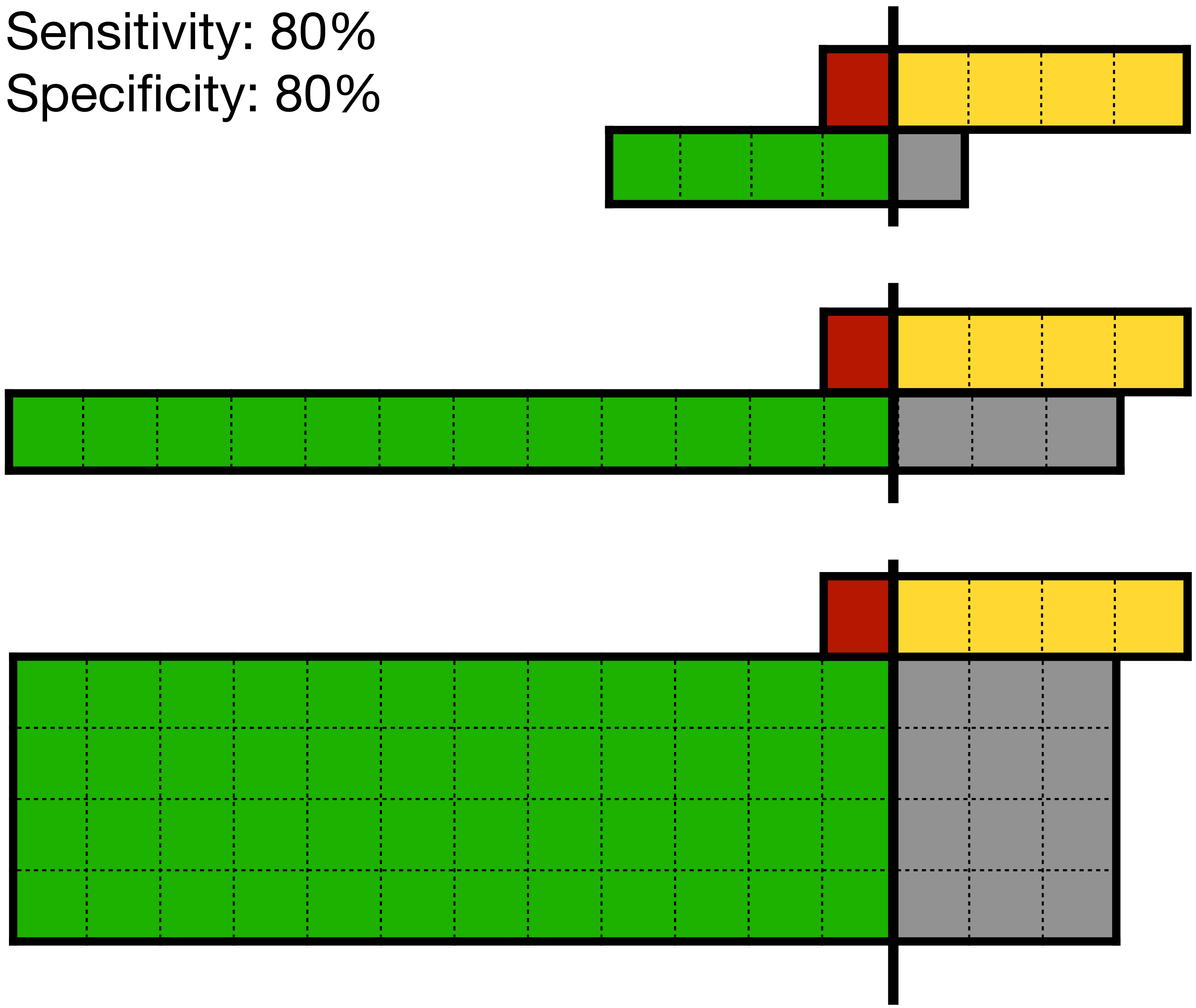
High specificity:
90/100 = 90%

High PPV:
90/100 = 90%
Those with positive test results, 90% do have the condition

