Digital health and computational epidemiology

Lesson 3

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Testing & Diagnostics

Identify cases

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…

Identify cases

How do we know that there are cases?

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

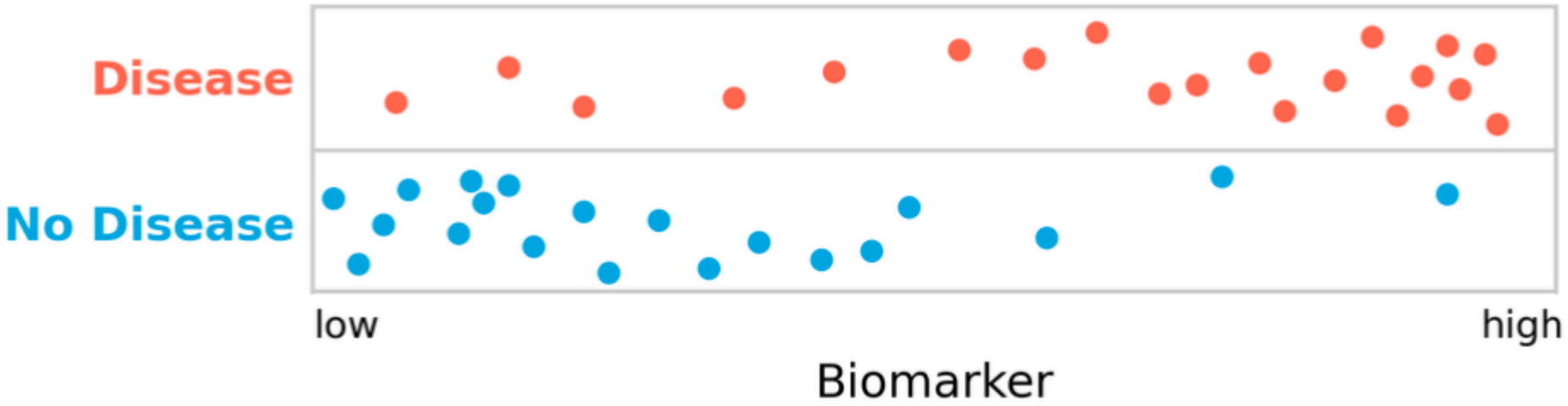
		Test: Positive	Test: Negative
Disease	Present	**True positive**	**False negative**
	Absent	**False positive**	**True negative**

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

False positives and false negatives

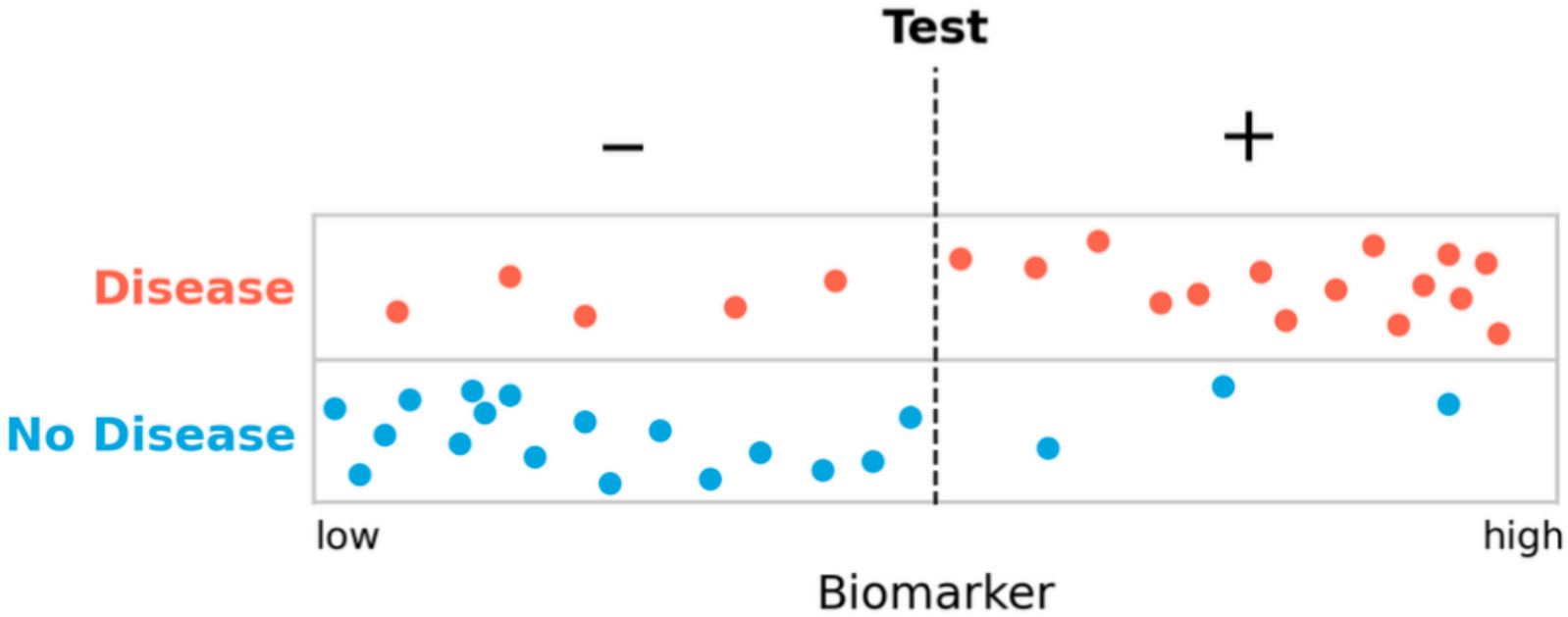
- **Type I error:** you think something is there but it is not - a false alarm.
- **Type II error:** you miss something that is actually there.
- Which error is worse usually depends on the situation.
- For example, a false positive test may lead to a treatment with very strong negative side effects. 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**.

