بسم الله الرحمن الرحيم

Clinical epidemiology:

Definition :

It is " the science concerned with counting clinical events occurring in human beings, and it uses epidemiologic methods to carry out and analyze the counts obtained ". The basic purpose of clinical epidemiology is to develop and apply methods of clinical observations which will lead to valid clinical conclusions.

Clinical epidemiology has 3 main fields :

A . Diagnosis.

B . Treatment.

C . Prognosis.

A clinical observation is valid if it corresponds to the true state in the person observed. Validity (صلاحية)

Two types of validity:

Internal validity

External validity

The internal validity is the degree to which the results of an observation are correct for the patients being studied.

The external validity (generalizability) is the degree to which the results of an observation are correct in other settings.

A . Diagnosis.

A diagnostic test is valid if it detects most people with the target disorder and excludes most people without the disorder. A positive test usually indicates that the disorder is present and a negative test usually indicates that the disorder is absent .
The performance of diagnostic indicators is assessed by epidemiologic methods to determine the:

Validity & Reliability.

Validity (صلاحية) **of a test expresses the magnitude of real values measured.**

e.g. when you measure the length of a child how much it is telling the real length?

Reliability (مصداقية) **expresses the consistency of the measurement if it is repeated many times. e.g. if you measure the systolic blood pressure it was 125 mm mercury if you repeat it another time or if two examiners measure it at the same time, would it be the same or will be other value?**

VALIDITY is assessed by determining :

Sensitivity, specificity, (+)ve and (-)ve predictive values and (+)ve and (-)ve likelihood ratios

The assessment of a diagnostic test could be the result of the components of the diagnosis; i.e.:

*** A symptom**

*** A sign**

*** A laboratory test**

Any one of theses indicators could be diagnostic by itself or one of them added to another.

The Test: A test is anything that produces evidence from a patient at any stage in the clinical process, based on which a different clinical course will be taken depending on the different possible test outcomes (positive or negative, normal or abnormal, present or absent, high or low, ...).

From the clinical epidemiology perspective, the following are examples of a "test": history taking (presence or absence of a component), clinical exam results (presence or absence of a sign), imaging findings (presence or absence of a feature on a radiograph), or response to therapy (as anticipated or not). Few if any tests in medicine are perfect; that is, produce results that can always be interpreted with absolute certainty on every patient to which the test is applied.

"Gold Standard" (Reference, Definitive) Test:

" The tests and procedures necessary to definitively establish to a high level of certainty the presence or absence of the disease in an individual" .

e.g. of gold standard tests : biopsy for cancer , endoscopy for duodenal ulcer , culture for bacterial infections.

-Some disease have no gold standard test like psychosis .

Some people have no disease but by these tests result is (+)ve. The result is called **false +ve** .

When the result of the test is (-)ve but gold standard says there is disease, it is called **false –ve** .

When the people is diseased and the result is +ve it is called **true +ve** , when there is no disease and the result is –ve called **true –ve** .

A 2x2 table:

Diagnostic indicator	Disease (according to gold standard)		Total
	Present	Absent	
(+)ve	a True +ve	b False +ve	a+b
(-)ve	c False –ve	d True –ve	c+d
Total	a+c	b+d	a+b+c +d

e.g.
In duodenal ulcer, we use endoscope (as a gold standard) and we assess the validity of barium test in diagnosing duodenal ulcer :-

Barium meal	Duodenal ulcer(according to endoscopy)		Total
	Present	Absent	
(+)ve	a True +ve	b False +ve	a+b
(-)ve	c False –ve	d True –ve	c+d
Total	a+c	b+d	a+b+c+d

SENSITIVITY OF THE TEST:

Is the ability of the test to detect those who are test (+)ve among all diseased persons.

$$\text{*Sensitivity rate} = \frac{\text{True (+) ve}}{\text{Total persons with disease}} \times 100\%$$

$$\text{Sensitivity rate} = \frac{a}{a + c} \times 100\%$$

The sensitivity is the true positive rate True (+)ve rate of the test.

