Diagnostic tests

Research Skill II

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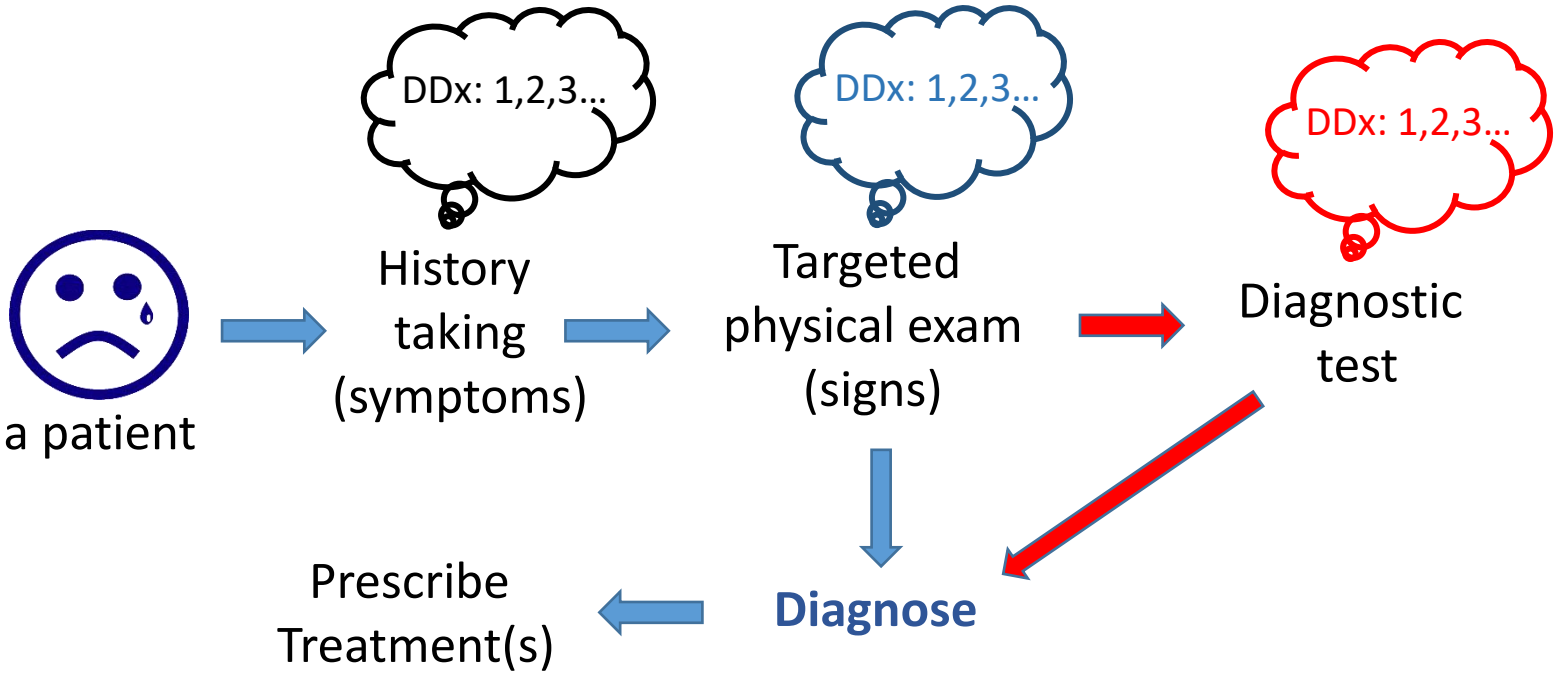
Typical steps in taking care a patient



DDx = Differential diagnoses

Diagnostic test

- A diagnostic test is a procedure performed to confirm, or determine the presence of disease in an individual suspected of having the disease
- Diagnostic tests provide doctors with needed information to come up with proper diagnosis.
- Selection of proper diagnostic tests and correct interpretation of the results is necessary for the accuracy of the diagnosis

Forms of diagnostic tests

- **Laboratories:** CBC, U/A, Blood sugar, lipid profile, tumor markers, serology tests, ECG, etc.
- **Imaging procedures:** X-rays, CT, MRI, Ultrasound, etc.
- **List of criteria (questionnaire) :** Apgar score, Glasgow coma scale, AUDIT, MMSE, etc.