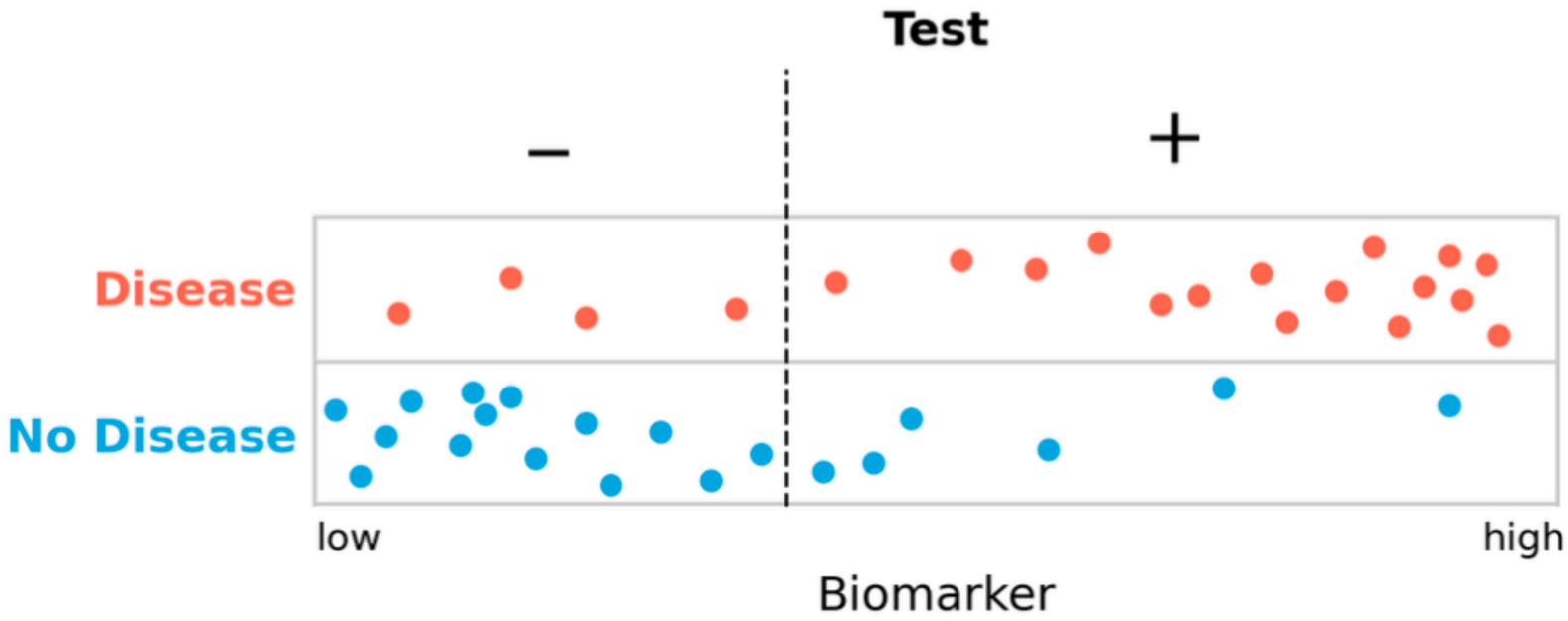
Testing



- 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

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

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

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:

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

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

Sensitivity and specificity

- It is immediate to see that:

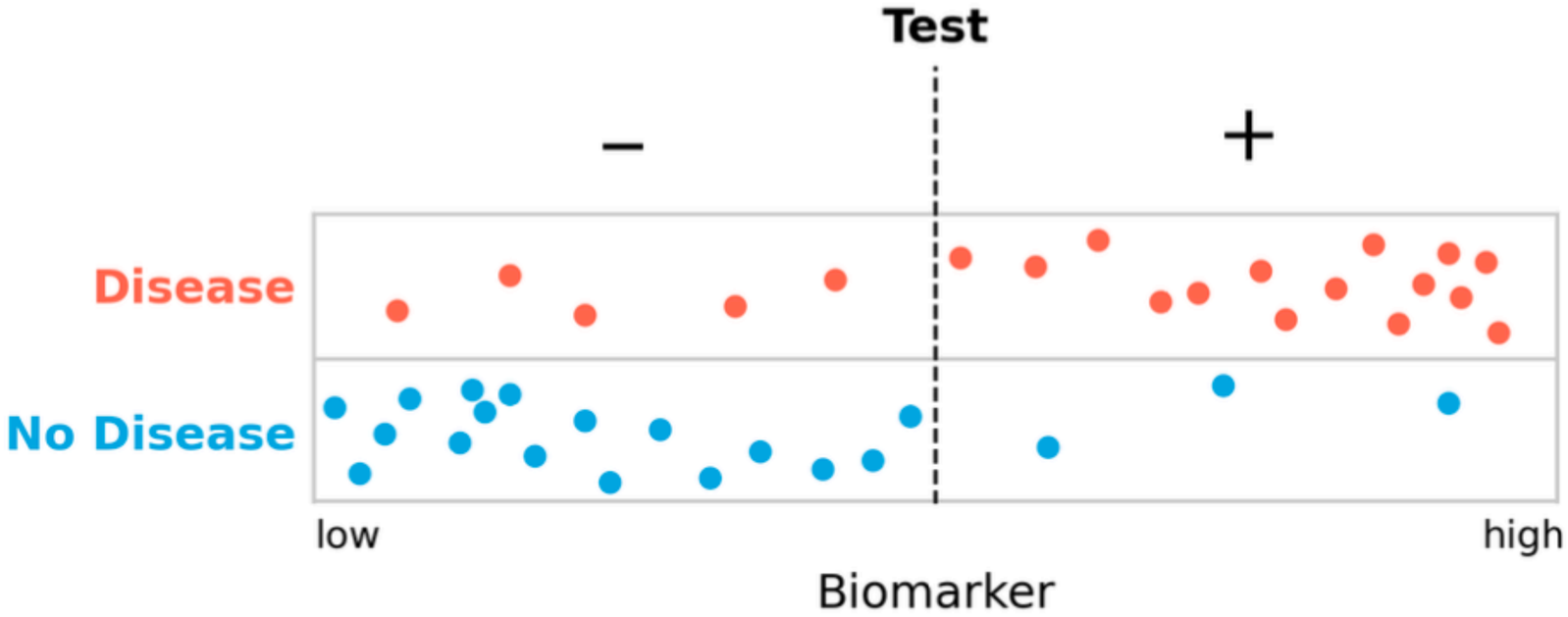
$$\textbf{Sensitivity} = \frac{TP}{TP + FN} = 1 - \textbf{FNR}$$