SPECIFICITY OF THE TEST

Is the ability of the test to detect those who are test (-)ve among all who are not diseased persons.

$$\text{*Specificity rate} = \frac{\text{True (-) ve}}{\text{Total persons without disease}} \times 100\%$$

$$\text{Specificity rate} = \frac{d}{b + d} \times 100\%$$

The Specificity is the true negative rate True (-)ve rate of the test

PREDECTIVE VALUES :-

They are the ability of the test to uncover those who have(or have not) disease among all those with a positive (or negative) test results.

Positive predictive value :

$$\text{Positive predictive value (PPV)} = \frac{\text{True positive}}{\text{All those with positive test results}} \times 100$$

It is the proportion of the diseased individuals among all those with a positive test result. It is also probability in % that individual with positive test result has the disease .

Negative predictive value :

$$\text{Negative predictive value (NPV)} = \frac{\text{True Negative}}{\text{All those with negative test results}} \times 100$$

It is the proportion of the diseased-free individuals among all those with a negative test result . It is also probability in % that an individual with negative test result doesn't have the disease .

Note :-

Sensitivity and specificity are pre-test criteria , while the positive and negative predictive values are post-test criteria and these are considered when the test level (result) are available .

The prevalence of disease = (a + c) / (a +b +c +d)

Example In validating the use of chest X-rays (CXR) for the diagnosis of pulmonary TB. Against what can its accuracy be compared? The gold standard for diagnosing TB is the culture of Mycob TB from the sputum. To validate the use of CXR, we would have to select a certain number of TB suspects and perform both CXRs & sputum cultures on them. Let us say 200 people were screened. Interpret the results given in the table:

Chest X-rays for TB	Sputum Culture for TB		Total
	Positive	Negative	
(+)ve	80(a)	70(b)	150 (a+b)
(-)ve	20(c)	30(d)	50(c+d)
Total	100 (a + c)	100 (b + d)	200 a+b+c+d

Using the 2x2 table, we could compute the sensitivity, specificity, positive

predictive value and the negative predictive value of the test.

Sensitivity: Sensitivity is the proportion of truly non-diseased person who are identified as diseased by the diagnostic test.

It is :a/ (a + c) = 80/ (80 + 20) = 80 %. 80% of all those with TB are successfully picked up by chest X-rays.

Specificity: Specificity is the proportion of truly non-diseased person who are so identified by the test.

it is : d/ (b + d) = 30 / (30 + 70) = 30%. 30% of all those without TB are picked up by chest X-rays as negative.

The positive predictive value of a test is the probability of a test positive person truly having the disease.

It is : a / (a + b) = 80 / (80 + 70) = 53% . In other words, only about half of those who are CXR positive are likely to have TB.

The negative predictive value of a test is the probability of a test negative person truly not having the disease.

It is :d / (c + d) = 30 /(30+20)=60%In other words, 60% of those who are CXR negative are likely to be sputum culture negative

What determines predictive value?

In general, the sensitivity and specificity of a test do not vary with the prevalence of the disease. Predictive values, however, are dependent on the disease prevalence.

Higher the prevalence of the disease, greater the(+)predictive values. Thus the usefulness of a test depends on the setting in which it is used. A test which is good in a clinical setting may be completely useless in a community setting (if used as a screening test) because prevalence rates tend to be lower in the community.

As can be seen by the TB example, CXR is very sensitive (true positivity rate is very high), but it has a very poor specificity (true negativity rate is very low).

The very poor specificity rate makes CXR invalid as a diagnostic tool in TB diagnosis.

- **The more sensitive the test, the better its – ve predictive value.**

- **The more specific the test, the better its + ve predictive value.**

It is important that all new tests should be validated by comparison

against a test which is established and considered a gold standard.

Diagnostic tests are generally not 100% accurate. If the sensitivity is very

high, the specificity tends to be low.

Likelihood Ratios:

The newer and more powerful approach to evaluating new diagnostic tests is based on the concept of likelihood ratios.

