

Digital epidemiology

Lesson 3

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**C2
S2** Center for
Computational Social Science
and Human Dynamics

Testing & Diagnostics

Identify cases

A decorative network diagram in the top right corner, featuring a complex web of interconnected nodes and edges. The nodes are represented by circles of varying sizes and colors (blue, grey, and white), and the edges are thin lines connecting them.

In the previous lecture we talked about these questions

- ▶ How do we find cases?
- ▶ How many cases are there?
- ▶ What causes them?
- ▶ What are the consequences?

But there is a more fundamental questions behind all of them...

A decorative network diagram in the bottom left corner, featuring a complex web of interconnected nodes and edges. The nodes are represented by circles of varying sizes and colors (blue, grey, and white), and the edges are thin lines connecting them.

Identify cases

A decorative network diagram in the top right corner, featuring a complex web of interconnected nodes and lines. Some nodes are solid grey circles, while others are hollow circles with a smaller solid circle inside. The lines are thin and grey, creating a mesh-like structure.

How do we know that there are cases?

A decorative network diagram in the bottom left corner, similar to the one in the top right. It shows a cluster of nodes connected by lines, with some nodes being solid grey and others being hollow with a central dot.

Identify cases

- ▶ For most of medical history, diagnosis was purely based on observations on symptoms and their history
- ▶ As science advanced, more tools became available to make a diagnosis. Today, laboratory tests are available for many diseases.
- ▶ However, **any diagnosis ultimately comes with uncertainty.**
- ▶ Even for modern, highly specific lab tests, the **accuracy is never 100%.**
- ▶ It is highly non-intuitive how a test that is almost perfect can lead to very misleading epidemiological conclusions.

False positives and false negatives

- ▶ Let's assume we know for absolute certainty whether a person has a disease or not. If we have a dichotomous test, there are 4 scenarios:
- ▶ You have the disease, the test is positive: **true positive**
- ▶ You have the disease, but the test is negative: **false negative**
- ▶ You don't have the disease, and the test is negative: **true negative**
- ▶ You don't have the disease, but the test is positive: **false positive**

False positives and false negatives

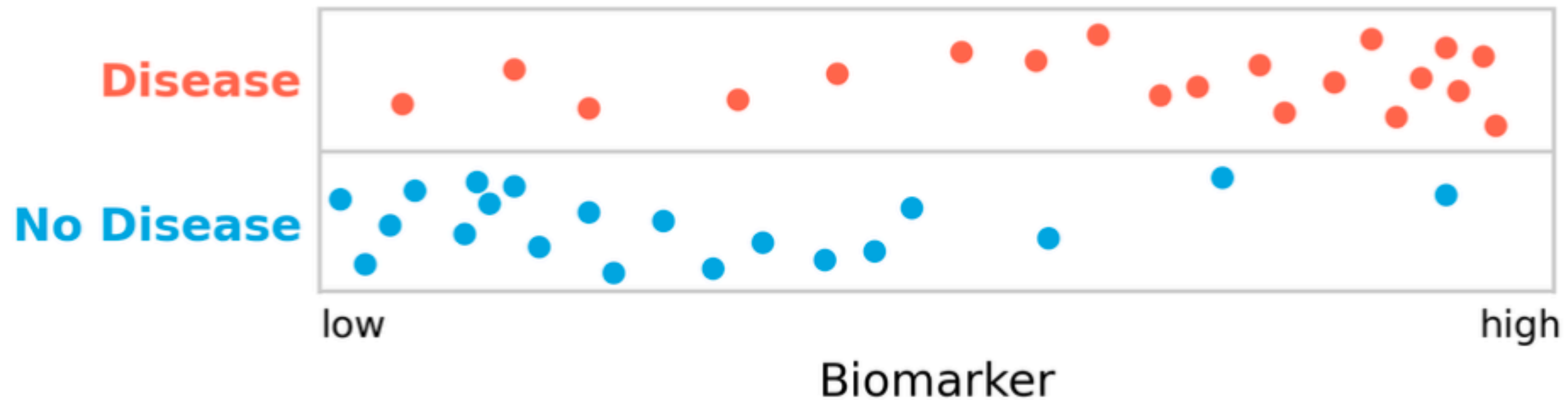
		Test	
		Positive	Negative
Disease	Present	True positive	False negative
	Absent	False positive	True negative

(For those familiar with classifiers, this is also called a confusion matrix)

False positives and false negatives

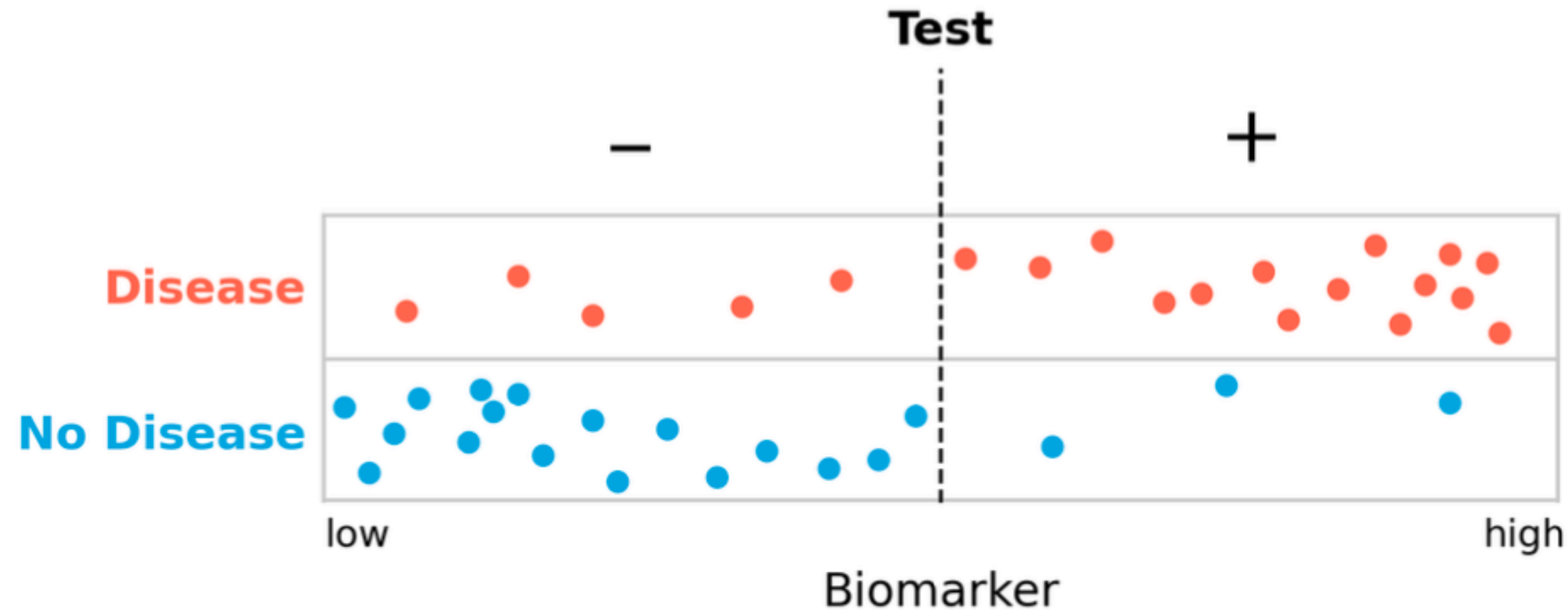
- ▶ **Type I error:** you think something is there but it is not - a false alarm.
- ▶ **Type II error:** you miss something that is actually there.
- ▶ Which error is worse usually depends on the situation.
- ▶ For example, a false positive test may lead to a treatment with very strong negative side effects. A rather bad Type I error.
- ▶ Missing a disease with a false negative test outcome can be just as bad, as the disease may not get the necessary treatment. A classic Type II error.