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

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.*

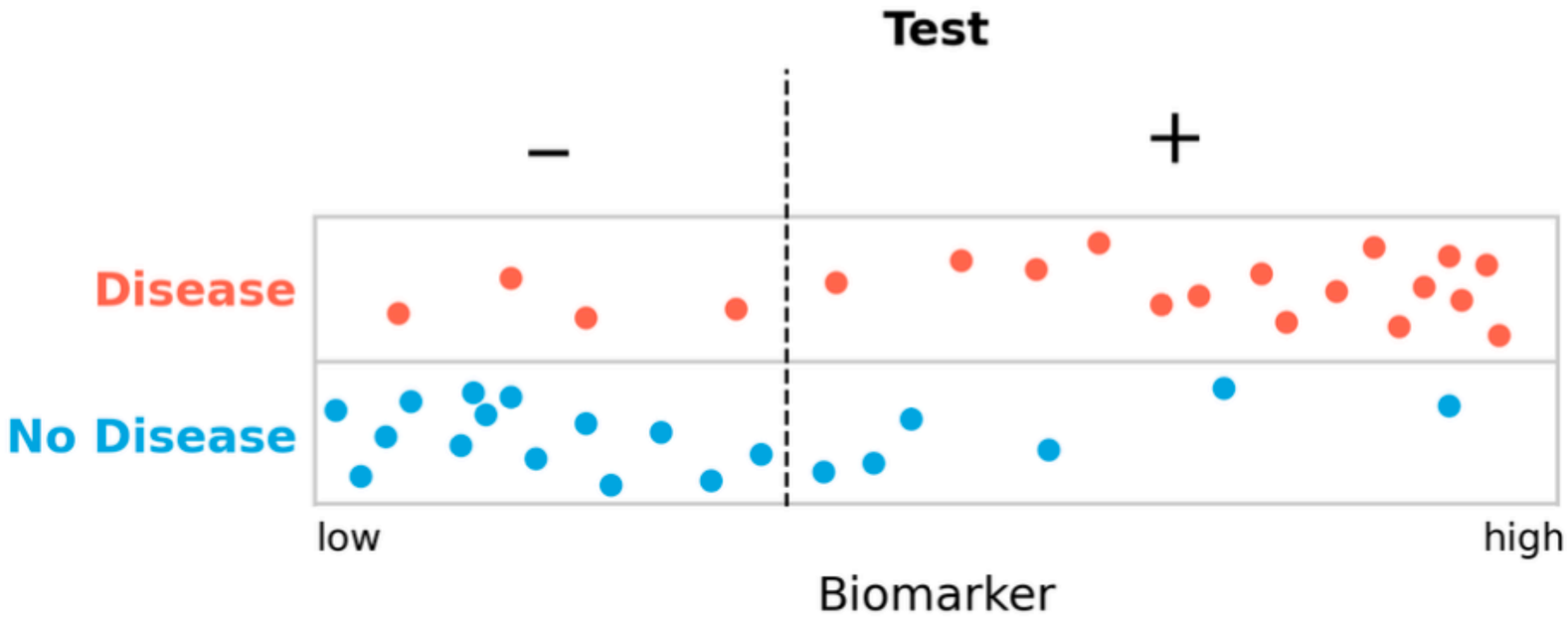
Sensitivity and specificity



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

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

Sensitivity and specificity



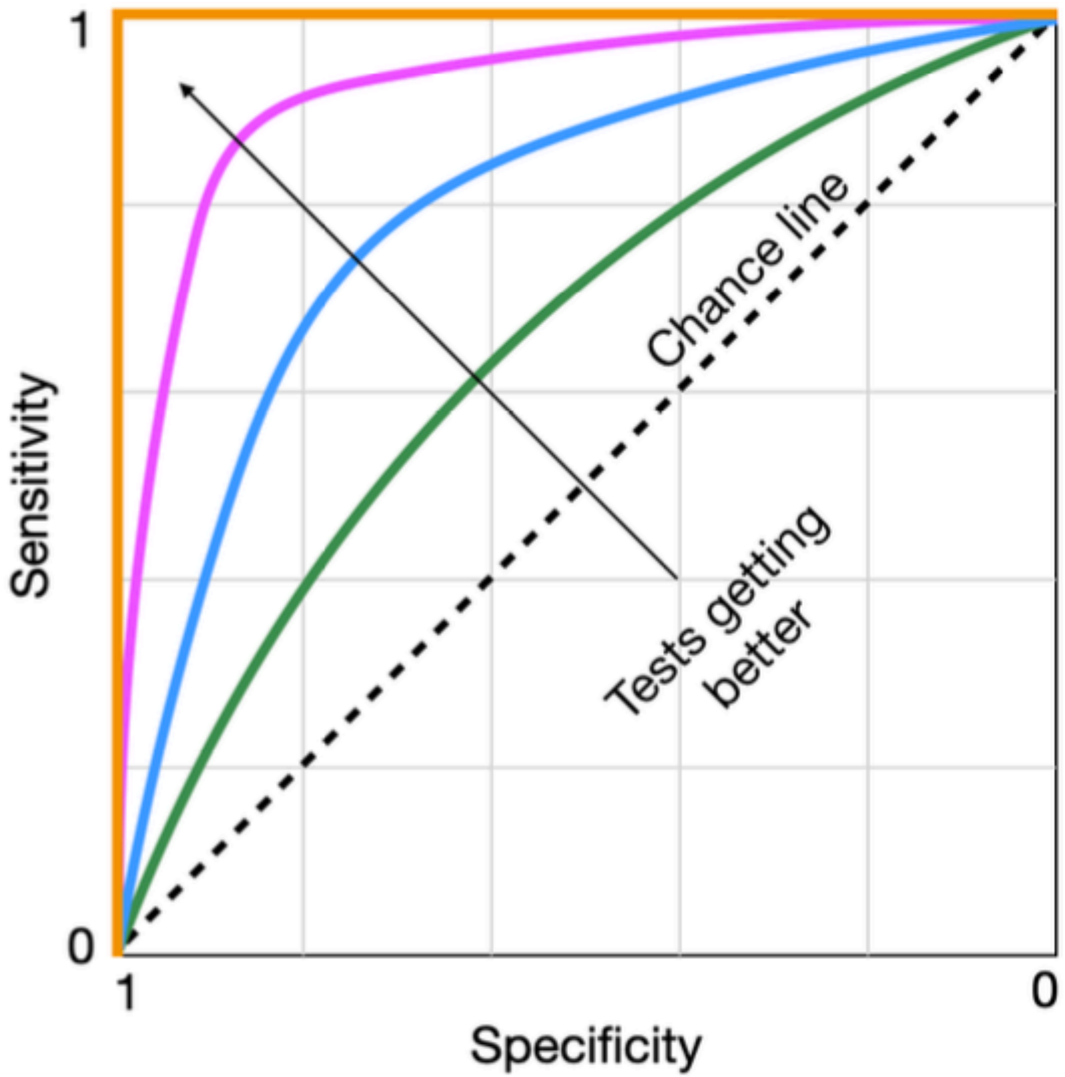
$$\textbf{Sensitivity} = \frac{TP}{TP + FN} = \frac{16}{20} = 80\,\%$$