Prevalence and PPV

Same sensitivity and specificity

Sensitivity: 80%
Specificity: 80%



Prevalence: 50%
PPV: 4/5 = 80%

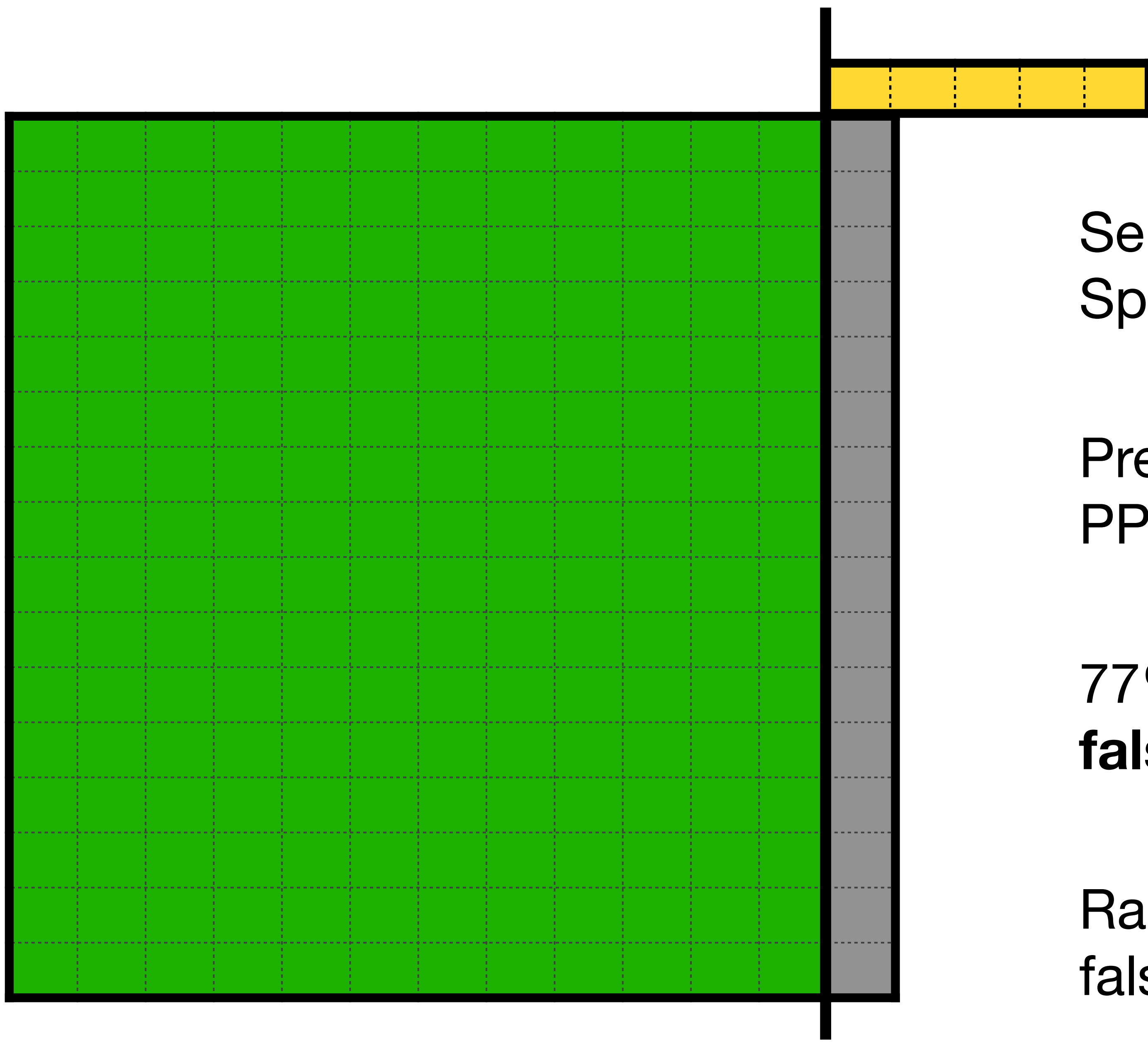
Prevalence: 25%
PPV: 4/7 = 57%

Prevalence: 7.6%
PPV: 4/16 = 25%

3/4 of the test positives are **false** positives

Prevalence and PPV

What about more sensitive and specific tests?