Testing



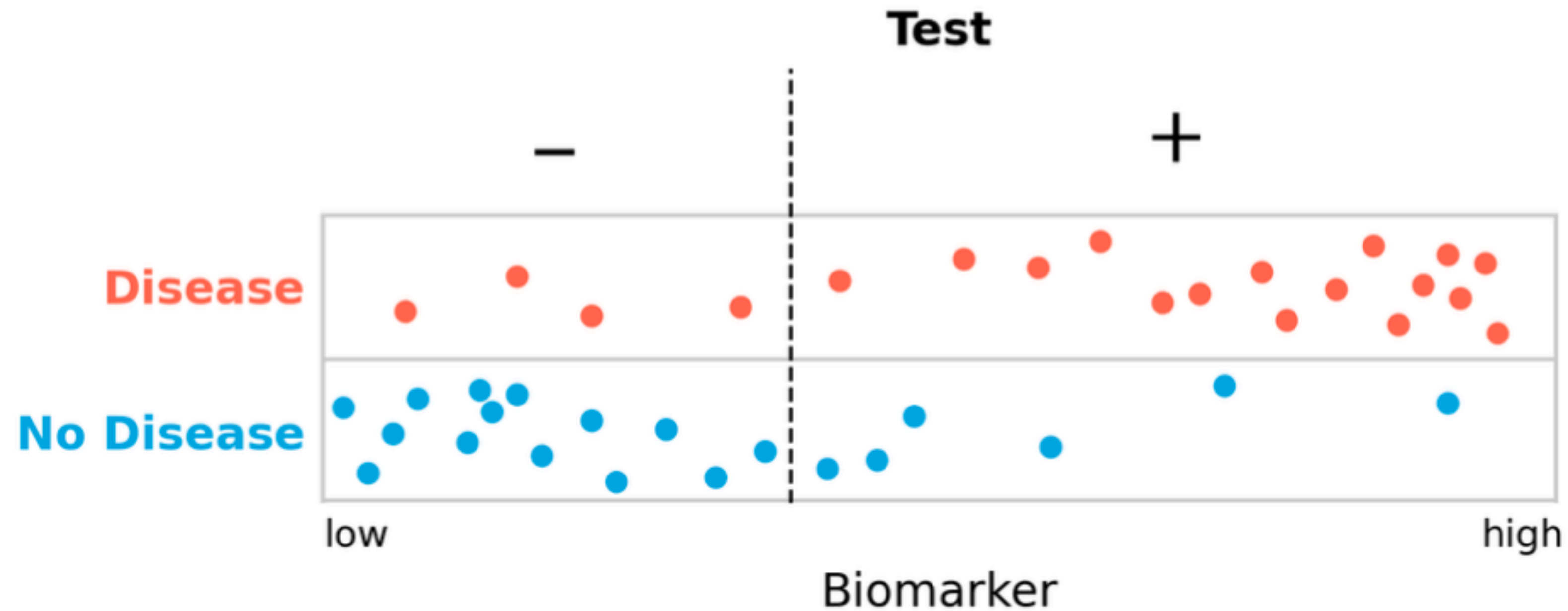
- Many diagnostics tests work by measuring the presence or amount of a **biomarker**.

Testing



- ▶ We need to define a **cutoff**, above which we declare the presence of the disease.
- ▶ There is **no perfect cutoff**. The choice will impact the number of false positive and false negatives. We now miss 5 individuals with the disease...

Testing



- ▶ Let's move the cutoff to the left, to reduce the number of false negatives...
- ▶ Of course, the number of false positives will increase...
- ▶ We need to a framework to deal with this uncertainty.

Sensitivity and specificity

- ▶ We may want a test to rarely miss people who have the disease. Thus, few false negatives. We want the test to be **sensitive**.
- ▶ Or, we may want the test to rarely misclassify as having the disease when they have not. Thus, few false positives. We want the test to be **specific**.
- ▶ **Sensitivity**
- ▶ **Specificity**

Sensitivity and specificity

$$\text{Sensitivity} = \frac{TP}{TP + FN}$$

$$\text{Specificity} = \frac{TN}{TN + FP}$$

Sensitivity and specificity

- ▶ Sensitivity is also called the true positive rate (TPR).
- ▶ Specificity is also called the true negative rate (TNR)
- ▶ False positive rate (**FPR**) and false negative rate (**FNR**) are defined as:

$$\mathbf{FNR} = \frac{FN}{TP + FN}$$

$$\mathbf{FPR} = \frac{FP}{TN + FP}$$

Sensitivity and specificity

- It is immediate to see that:

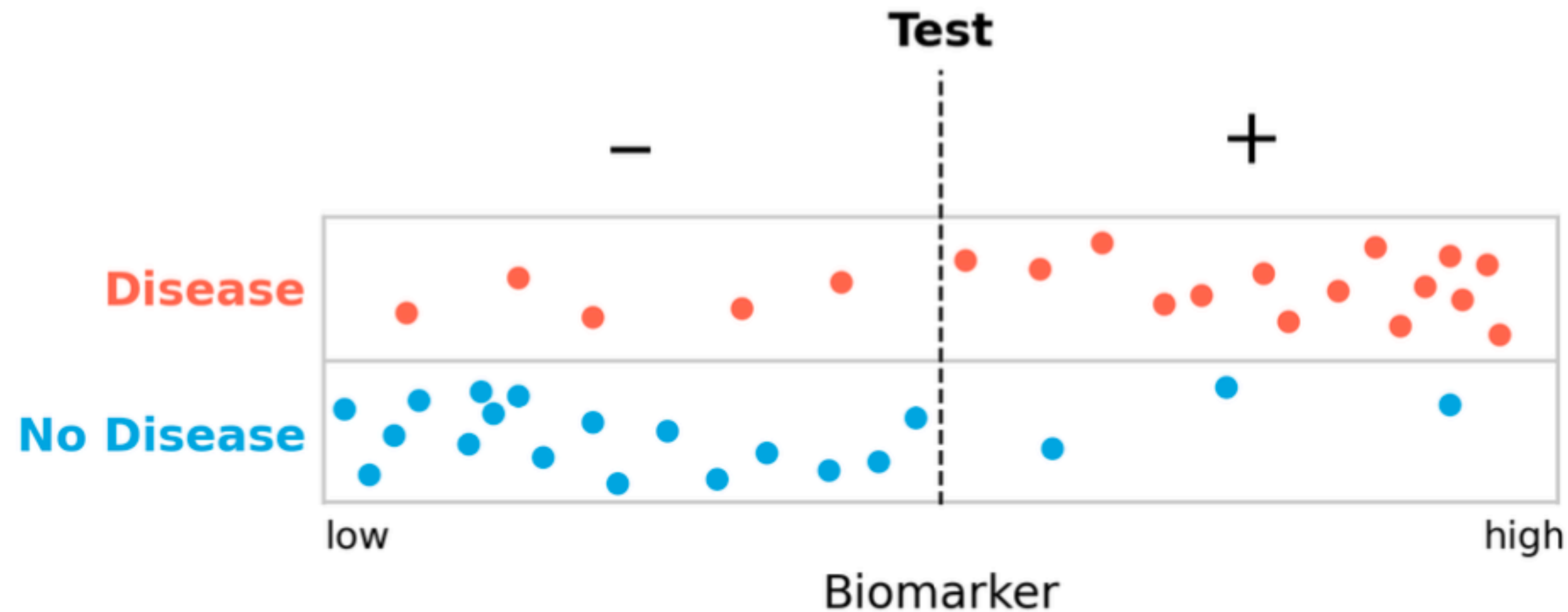
$$\textbf{Sensitivity} = \frac{TP}{TP + FN} = 1 - \textbf{FNR}$$

$$\textbf{Specificity} = \frac{TN}{TN + FP} = 1 - \textbf{FPR}$$

Sensitivity and specificity

- ▶ Both sensitivity and specificity need each other in order to be meaningful.
- ▶ In the expression for sensitivity there is no false positive term, so sensitivity does not tell anything about false positives.
- ▶ The same can be said for the specificity, without any reference to false negatives.
- ▶ Let's imagine we have a "test" that is always positive. This is useless test but it will have a sensitivity of 100%.
- ▶ Of course, it will have a specificity of 0%, too.
- ▶ *Specificity and sensitivity always go together.*