Reduction of complexity of data

- Raw data can be Nominal, Ordinal, Discrete, or Continuous
- Data usually be reduced to nominal dichotomous variable in order to easier interpret and use.
  - e.g., disease/no disease, normal/abnormal, positive/negative
- It is done by determining the cutoff value.
  - e.g., PS $\geq$ 140 mm.Hg. or PD $\geq$ 90 mm.Hg. = Hypertension
- Sometimes reduced to ordinal variables

Estimated GFR For Staging Chronic Renal Disease

Stage	GFR mL/min/1.73m^2	Description	Colour representation in graph
1	More than 90	Slight kidney damage with normal or increased GFR	
2	60-89	Mild decrease in kidney function	
3	30-59	Moderate decrease in kidney function	
4	15-29	Severe decrease in kidney function	
5	Less than 15	End-stage kidney failure	

The Gold Standard test

- The best diagnostic test for particular condition is called **gold standard test**.
- It is used to determine whether the patient really suffers from the disease or not.
- Gold standard tests are usually complex, expensive, and may harm the patients.

Examples of gold standard test

Target Disorder	Gold Standard	Diagnostic test
Breast cancer	Excisional biopsy	Breast MRI
Coronary stenosis	Angiography	Electrocardiogram
Pulmonary Tuberculosis	Sputum culture	AFB stain
Strep throat	Throat culture	Centor clinical criteria
HIV infection	Western blot	ELISA, Latex agglutination

The Gold Standard test

- The best diagnostic test for particular condition is called **gold standard test**.
- It is used to determine whether the patient really suffers from the disease or not.
- Gold standard tests are usually complex, expensive, and may harm the patients.
- Therefore, other diagnostic tests are used instead in real life clinical practices.
- The characteristics of these diagnostic tests are then compared to the gold standard tests.

Accuracy of a diagnostic test

- Diagnostic tests usually not provide the results that 100% correct.
- 4 possible interpretations of the test results
  - True positive: disease present & test positive
  - True negative: disease absent & test negative
  - False positive: disease absent & test positive
  - False negative: disease present & test negative
- Accuracy of a diagnostic test is the proportion of accurate results out of all results.

Association between test results and disease

		Disease (gold standard)	
		Present	Absent
Test	Positive	True positive	False positive
	Negative	False negative	True negative

Sensitivity

- The proportion of patients with disease who test positive.
- The percentage of sick people who are correctly identified as having the condition
- The diagnostic test with high sensitivity won't miss the diagnosis (low false negative)
- Sensitivity = Probability of true positive

  ~ Power

  ~ 1 - type II error

Specificity

- The proportion of patients without disease who test negative
- The percentage of healthy people who are correctly identified as not having the condition
- The diagnostic test with high specificity won't missed diagnose healthy person as sick person (low false positive)
- Specificity = Probability of true negative
  = 1 - type 1 error

Sensitivity and Specificity

		Disease		
		Present	Absent	
Test	Positive	a	b	a+b
	Negative	c	d	c+d
		a+c	b+d	a+b+c +d

Sensitivity = a / a+c
Specificity = d / b+d

Accuracy = a+d / a+b+c+d

Example: results of new test and gold standard test on diagnosis of Dengue hemorrhagic fever

		Gold standard test		รวม
		+	-	
New test	+	250	100	350
	-	50	600	650
Total		300	700	1,000

Sensitivity = a / a+c = 250 / 300 = 0.83 = 83%

Specificity = d / b+d = 600 / 700 = 0.86 = 86%

Accuracy = a+d / a+b+c+d = 850 / 1,000 = 0.85 = 85%

How to choose a proper diagnostic test

- Choose high sensitivity test:
  - In early steps of the diagnosis
  - To eliminate suspected diseases (**negative** high sensitivity test rule out the disease)
  - In severe but treatable disease (don’t want to miss the diagnosis)

How to choose a proper diagnostic test

- Choose high specificity test:
  - In later steps of the diagnosis
  - To confirm the diagnosis (**positive** high specificity test confirm the disease)
  - In severe untreatable disease
  - In case false positive would
    - cost a lot of money for treatment
    - affect the patient psychologically or socially