Basically the concept likelihood ratios takes into account both the pre-test probability of a disease (this is reflected by the baseline prevalence of the disease) and the post-test probability (this is reflected by the positive and negative predictive values of the test).

$$\text{Positive likelihood ratio} = \frac{a}{a + c} \text{ divided by } \frac{b}{b + d}$$

i.e. true (+) ve rate / false (+) ve rate

$$\text{Negative likelihood ratio} = \frac{c}{a + c} \text{ divided by } \frac{d}{b + d}$$

i.e. false (-) ve rate / true (-) ve rate

An ideal test of 100% sensitivity and 100% specificity does not exist. We generally have to choose from the available range of tests with varying sensitivities and specificities.

<u>How does one choose the right test?</u>

If very important not to miss a disease which is serious and potentially treatable (cancer, for example), it would be better to use a test which has greater sensitivity. One would like to pick up as many cases as possible doing this test. On the other hand, if making a positive diagnosis would result in much worry, stigma (HIV, for example) or cost, then it would be better to use a test which has high specificity.

Uses of a sensitive test:

A sensitive test is used :

1- when there is a harmful effect of false negative results , e.g. missing

a case of meningitis as a case of flue like disease is fatal in emergency

clinics.

2- to rule out differential diagnoses e.g. tuberculin test is used to rule out

a suspected TB case.(if negative we are sure there is no TB)

3- low frequency of a disease in screening process.

Uses of a specific test:

A specific test is used :

1- when there is a harmful effect of false positive results , e.g. wrong
diagnosis of leukemia is very harmful emotionally and financially to a person with mild disease like iron deficiency anemia. Mostly useful in non-emergency situations.

2- to rule in differential diagnoses e.g. endoscopic exam after barium meal
testing is used to rule out a suspected gastric cancer case.(if positive
confirms the diagnosis).

Most useful result of a highly sensitive test is when it is negative.

Most useful result of a highly specific test is when it is positive.

Accuracy: (الدقة)

Is the degree to which, on average, a test represents the true value (that is, it is unbiased).

$$\text{Accuracy rate} = \frac{a + d}{a + b + c + d} \times 100\%$$

Reliability: (المصداقية)

The degree to which a test yields the same results when repeated under identical conditions on identical specimens. How good is a procedure when applied by different users. The degree to which different clinicians (observers) applying the procedure classify diseased individuals into the same diagnostic, prognostic or treatment categories.

Sources of Variability

1. **Biological variation : because the measures are not constant over time**

   e.g. Bd Pressure, blood sugar, pulse rate, resp. rate

2. **Instrumental variation : due to calibration & standardization.**

3. **Intra-observer variability : among the same person. As in reading**

   an X-ray which is not a 100% fixed.

4. **Inter-observer variability : variation among different people.**

Screening of diseases (استكشاف المرض)

Screening :- it is the process by which a specified diagnostic test is

applied in order to sort out a group of people into two categories :-

1.those who probably have the disease .

2.those whop probably have not the disease .

Screening of the disease is usually done to detect the disease process early in order to minimize its complications and consequences .

The population being tested is comprised predominately of normal individuals that have not been identified as possibly having a clinical case of the disease. Thus, the probability that such an individual has the disease is the prevalence of the disease in the population being screened.

Because the disease manifestations are likely minimal in affected individuals, the spectrum of disease is generally less severe in a screening than in a diagnostic setting.

Criteria of good screening test

The screening test should have the following characteristics:-

***It has high validity in term of sensitivity and specificity .**

***The test should be simple, and it should be accomplished easily and quickly . Sample of urine, prick of a needle**

***The test should be applicable and acceptable to a large no. of individuals .**

***The test should be a safe procedure and not producing harm to the individual being rested , also should be non-invasive.**

***Should be with beneficial effect for the people .**

***There should be detectable preclinical stage .**

e.g. for diseases which are suitable for screening :- essential hypertension , hypercholesterolemia , mammography for breast cancer.