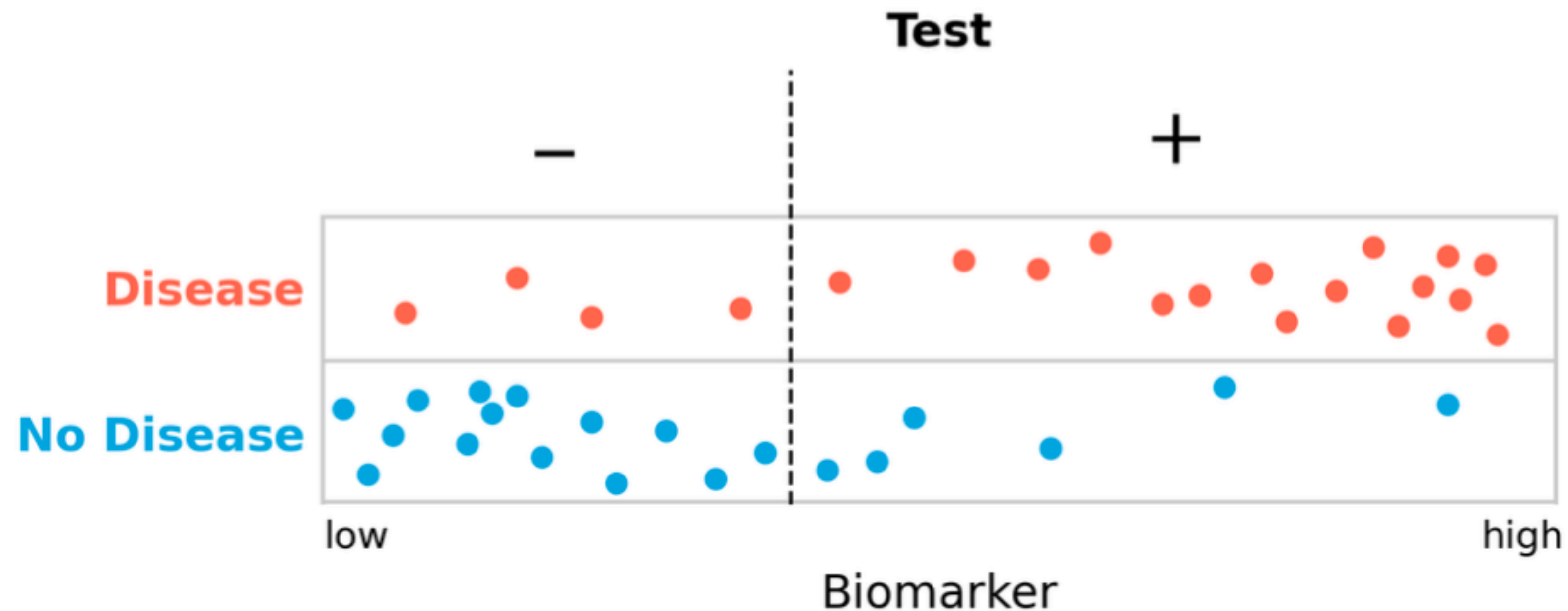
Sensitivity and specificity



$$\text{Sensitivity} = \frac{TP}{TP + FN} = \frac{15}{20} = 75 \%$$

$$\text{Specificity} = \frac{TN}{TN + FP} = \frac{17}{20} = 85 \%$$

Sensitivity and specificity



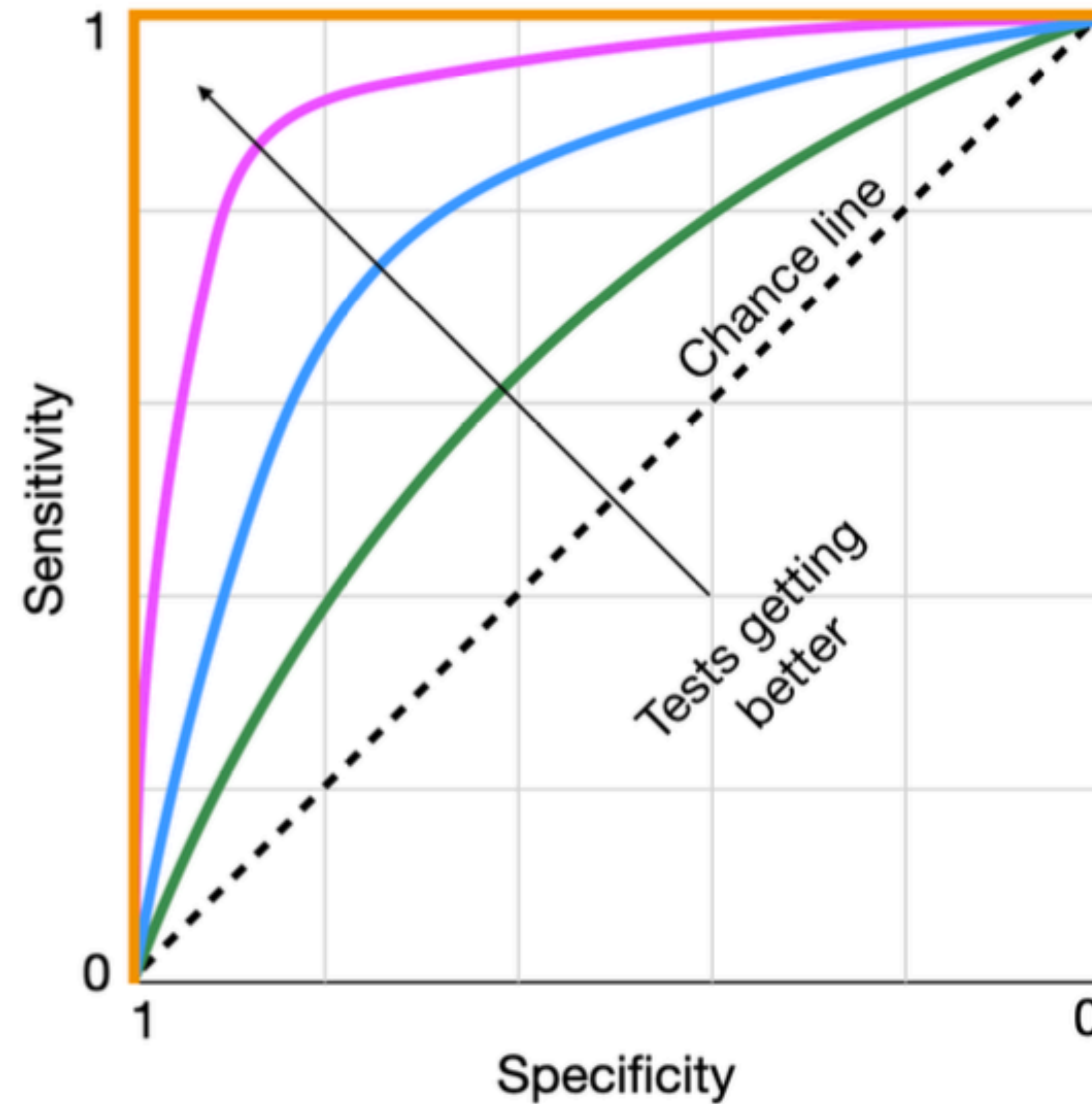
$$\text{Sensitivity} = \frac{TP}{TP + FN} = \frac{16}{20} = 80\%$$