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

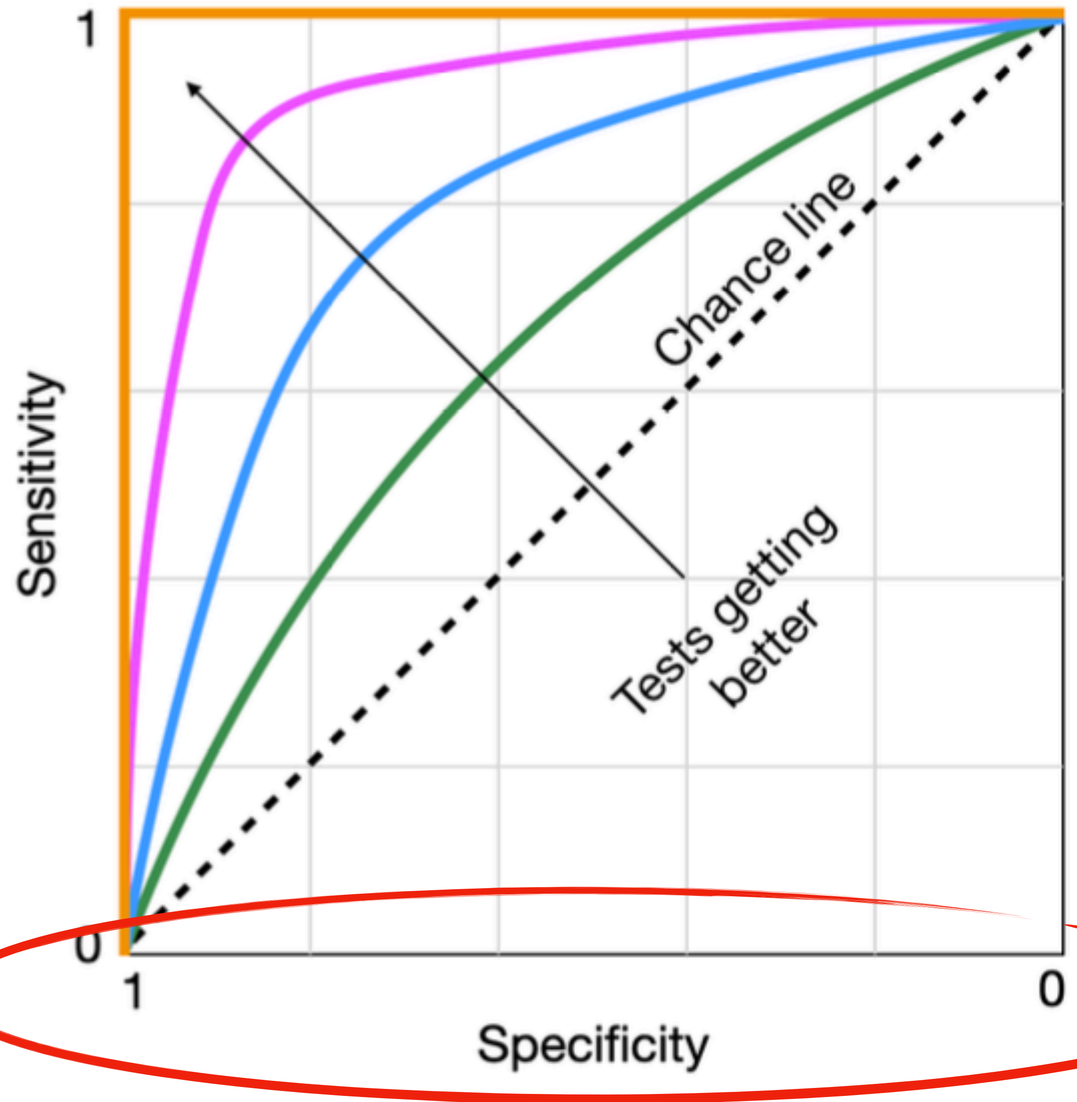
The ROC curve

- 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



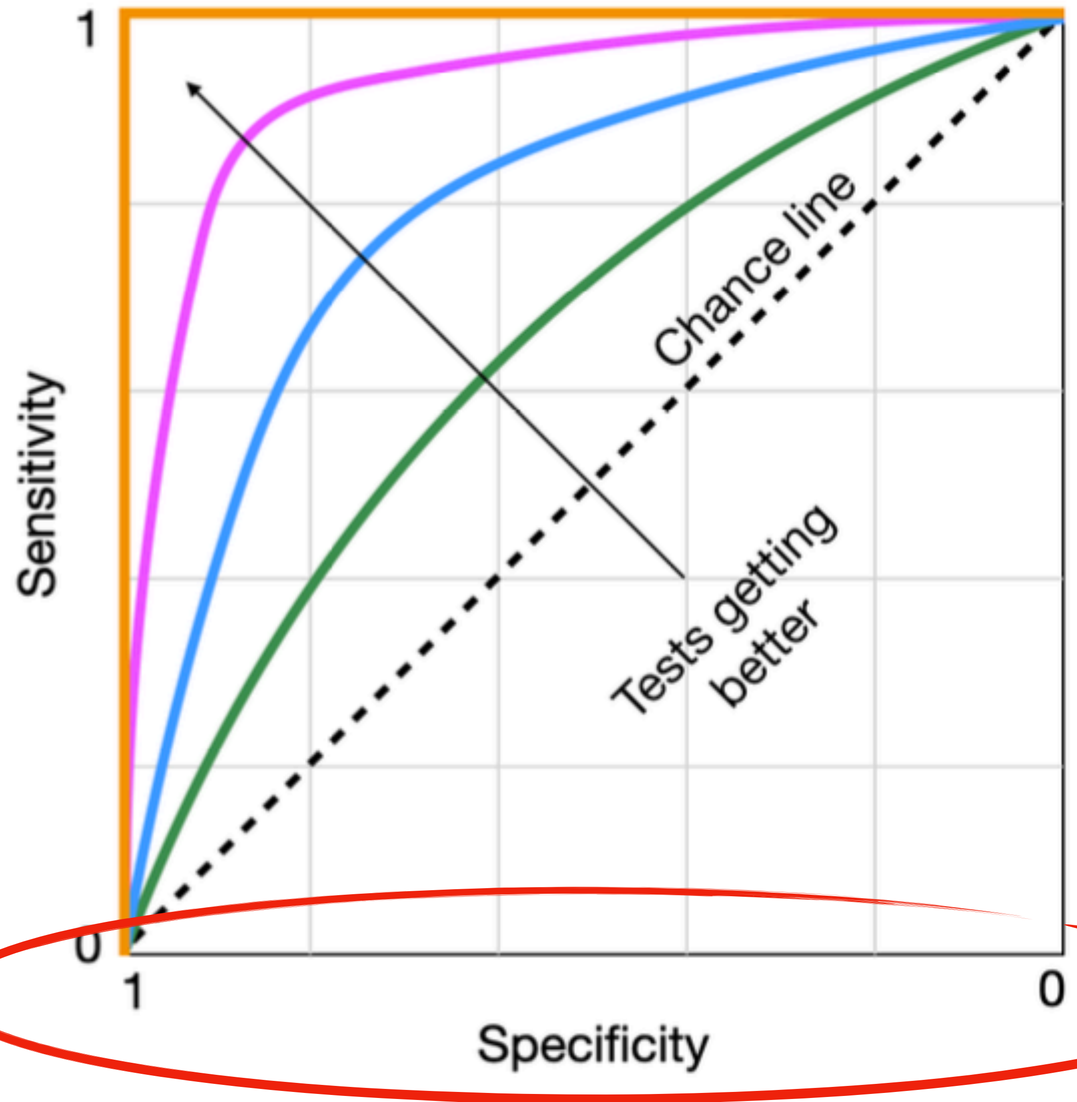
Note that we have inverted the x-axis

Otherwise, the x-axis should show

1-specificity

that is the FPR

The ROC curve



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1-specificity