Sensitivity and specific of diagnostic tests are usually fixed

Alere™ Determine™ HIV–1/2 Ag/Ab Combo

INTENDED USE

The sensitivity of Alere Determine™ HIV-1/2 Ag/Ab Combo for serum specimens was estimated using 926 true HIV-1 positives (903 known positives and 23 true positives identified from the high risk population) (see Table 6). Of these, 925 tested Reactive using Alere Determine™ HIV-1/2 Ag/Ab Combo (902 known positive and 23 high risk). Alere Determine™ HIV-1/2 Ag/Ab Combo gave false Nonreactive results for one specimen (known positive). The estimated sensitivity of Alere Determine™ HIV-1/2 Ag/Ab Combo for serum specimens in these studies was 925/926 = 99.9% (95% confidence interval 99.4 to 100.0%).

Table 6: Detection of HIV-1 Antibodies and/or p24 Antigen in Serum Specimens from Individuals Known to be Infected with HIV-1 and at High Risk for Infection with HIV-1

True Status	Alere Determine™ HIV-1/2 Ag/Ab Combo		
	Reactive	Nonreactive	Total
Positive[1]	925	1	926
Negative	7[2]	625	632
Total	932	626	1558

Predictive Value

- When the results are already come out, sensitivity and specificity are no longer useful.
- What the doctor wants to know now is the probability/chance that the result is correct.
  - Positive predictive value (PPV): the proportion of patients with positive tests who have disease
  - Negative predictive value (NPV): the proportion of patients with negative tests who do not have disease

Predictive Value of a Test Result

		Disease		
		Present	Absent	
Test	Positive	a	b	a+b
	Negative	c	d	c+d
		a+c	b+d	a+b+c +d

Positive Predictive Value (PPV) = a / a+b

Negative Predictive Value (NPV) = d / c+d

Example: results of new test and gold standard test on diagnosis of Dengue hemorrhagic fever

		Gold standard test		รวม
		+	-	
New test	+	250	100	350
	-	50	600	650
total		300	700	1,000

PPV = a / a+b = 250 / 350 = 0.71 = 71%

NPV = c / c+d = 600 / 650 = 0.92 = 92%

Predictive Value and Prevalence

- Predictive value varies according to the prevalence of disease in the population.
  - If the prevalence increase: PPV will be increase and NPV will be decrease
  - If the prevalence decrease: NPV will be increase and PPV will be decrease
- Sensitivity and specificity are not affected by prevalence.

Low prevalence

		Disease		
		OGTT +	OGTT -	
Urine sugar	+ ve	90	90	180
	- ve	10	810	820
		100	900	1,000

Sensitivity	90/100	= 90%
Specificity	810/900	= 90%
Accuracy	(90+810)/1000	= 90%
Prevalence	(90+10)/1000	= 10%
PPV	90/180	= 50%
NPV	810/820	= 98.8%

High prevalence

		Disease		
		OGTT +	OGTT -	
Urine sugar	+ ve	450	50	500
	- ve	50	450	500
		500	500	1,000

Sensitivity	450/500	= 90%
Specificity	450/500	= 90%
Accuracy	(450+450)/1000	= 90%
Prevalence	(450+50)/1000	= 50%
PPV	450/500	= 90%
NPV	450/500	= 90%

Likelihood ratio (LR)

"How likely that a given test result would be expected in a patient who have the disease compared to how likely that a given test result would be expected in a patient who do not have the disease"

Positive likelihood ratio (LR+)

- LR+ = Probability of a person who has the disease testing positive divided by the probability of a person who does not have the disease testing positive.