$$\text{Specificity} = \frac{TN}{TN + FP} = \frac{14}{20} = 70\%$$

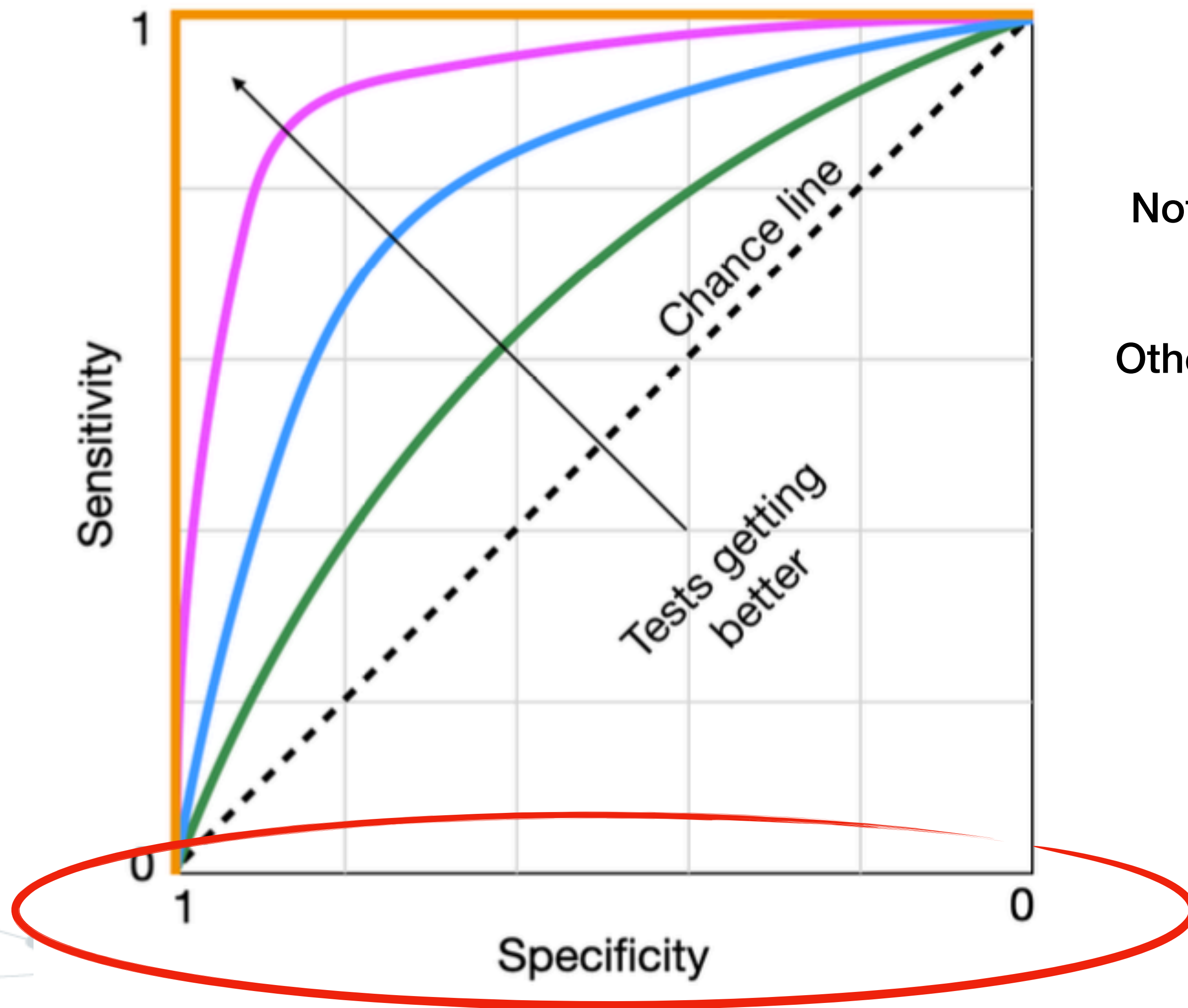
The ROC curve

- ▶ How do we make a decision about the cutoff?
- ▶ We try different cutoff and we see what that does to the tradeoff of the sensitivity and specificity of the test.
- ▶ The most common way to visualize this is the **ROC curve** (receiver operating characteristics)
- ▶ Very common in classification tasks for machine learning and several other domains.