Evaluation Of Screening Programs

1. Feasibility: determined by :

a- Acceptability (by the no. of people who accept to undergo the test).

b- Cost-effectiveness (cost per detected case).

c-provision of follow up

d-Yield : no. of cases detected by a screening test in a screening
program , it is measured by the Predictive Values (+ ve and – ve PV)

2. Effectiveness :

It is impact of the screening program in decreasing mortality and morbidity from the disease. It is determined by:

a- Severity of the disease at the time of diagnosis. (differences between screen detected cases vs symptoms detected cases).

b- Comparison of cause-specific mortality rate among screen detected vs symptom detected. So if we detect a significant difference in the screening then it is effective'.

e.g. Breast cancer mortality rates at different times after the start of the follow-up among women receiving screening (mammography) and controls.

Types of Screening

1. Mass Screening : Screening the whole population. e.g. Hypertension, diabetes .. .etc

2. Multiple or Multiphase Screening. Using multiple screening tests at the same time as in Parallel & Series.

3. Targeted Screening : Screening of groups with specific exposures either:

a-Occupational : lead factory workers should be checked for the level of lead in blood. b-Environmental : as in the Chernobyl Nuclear disaster.

4. Case-Finding (Opportunistic Screening): Screening of patients who consult a health facility for other purposes e.g. Malaria blood film.

Criteria For Instituting A screening program :

*** Disease :**
- serious
- high prevalence of preclinical stage
- natural history understood.
-long period between first signs & overt of the disease .

***Diagnostic test:**
-sensitive & specific
- simple & cheap
- safe& acceptable
-reliable .

***Diagnosis & Treatment:**
-facilities are adequate
-effective, acceptable & safe treatment available.

MULTIPLE TESTING (COMBINATION OF TESTS)

It is the procedure by which we increase the validity criteria by applying

two or more tests in a special sequence and consideration .

There are two ways of combination :-

1. Combination in parallel :

2. Combination in series :

1. Combination in series :Sequential (Two-stage) Testing

In sequential or two-stage screening, a less expensive, less invasive, or less uncomfortable test is generally performed first, and those who screen positive are recalled for further testing with a more expensive, more invasive, or more uncomfortable test, which may have greater sensitivity and specificity. It is hoped that bringing back for further testing only those who screen positive will reduce the problem of false positives.

the combination is considered to be positive (+ve) when all the tests are +ve , and considered to be –ve when any one of them is –ve . Serial tests should be used when rapid assessment is not necessary or when some of the available tests are expensive or risky . All tests must have positive results for the sequence to be considered positive for the disease. A conclusion: in this combination , the specificity will be increased because rarely normal persons considered to be ill, but the sensitivity will be decreased .