Sensitivity: 100%
Specificity: 92.3%

Prevalence: 5/(5+208) = 2.3%
PPV: 5/21 = 23.8%

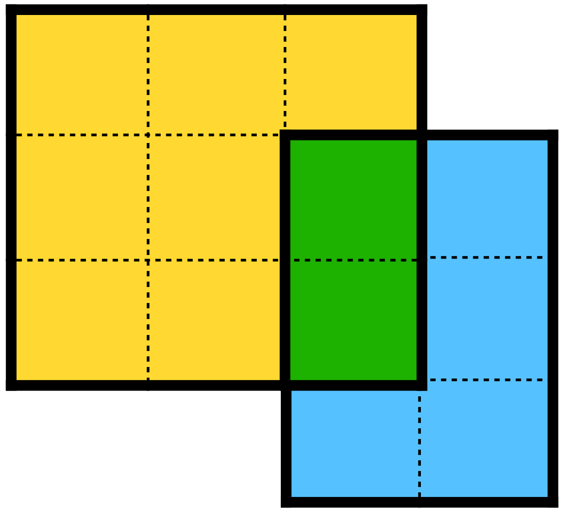
77% of the test positives are **false** positives

Rare disease screening: many false positives

Prevalence and PPV

Bayes Law

$$P(A|B) = \frac{P(B|A)P(A)}{P(B)}$$



$$P(A|B) = \frac{P(B|A)P(A)}{P(B|A)P(A) + P(B|\text{not } A)\, P(\text{not } A)}$$

Prevalence and PPV

Bayes Law

$$P(A|B) = \frac{P(B|A)P(A)}{P(B)}$$

$$P(A|B) = \frac{P(B|A)P(A)}{P(B|A)P(A) + P(B|\text{not } A)\, P(\text{not } A)}$$

$$P(\text{HIV}|\text{positive test}) = \frac{P(\text{positive test}|\text{HIV})\, P(\text{HIV})}{P(\text{positive test})}$$

$$\frac{P(\text{positive test}|\text{HIV})\, \mathbf{P(HIV)}}{P(\text{positive test}|\text{HIV})\, \mathbf{P(HIV)} + P(\text{positive test}|\text{not HIV})\, \mathbf{P(not\ HIV)}}$$

$$\text{PPV} = \frac{\text{Sensitivity} \times \mathbf{prevalence}}{\text{Sensitivity} \times \mathbf{prevalence} + (1\text{-specificity}) \times (\mathbf{1\text{-}prevalence})}$$

Prevalence and PPV

Bayes Law

$$\text{PPV} = \frac{\text{Sensitivity x prevalence}}{\text{Sensitivity x prevalence + (1-specificity) x (1-prevalence)}}$$

$$\text{NPV} = \frac{\text{Specificity x (1-prevalence)}}{\text{(1-sensitivity) x prevalence + specificity x (1-prevalence)}}$$

Example: HIV testing

Method II

Prevalence = 0.1%, specificity = 99.8%, sensitivity = 98%

$$PPV = \frac{\text{Sensitivity x prevalence}}{\text{Sensitivity x prevalence + (1-specificity) x (1-prevalence)}}$$

PPV = (0.98 x 0.001)/
[(0.98 x 0.001) + (0.002 x 0.999)] = 0.329

When prev = 0.1%, 1%, 10%
PPV = 33%, 83%, 98%

For 100,000 people		Test result	
		P	N
Have HIV	P	98	2
	N	200	99700

PPV = 98/(98+200) = 32.9%