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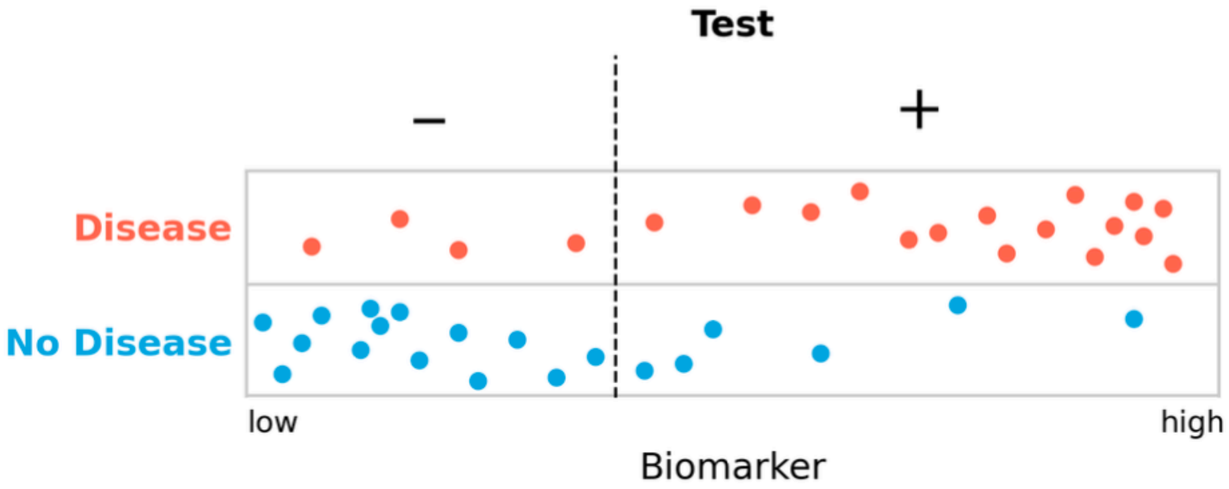
The ROC curve

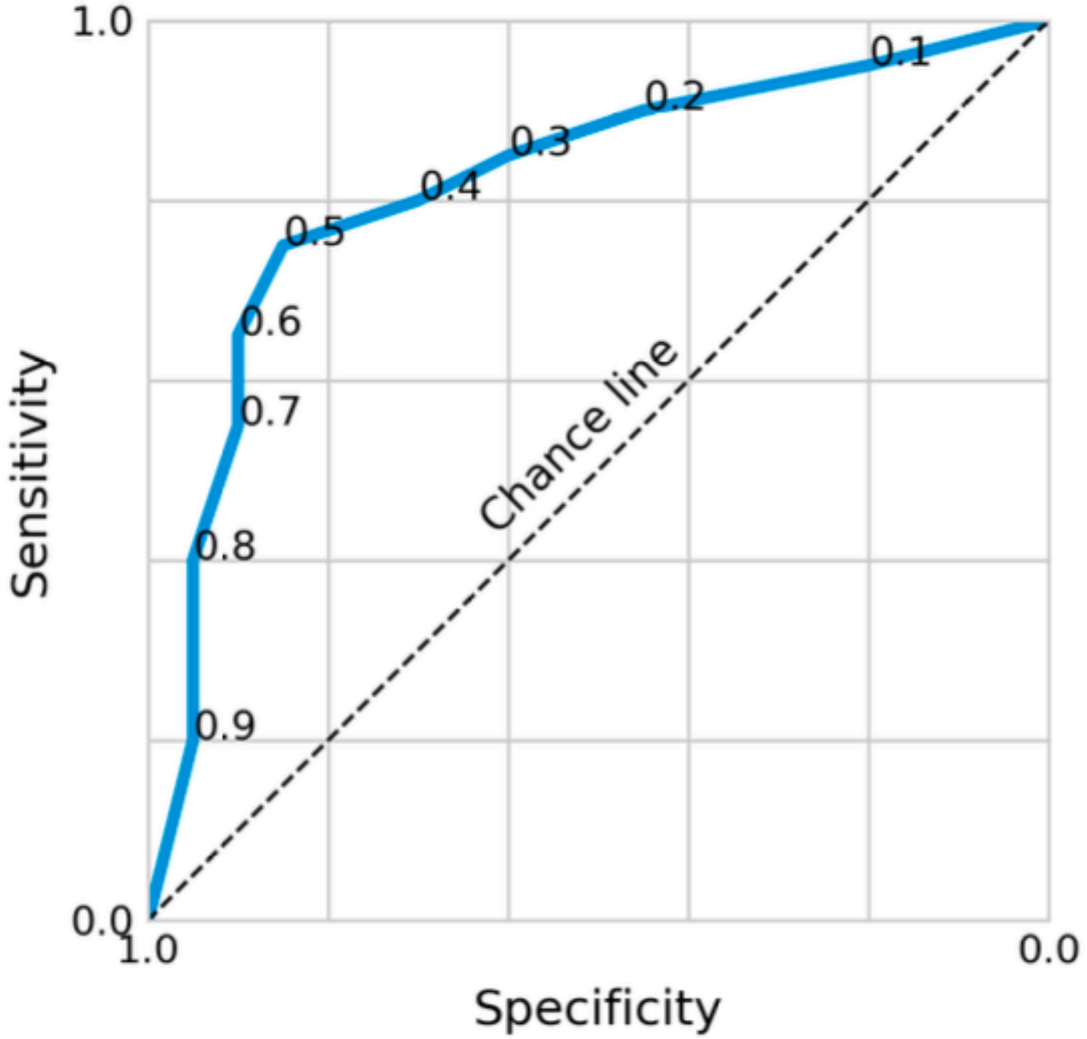
- If we start following a line at the bottom left, we start with highly specific tests that very rapidly also achieve high levels of sensitivity, without having to sacrifice a lot of specificity.

- 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.