$$LR+ = \frac{\text{Sensitivity}}{1 - \text{specificity}}$$

Good LR+ if > 10

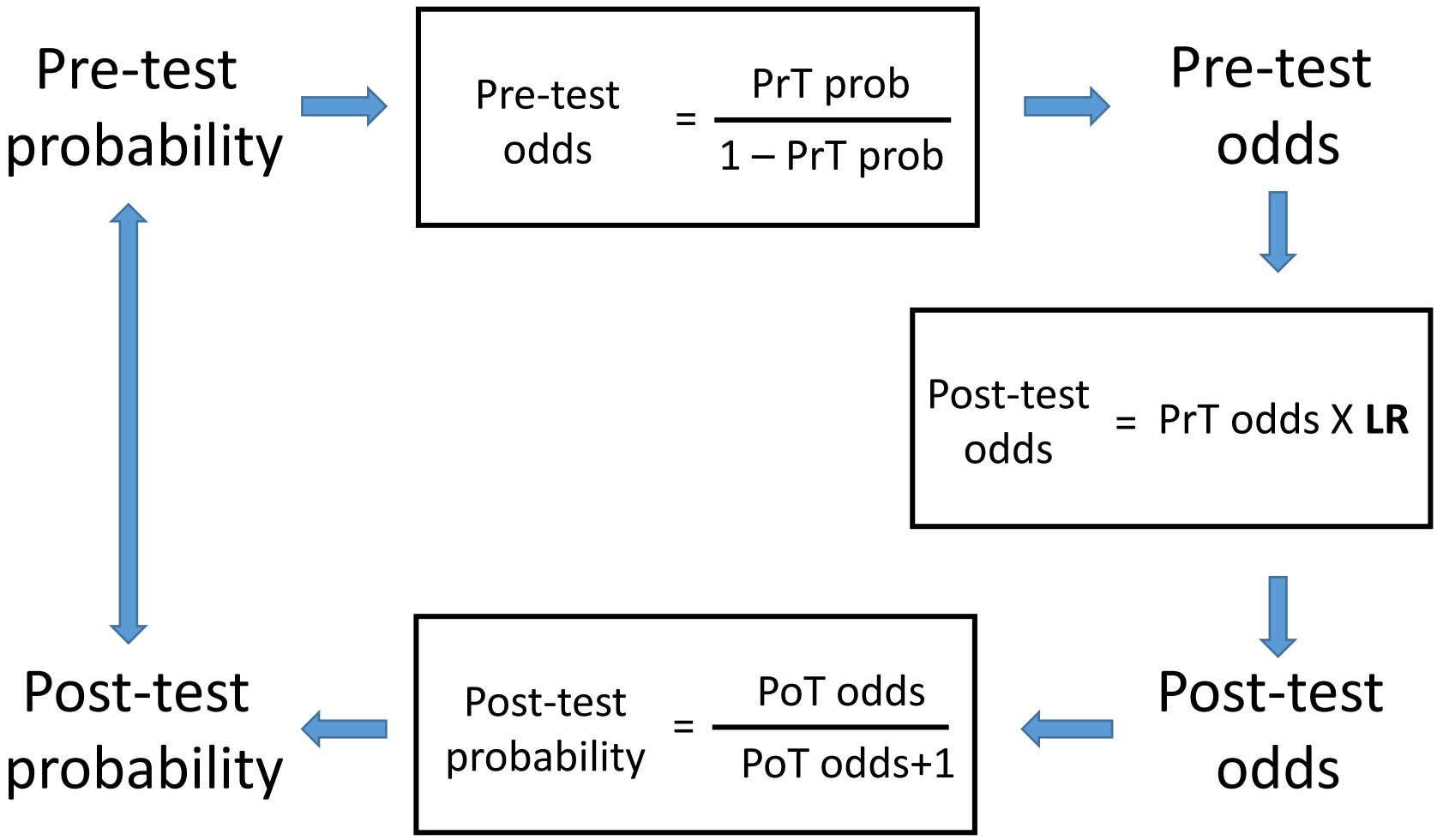
Negative likelihood ratio (LR-)

- LR- = Probability of a person who has the disease testing negative divided by the probability of a person who does not have the disease testing negative.

$$LR- = \frac{1 - \text{Sensitivity}}{\text{Specificity}}$$

Good LR- if < 0.1

Application of LR



Application of LR+

Serum ferritin and iron deficiency anemia

If the patient's chance of iron deficiency anaemia prior to doing the serum ferritin was 50%

Pre-test odds = Pre-test probability / (1 – Pre-test probability)
= 0.5 / (1-0.5) = 1

If the sensitivity of serum ferritin of 60 mmol/l = 90 % and specificity = 85 %

LR+ = sensitivity / (1-specificity) = 0.90/(1-0.85) = 6

Post-test odds = pre-test odds * LR+ = 1*6 = 6

Post-test probability = post test odds / (1 + post test odds) = 6 / (6 + 1)
= 86 %

The post-test probability of the patient having iron deficiency anaemia is increased from 50 % to 86 % with **positive** serum ferritin test

Application of LR-

Serum ferritin and iron deficiency anemia

If the patient's chance of iron deficiency anaemia prior to doing the serum ferritin was 50-50