Assume: Disease Prevalence = 5%,

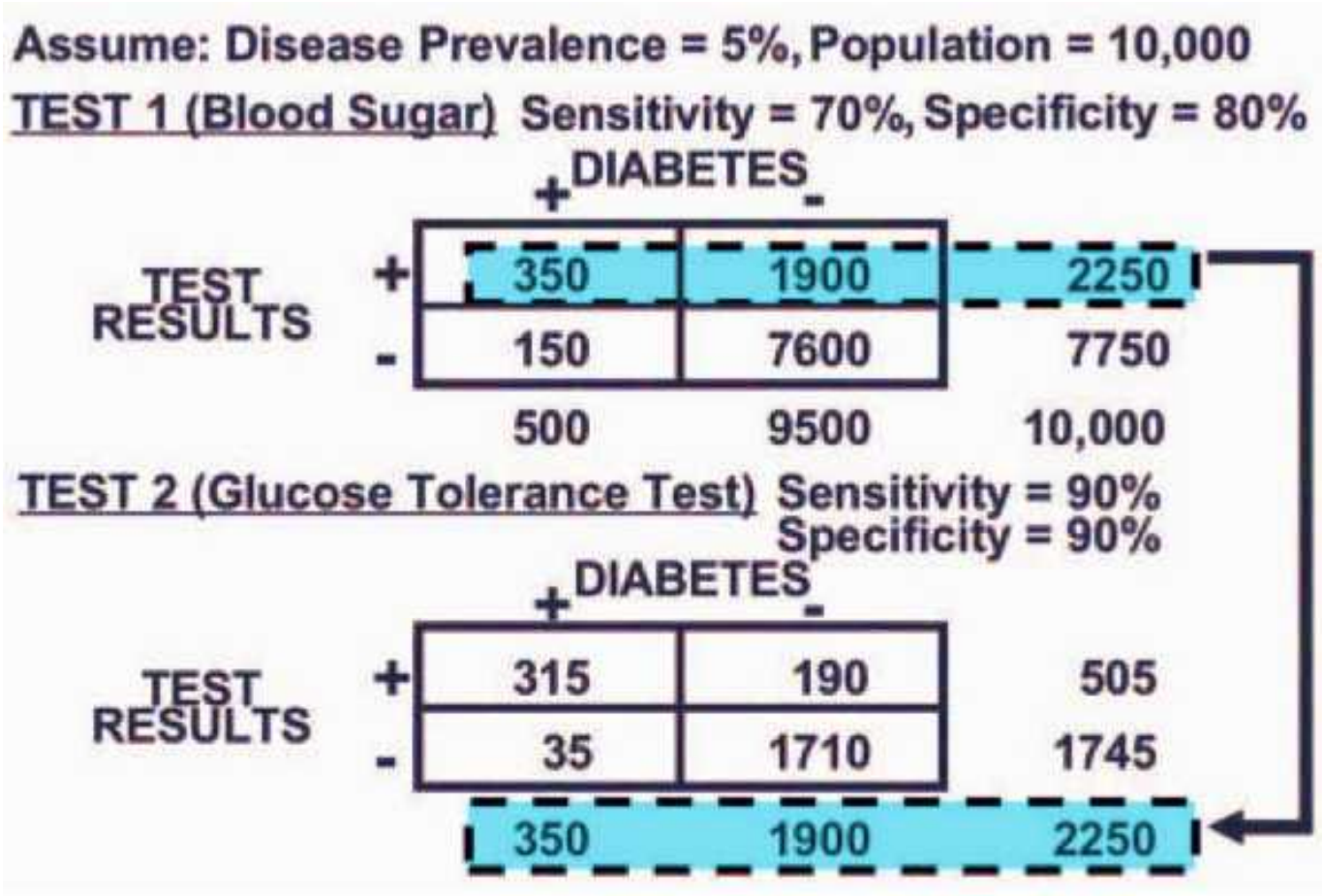
Population = 10,000

TEST 1 (Blood Sugar)

Sensitivity = 70%

Specificity = 80%

		DIABETES +	DIABETES -	
TEST RESULTS	+	350	1900	2250
	-	150	7600	7750
		500	9500	10,000



315/500 = 63% ***net sensitivity***

a total of 7,600 + 1,710 = 9,310of the 9,500 non diabetics were correctly called negative

9,310/9,500 = 98% *net specificity*

2. **Combination in parallel :Simultaneous Testing**

We apply two or more tests at the same time , if any one of them is +ve then the combination set is considered to be +ve . And it is considered –ve when all the tests are –ve . Should be used when rabid assessment is needed (as in emergencies) or for routine physical examination . A conclusion in this combination , the sensitivity will increase but the specificity will be decreased , because every (+) ve is considered as patient and ill while he is normal .