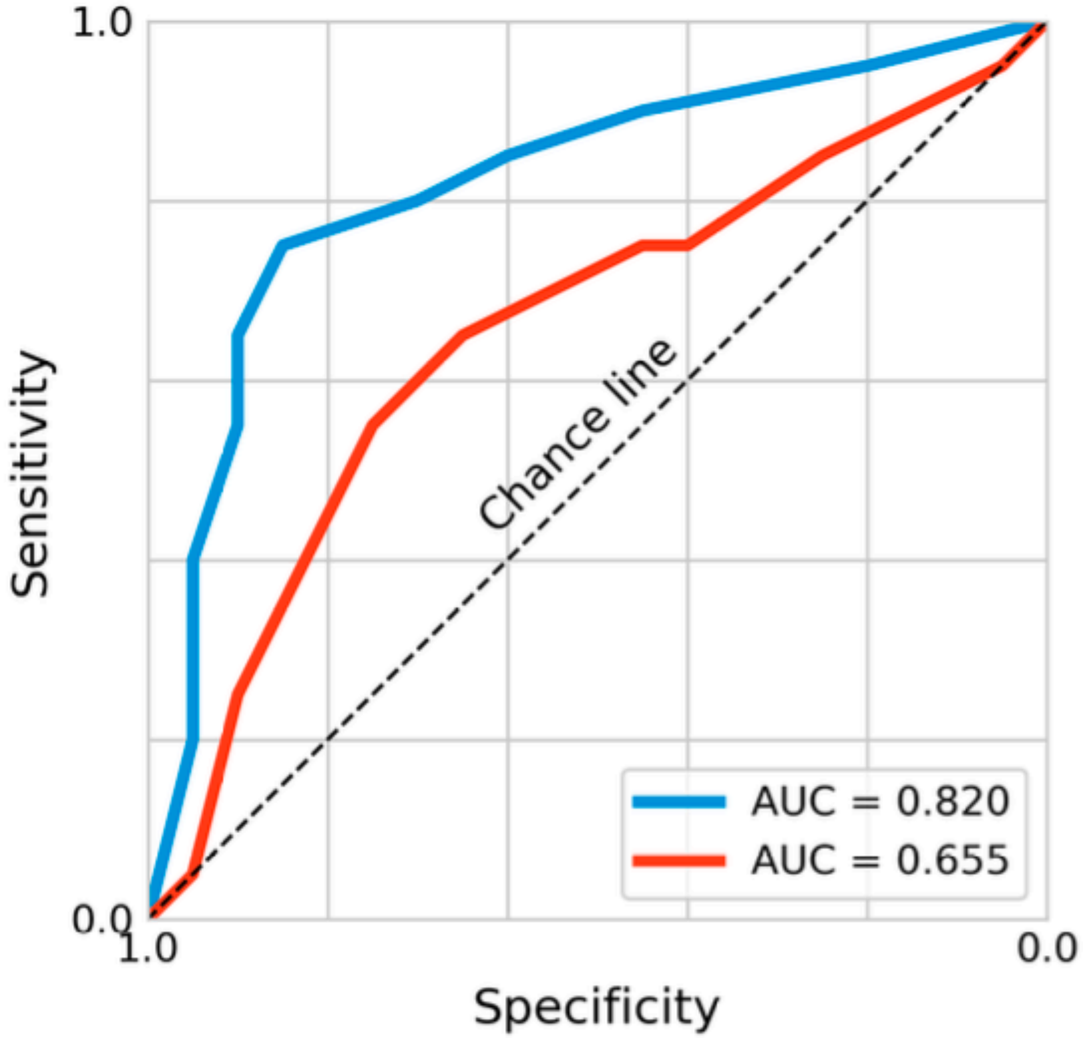
The ROC curve





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

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

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

Bayes' theorem

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