Pre-test odds = Pre-test probability / (1 – Pre-test probability)
= 0.5 / (1-0.5) = 1

If the sensitivity of serum ferritin of 60 mmol/l = 90 % and specificity = 85 %

LR- = (1-sensitivity) / spec = (1-0.90/(0.85) = 0.17

Post-test odds = pre-test odds * LR- = 1*0.17 = 0.17

Post-test probability = post test odds / (1+post test odds) = 0.17 / (0.17 + 1)
= 8.5 %

The post-test probability of the patient having iron deficiency anaemia is decreased from 50 % to 8.5 % with **negative** serum ferritin test

Aortic dissection: high risk clinical features

Case-control study: patients >18y, acute atraumatic truncal pain

Cases n=194, controls n=776

Tearing/ripping pain

Sens 13.6%, Spec 99.7%
LR- 0.87, LR+ 42.07

New murmur

Sens 20.6%, Spec 97.8%
LR- 0.81, LR+ 9.41

Pulse deficit

Sens 20.6%, Spec 99.3%
LR- 0.8, LR+ 31.14

Chest Xray*

Sens 52.4%, Spec 94.9%
LR- 0.5, LR+ 10.23
Widened mediastinum
/absent aortic notch

Hypotension

Sens 22.2%, Spec 98.7%
LR- 0.79, LR+ 17.2

Abrupt-Onset pain

Sens 95.9%, Spec 61.3%
LR- 0.07, LR+ 2.48

Ohle 2018 doi 10.1111/acem.13356

Aortic dissection: high-risk clinical features.
Credit: Kirsty Challen, B.Sc., MBChB, MRes, Ph.D., Lancashire Teaching Hospitals, United Kingdom.

AEM Academic Emergency Medicine

Multiple tests

- **Parallel testing** (Simultaneous testing)
- **Serial testing** (Sequential testing)

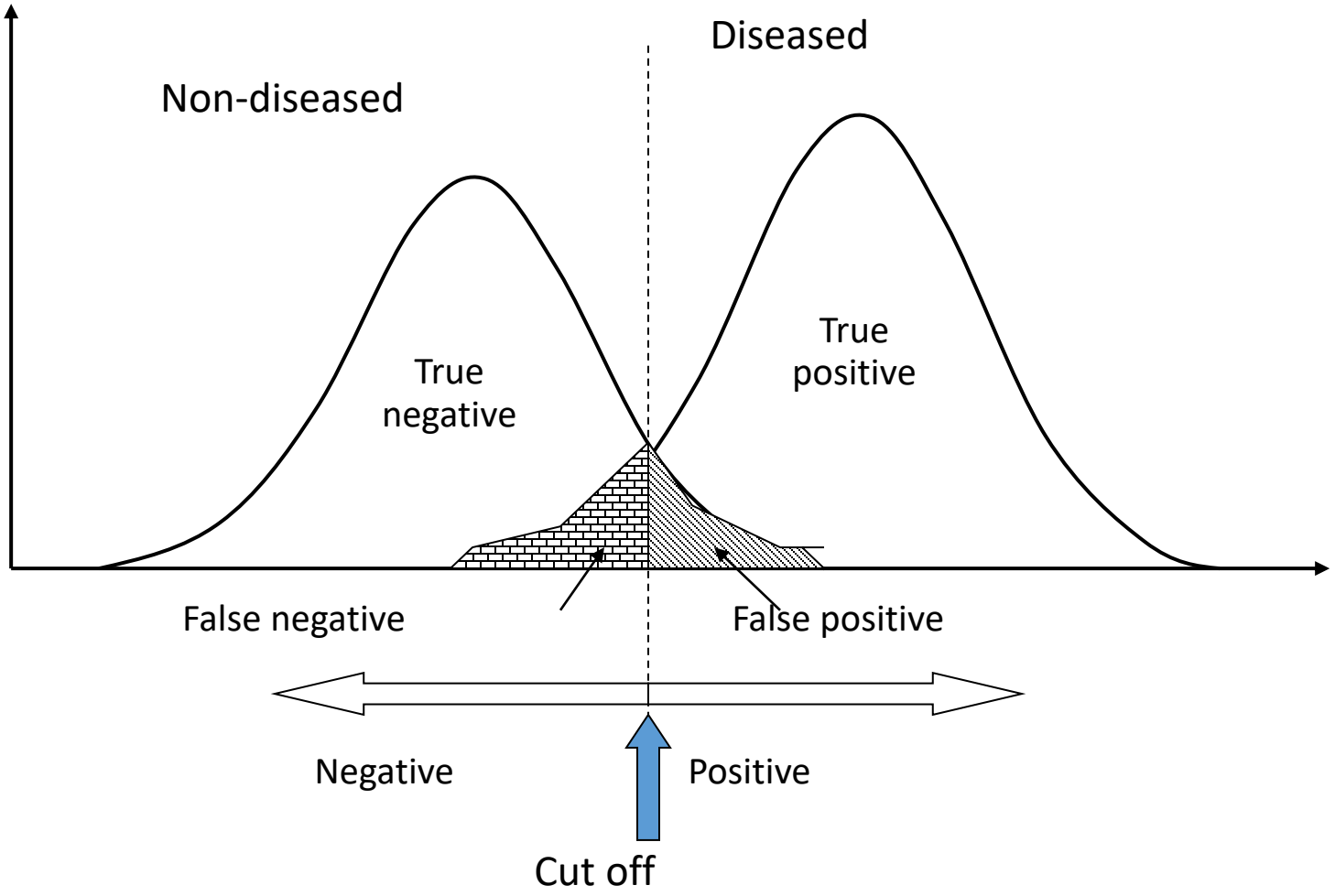
Parallel testing (Simultaneous testing)