The ROC curve



The ROC curve



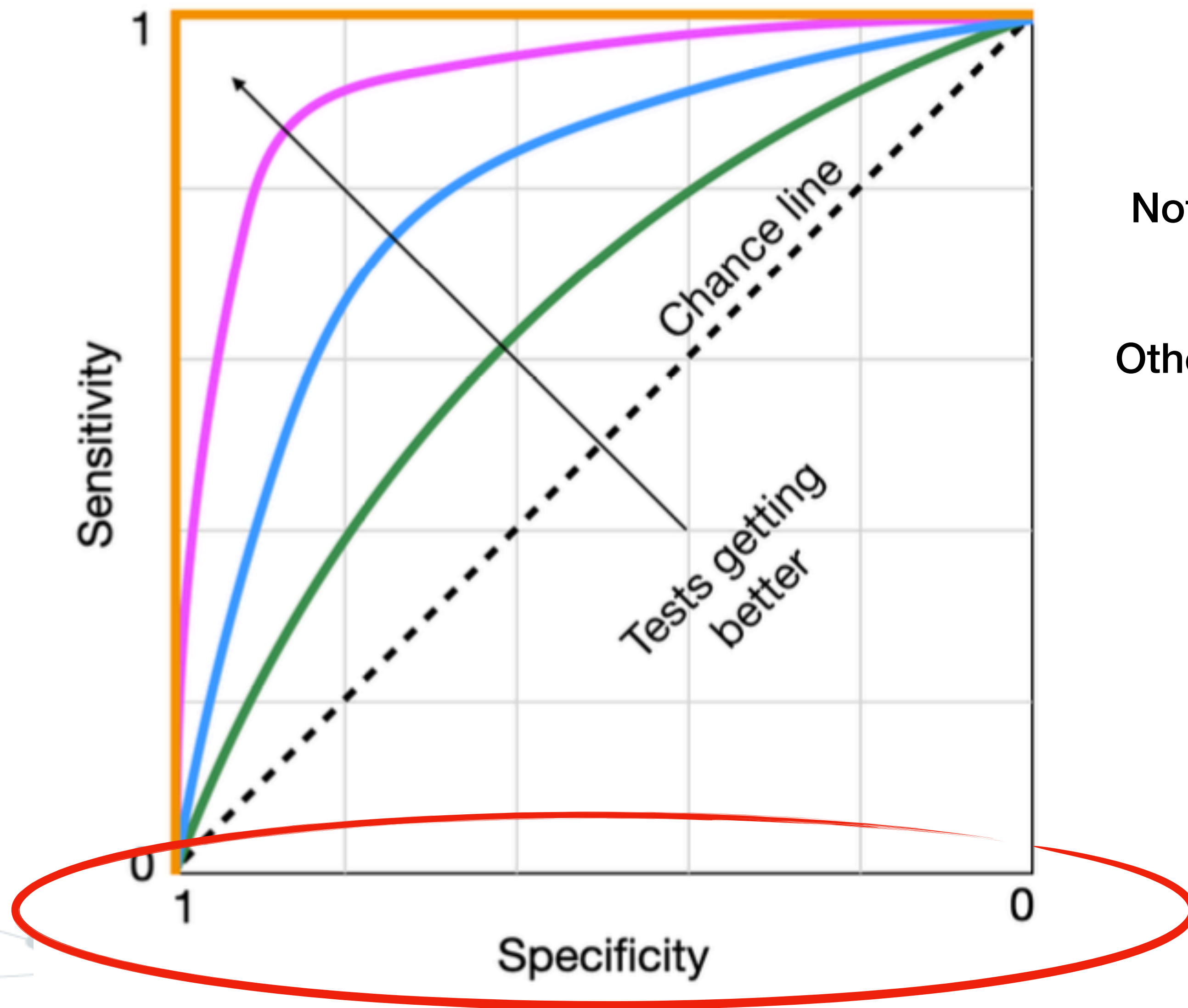
Note that we have inverted
the x-axis

Otherwise, the x-axis should
show

1-specificity

that is the FPR

The ROC curve



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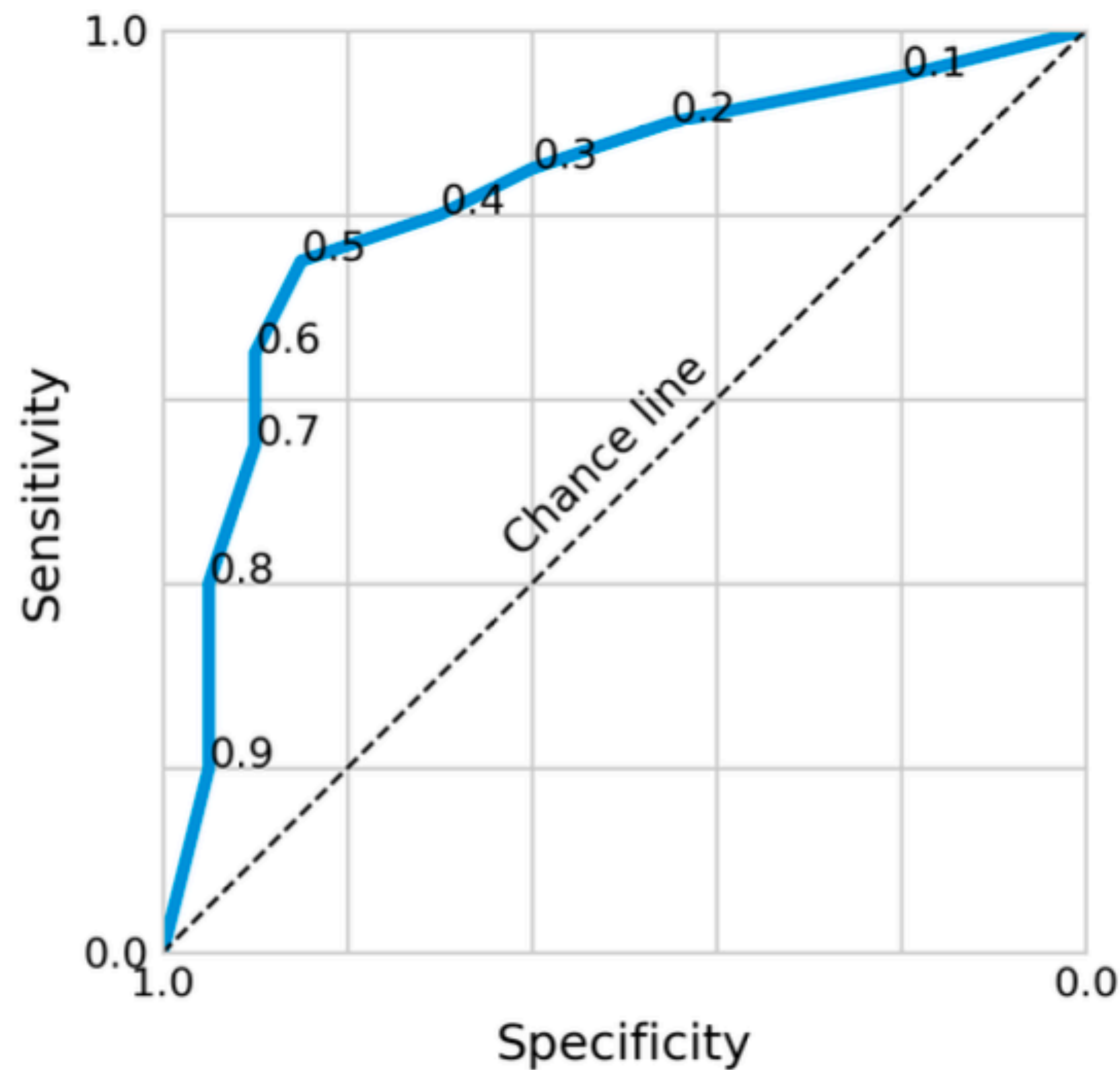
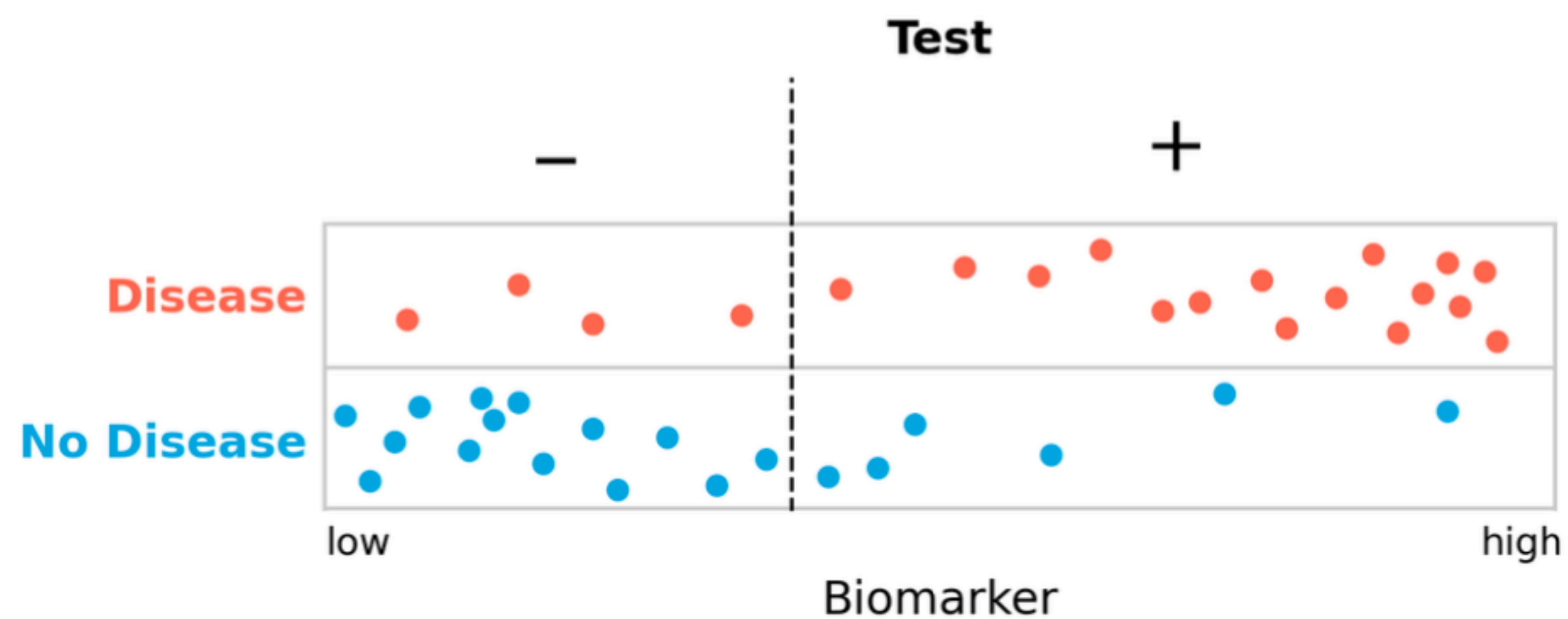
1-specificity