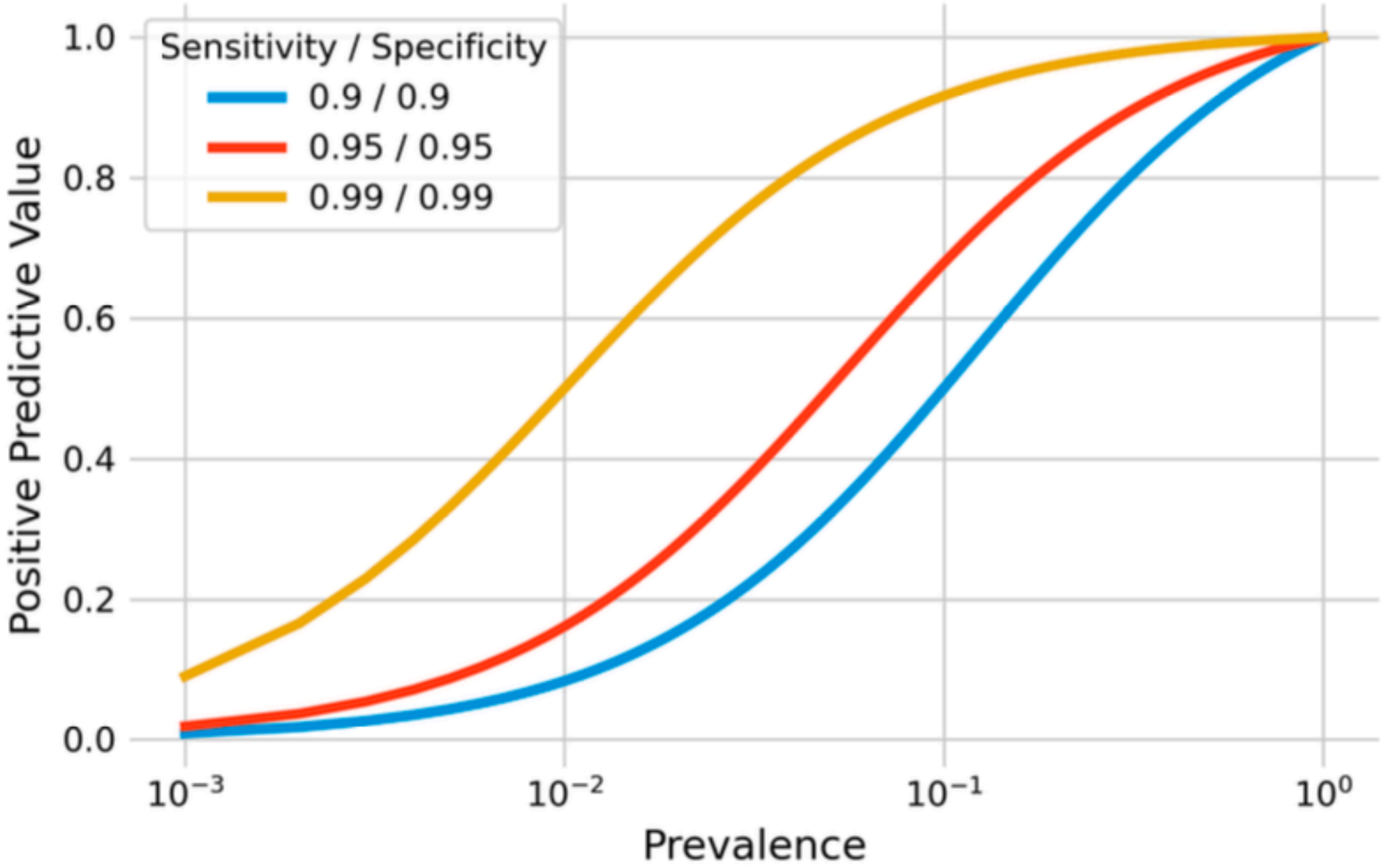
Bayes' theorem

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

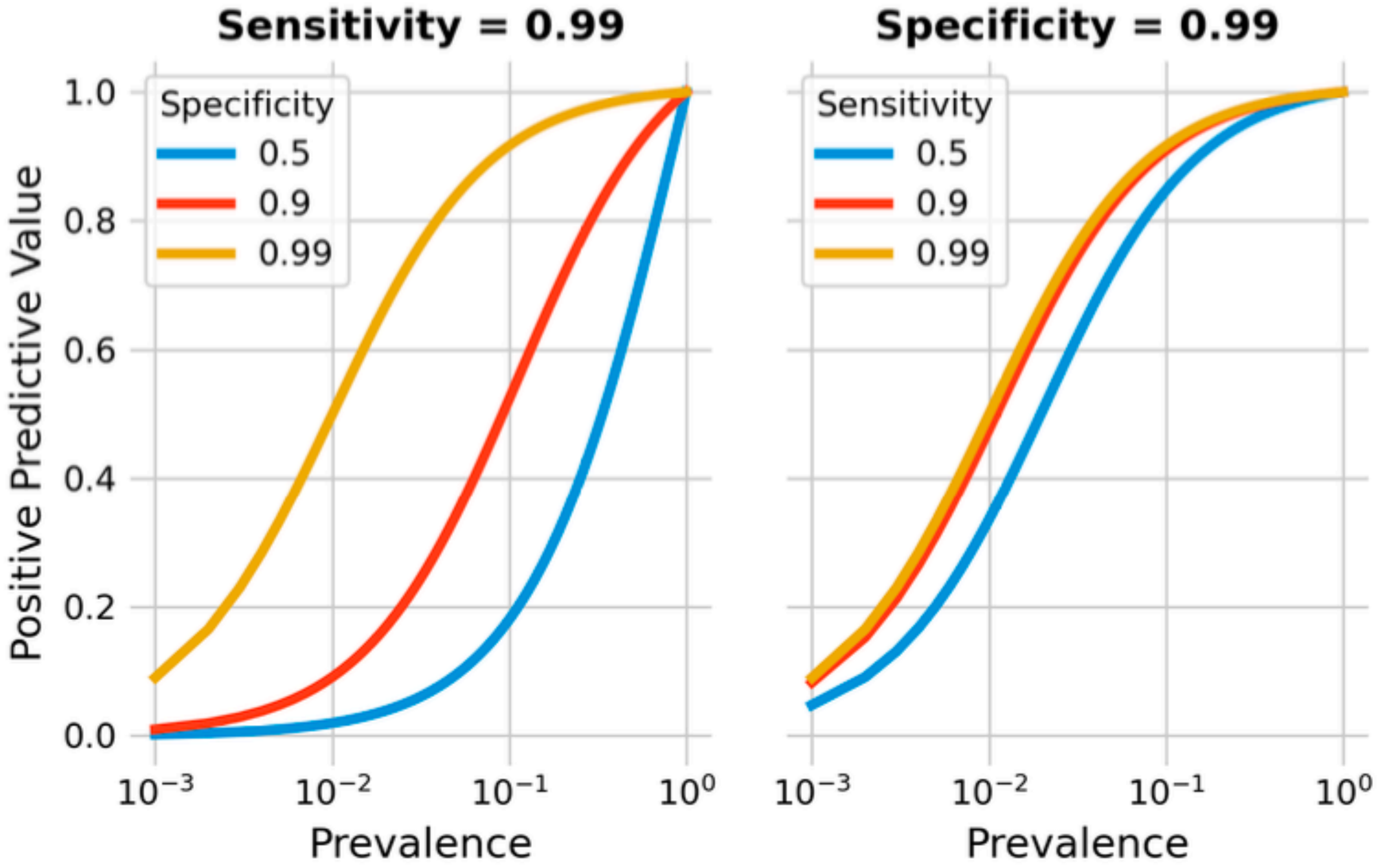
$$P(D \mid T+) = \frac{\textbf{Sensitivity} * \textbf{Prevalence}}{\textbf{Sensitivity} * \textbf{Prevalence} + \textbf{1-Specificity} * \textbf{1-Prevalence}}$$