- Use and interpret at least two diagnostic tests at the same time
- Conclude as positive if either one of the test or both test give positive results
- Used this algorithm when need a prompt result such as at emergency room or at mobile clinic
- **increase Sensitivity and NPV decrease Specificity and PPV**

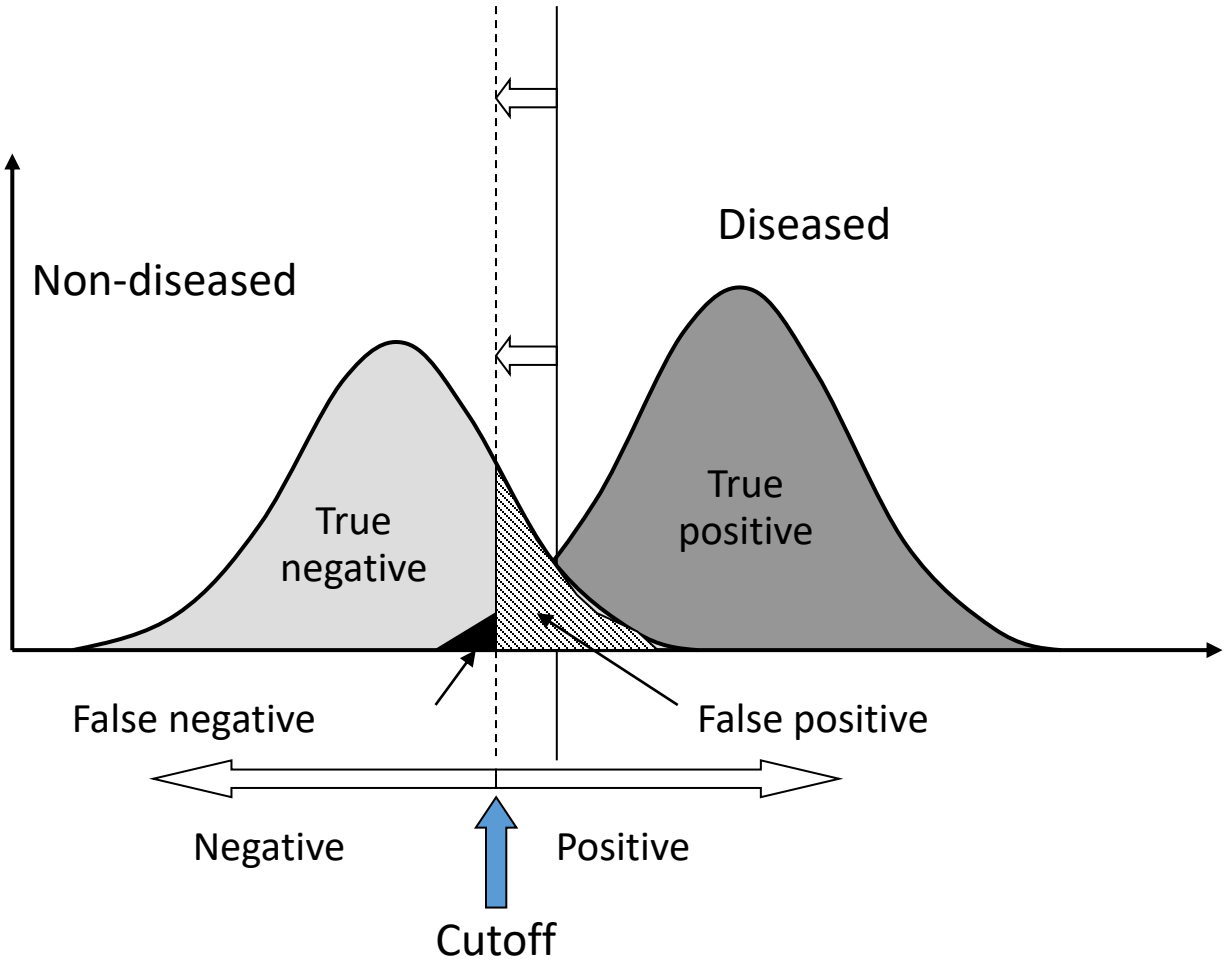
Serial testing (Sequential testing)