that is the FPR

The ROC curve

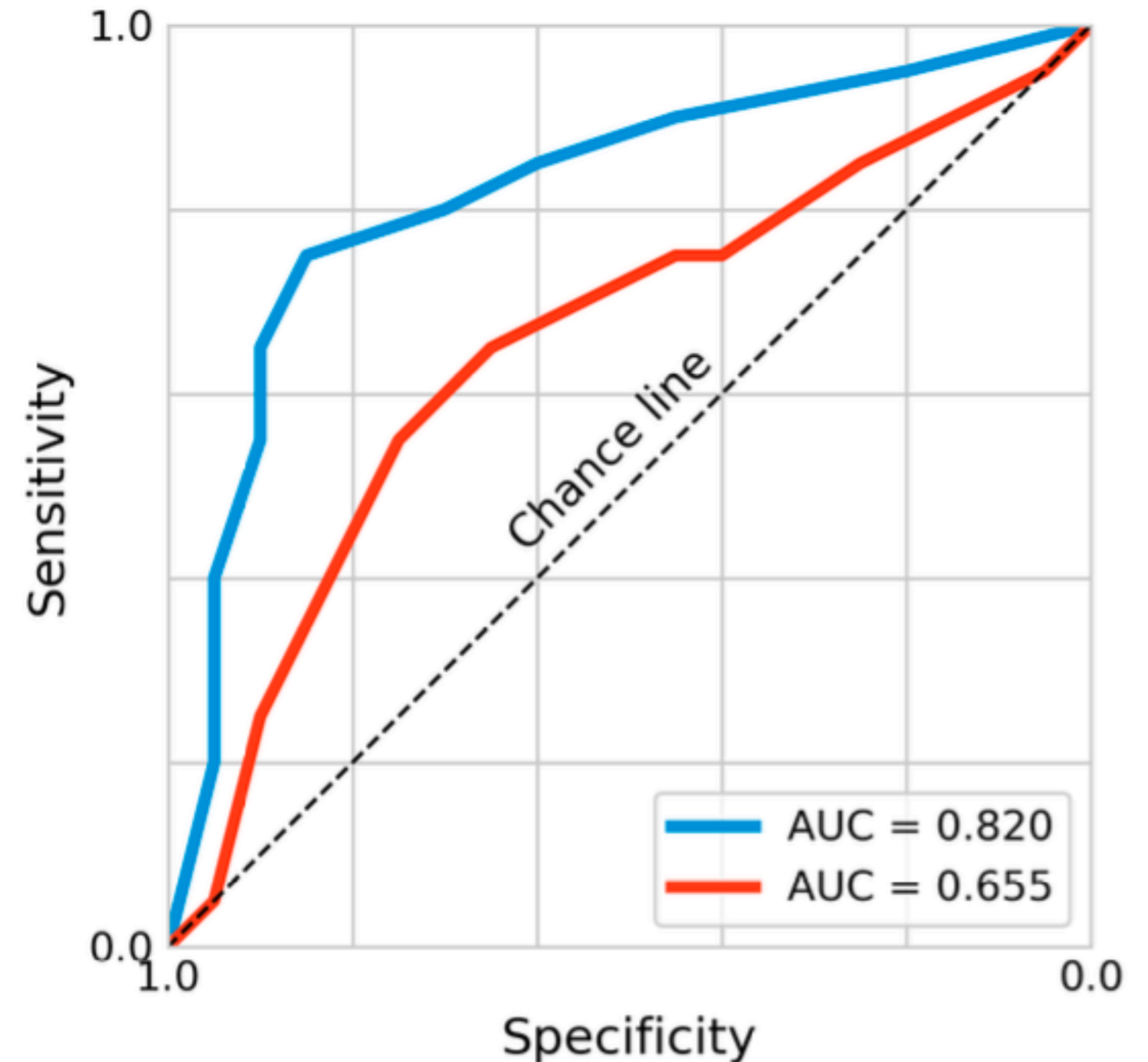
- ▶ If we start following a line at the bottom left, we start with highly specific tests that very rapidly also achieve high levels of sensitivity, without having to sacrifice a lot of specificity.
- ▶ However, eventually, we reach a point where each additional small reduction in specificity does not gain us a lot of sensitivity in exchange, and the tradeoff stops being valuable.
- ▶ These points typically sit “on the shoulder” of the curve towards the top left corner. This is our ideal cutoff.

The ROC curve



The AUC

- ▶ The Area Under the Curve (AUC) allows to compare two or more different tests.
- ▶ In the figure, two hypothetical tests are compared and the blue one performs better for any given cutoff.



Positive predictive value

- ▶ We have focused on a question that is: how accurate is this test in discriminating between disease and no disease?
- ▶ Sensitivity and specificity need to be evaluated before the tests can be used in practice. They are estimated in lab experiments.
- ▶ Once the test enters the daily medical practice, another question becomes relevant:
 - ▶ **If I tested positive, what is the probability that I actually have the disease? This is the positive predictive value.**

Positive predictive value

- ▶ In a given population, the prevalence of a disease is 0.9%.
- ▶ You have a rather accurate test for the disease, with a sensitivity of 92%, and a specificity of 91%.
- ▶ You now test a random person of this population, and the test result is positive. What is the actual probability that the person truly has the disease?
- ▶ (When physicians were presented with this problem, only 10% got it right*)

**Hoffrage, Ulrich, and Gerd Gigerenzer.
"Using natural frequencies to improve diagnostic inferences."
Academic medicine 73.5 (1998): 538-40.*

Positive predictive value

- ▶ Of course, that key insight is that the prevalence in the population is very low and a random person getting tested most likely doesn't have the disease to begin with.
- ▶ 1000 people, 9 have the disease, 991 don't.
- ▶ 9% of 991 will get a false positive test (91% specificity) = 89 people
- ▶ 92% of 9 people will get a true positive test (92% TPR) = 8 people
- ▶ Only 8 people out of 97 truly have the disease. That is 8.2%.