$$P(D \mid T+) = 0.085$$

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

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

$$LR+ = \frac{\textbf{sensitivity}}{1 - \textbf{specificity}}$$

Negative likelihood ratio

$$LR- = \frac{P(T- \mid D)}{P(T- \mid \neg D)}$$

$$LR- = \frac{1 - \textbf{sensitivity}}{\textbf{specificity}}$$

Odds

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

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

Likelihood ratios

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

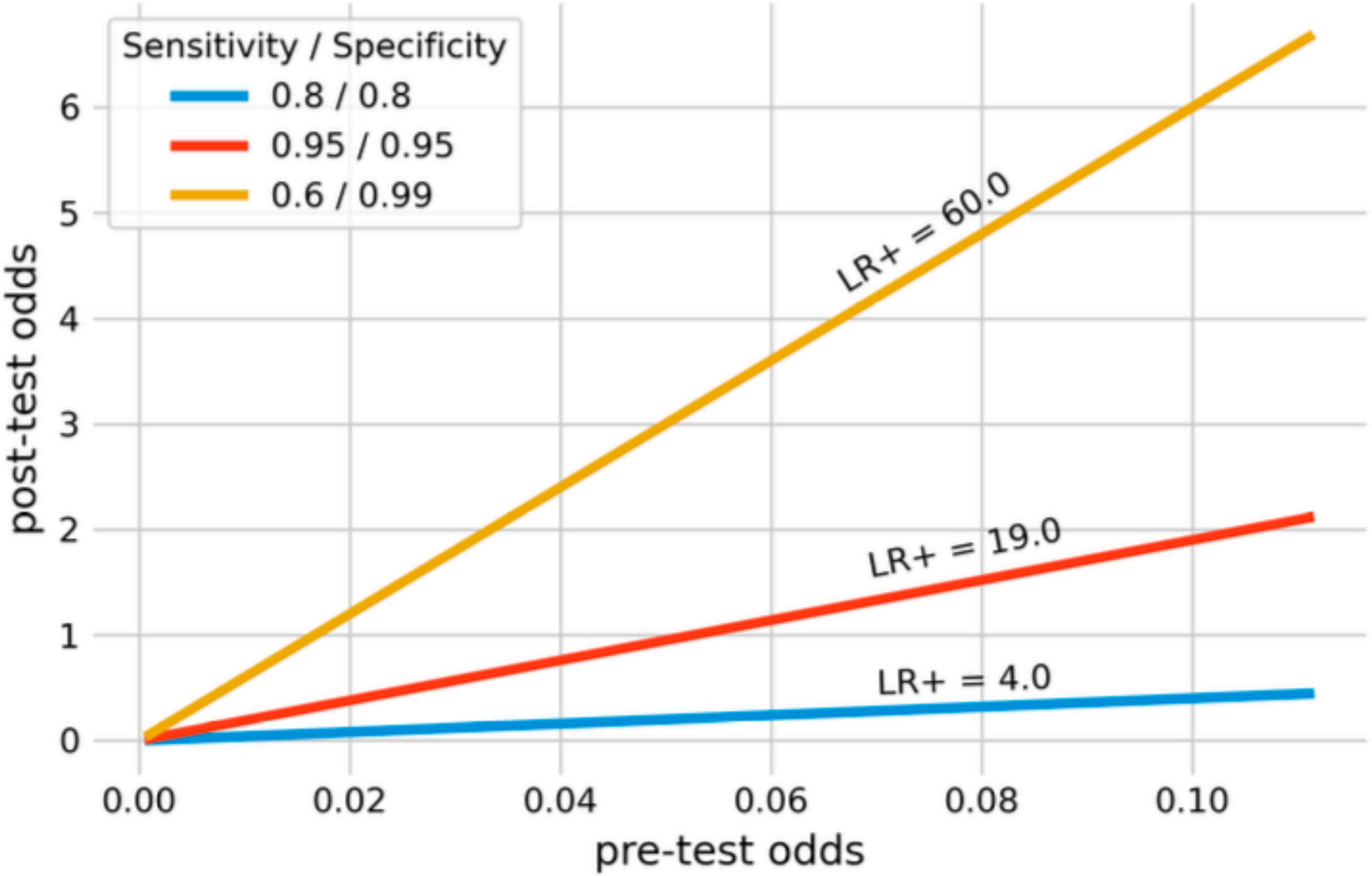
$$\textbf{Post-test odds} = \textbf{likelihood ratio} \times \textbf{pre-test odds}$$

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

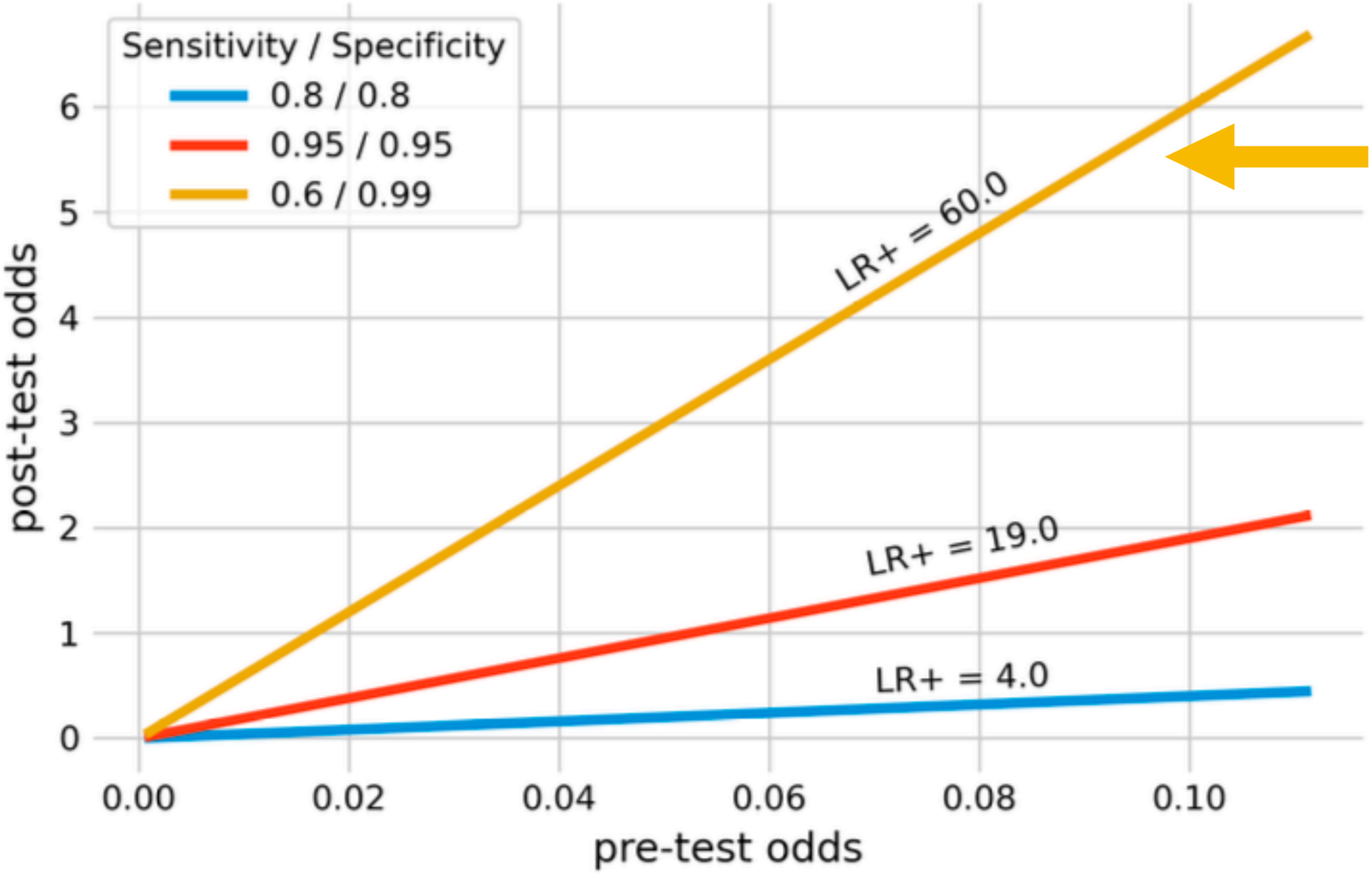
This depends only on the test

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