- Use diagnostic test one at a time, use the second one only when the first test is positive
- Conclude as positive only when both diagnostic tests give positive results
- Use this algorithm when not in rush and want to make sure with the diagnosis that the patient has disease
- **increase Specificity and PPV** **decrease Sensitivity and NPV**

Determining Cut off value for continuous lab results

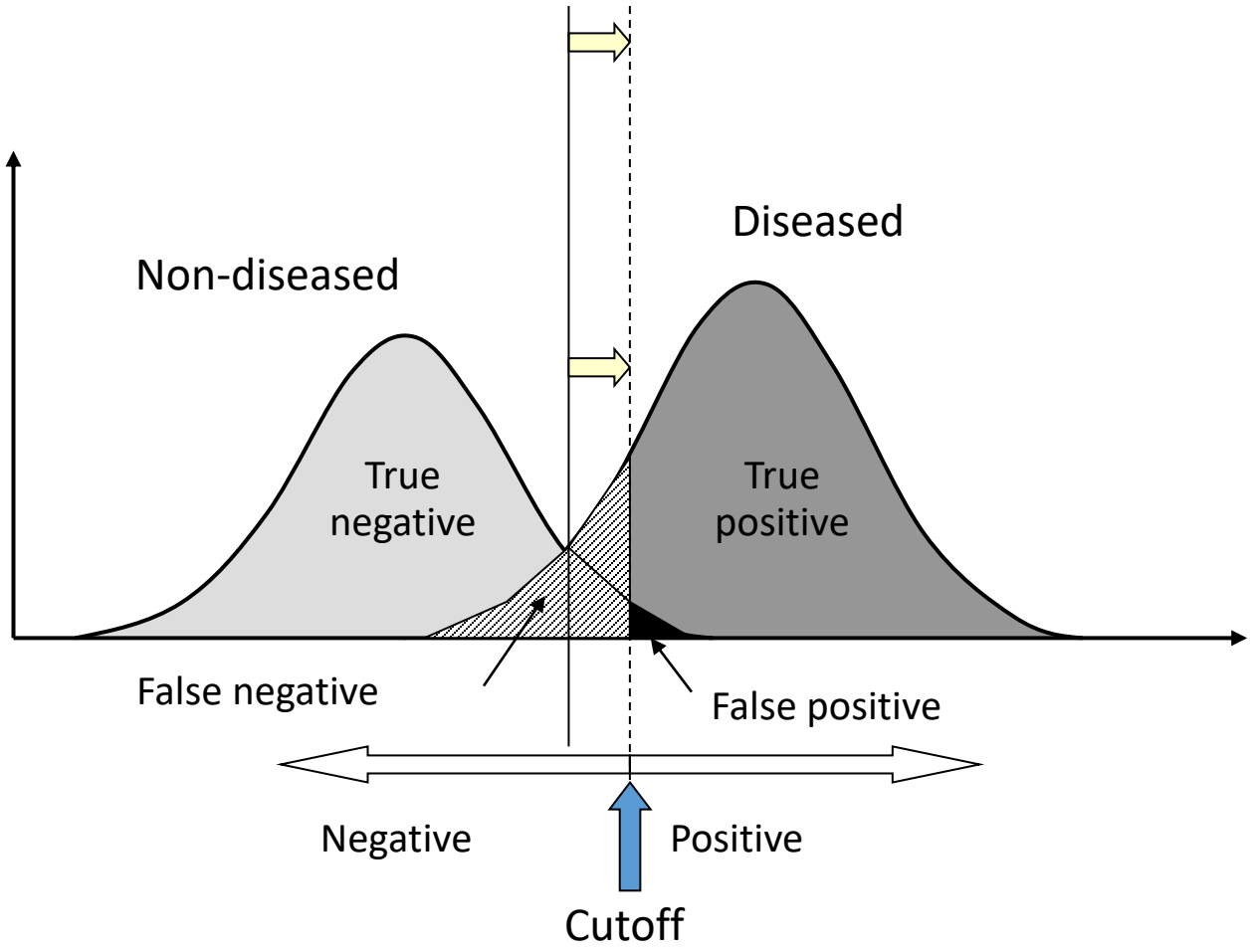


Move cutoff point to the left



Increase sensitivity / Decrease specificity

Move cutoff point to the right



Increase specificity / Decrease sensitivity

Receiver operator characteristic (ROC) curve

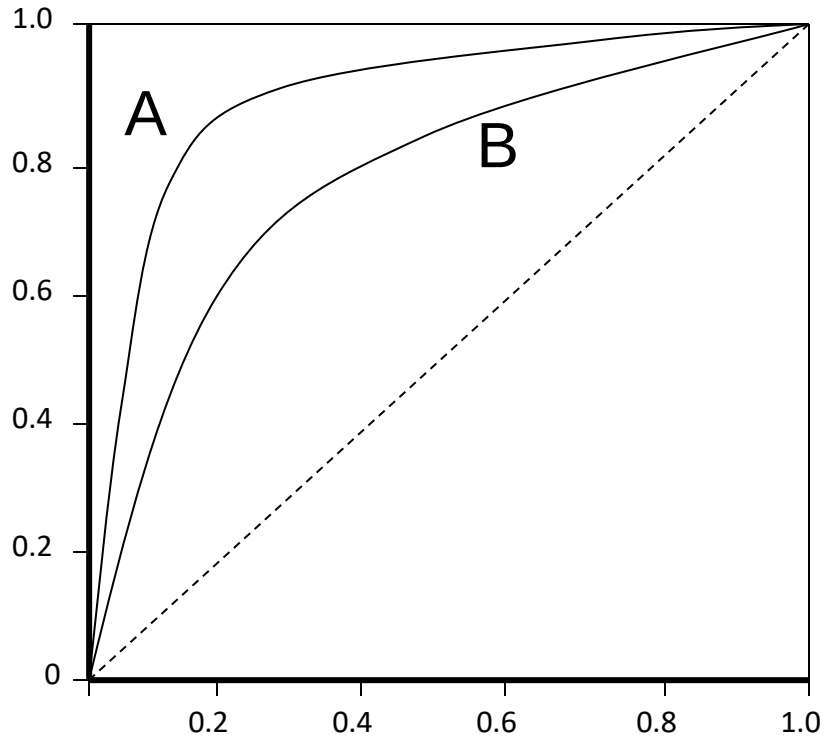
- A diagram used to determine proper cutoff point for a diagnostic test
- Plot sensitivity (True positive rate) and 1- specificity (False positive rate) that the diagnostic test could provide at different cut off in Y axis and X axis respectively
- Area under graph shows probability that the diagnostic test could provide accurate results.
- Better diagnostic test would have larger area under graph and its peak would be nearer to the left upper corner.

Receiver operator characteristic (ROC) curve

- Generally, the cut off on the graph which is nearest to the upper left corner would be the best cut off
- Move cut off to the right along the X axis will give a diagnostic test with higher sensitivity
- Move cut off to the left along the X axis will give a diagnostic test with higher specificity

Receiver operator characteristic (ROC) curve

Sensitivity
(True positive rate)



1-specificity
(False positive rate)