Bayes' theorem

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

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

Bayes' theorem

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

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

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

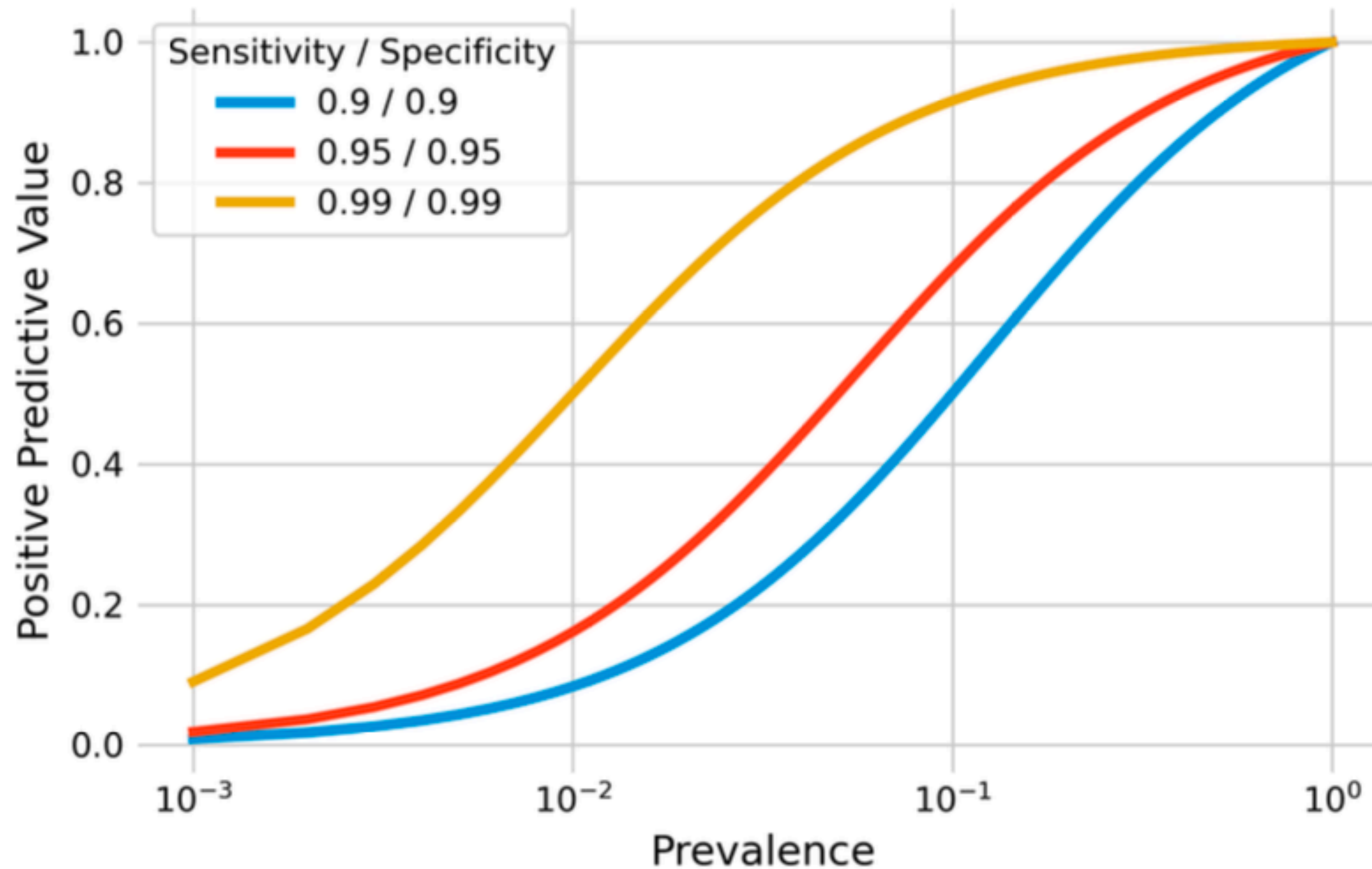
Bayes' theorem

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

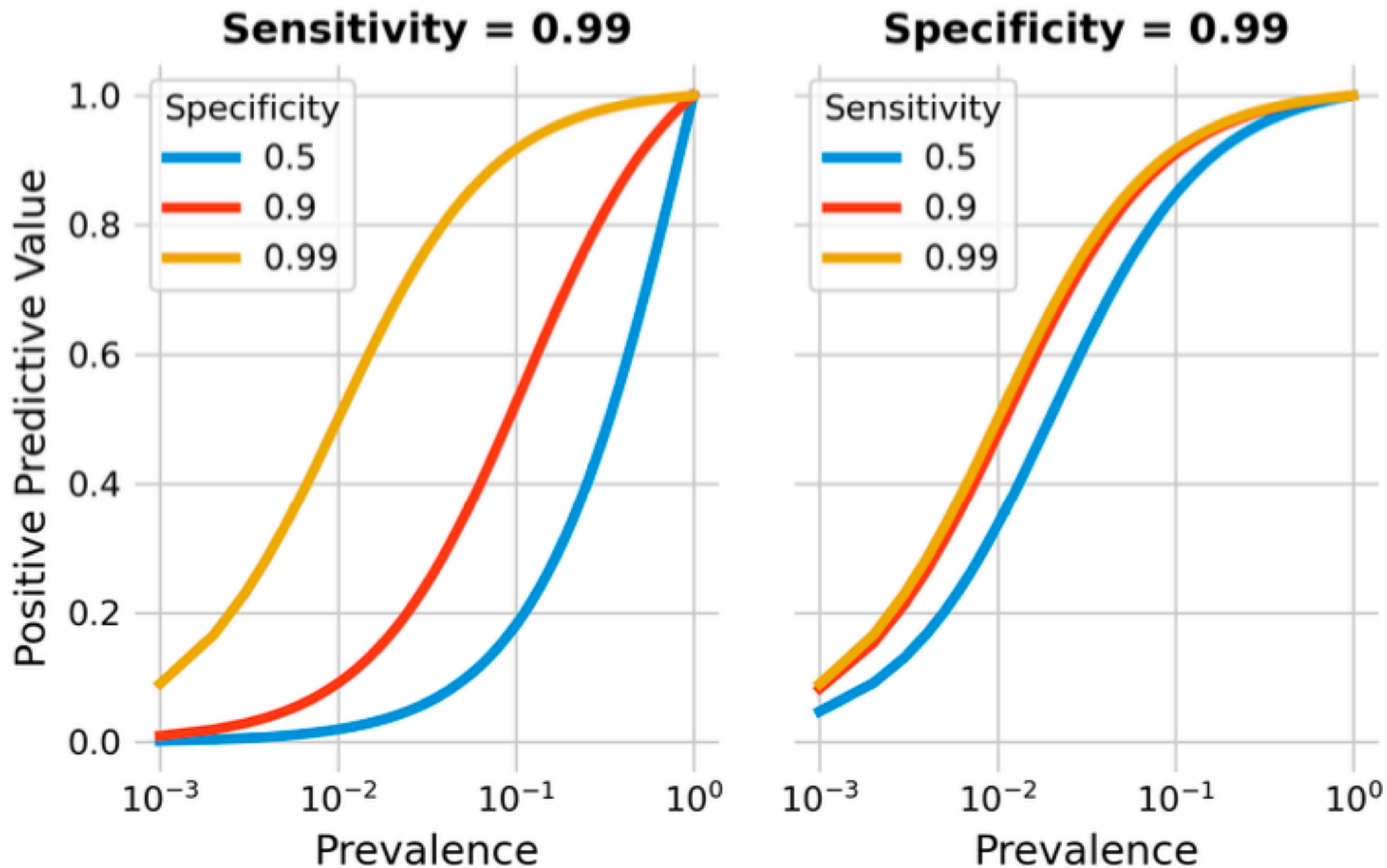
$$P(D | T+) = \frac{\text{Sensitivity} * \text{Prevalence}}{\text{Sensitivity} * \text{Prevalence} + 1 - \text{Specificity} * 1 - \text{Prevalence}}$$

$$P(D | T+) = 0.085$$

Positive predicted value



Specificity matters a lot



Positive predictive value

- ▶ Testing low-prevalence populations can thus easily be a waste of resources.
- ▶ While we can't change the prevalence in itself, we can change the population that we test.
- ▶ If we ensure that pre-test probability is higher - for example by focusing on high-risk groups for a given disease - we can increase the positive predictive value of a test.

Likelihood ratios

- ▶ It would be very convenient to have some idea about how performant a test is in providing a jump from the pre-test probability to the post-test probability - independent of the prevalence when the test is performed.
- ▶ This is what the **likelihood ratio of a test** is doing.
- ▶ The likelihood ratio of a test can be computed using specificity and sensitivity only.

Positive likelihood ratio

$$LR_+ = \frac{P(T_+ | D)}{P(T_+ | \neg D)}$$

$$LR_+ = \frac{\text{ sensitivity }}{1 - \text{ specificity }}$$

Negative likelihood ratio

$$LR_{-} = \frac{P(T_{-} | D)}{P(T_{-} | \neg D)}$$

$$LR_{-} = \frac{1 - \text{ sensitivity }}{\text{ specificity }}$$

Odds

- ▶ Likelihood ratios are meant to work with odds rather than probabilities
- ▶ The odds of an event with probability p are defined as

$$\text{odds} = \frac{p}{1 - p}$$

Likelihood ratios

- ▶ The power of likelihood ratios lies in transforming *pre-test odds* to *post-test odds* in the most simple way:

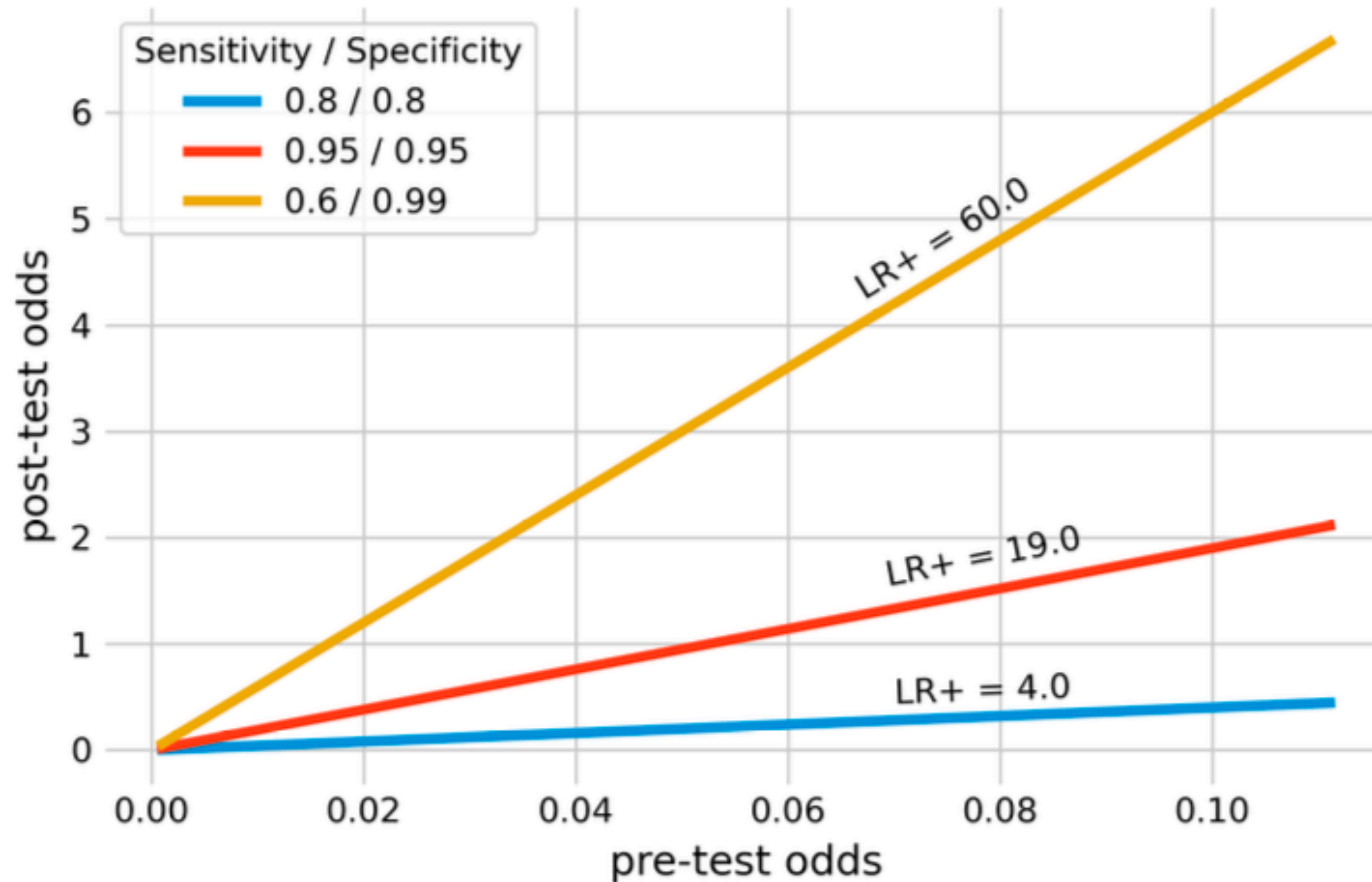
$$\text{Post-test odds} = \text{likelihood ratio} \times \text{pre-test odds}$$

*This corresponds to the ratio
between the positive
predicted value (PPV), and 1-
PPV*

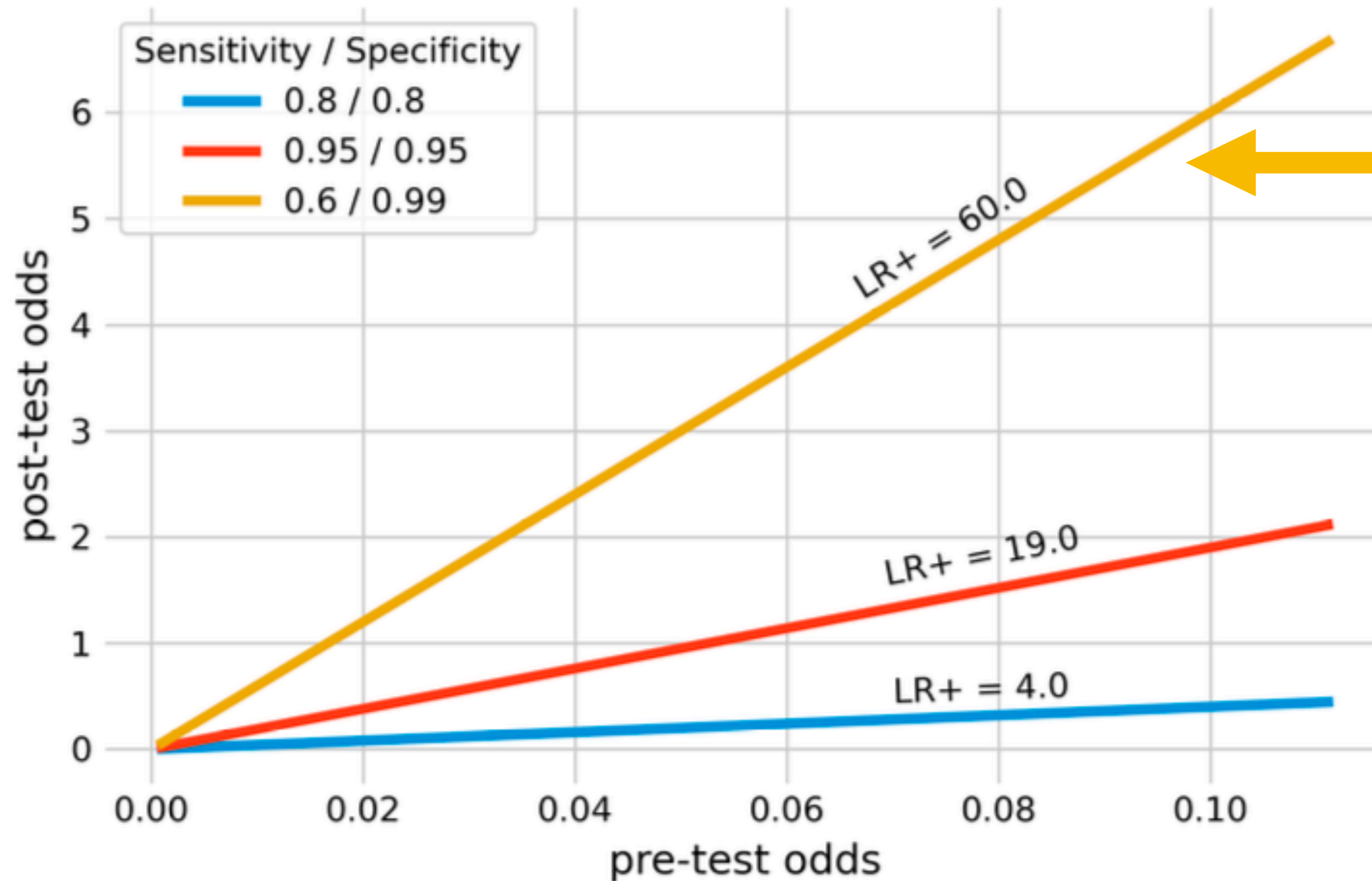
This depends only on the test

*These are the odds given by
the prevalence*

Likelihood ratios



Likelihood ratios



*This is the case of
SARS-CoV-2 antigen
tests*

Next... Epidemiological studies