In a population of 1,000 people, the prevalence of a disease is 20%. Therefore, 200 people have the disease, but we do not know who they are. In order to identify the 200 people who have this disease, we screen this population of 1,000 using 2 tests for this disease, test A and test B, at the same time. Let us assume that the sensitivity and specificity of the two tests are as follows:

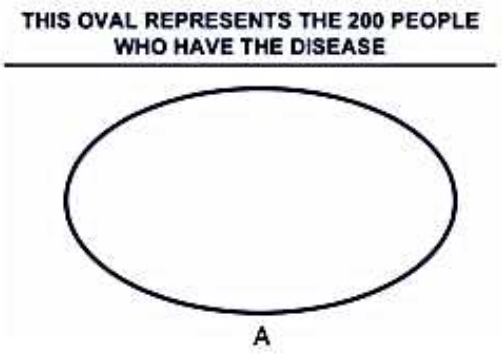
Test A	Test B
Sensitivity = 80%	Sensitivity = 90%
Specificity = 60%	Specificity = 90%

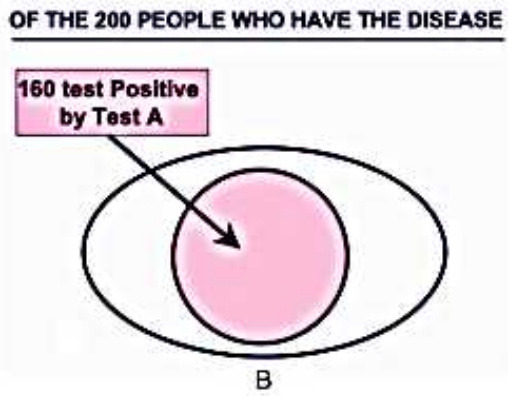
TABLE 5-3 -- Results of Screening with Test A

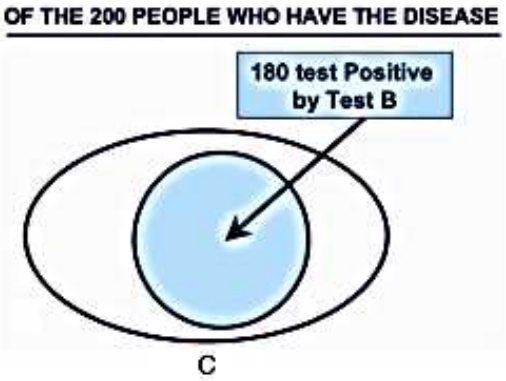
	POPULATION	
Results of Screening	**Disease**	**No Disease**
Positive	160	320
Negative	40	480
Total	200	800
	Sensitivity = 80%	
	Specificity = 60%	

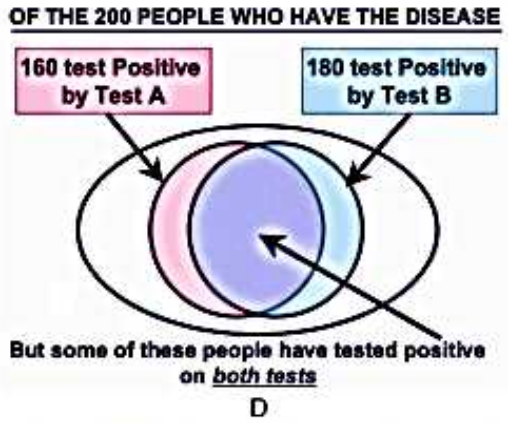
TABLE 5-4 -- Results of Screening with Test B

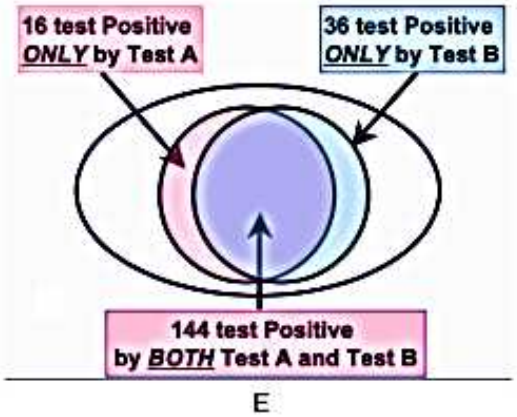
	POPULATION	
Results of Screening	**Disease**	**No Disease**
Positive	180	80
Negative	20	720
Total	200	800
	Sensitivity = 90%	
	Specificity = 90%	

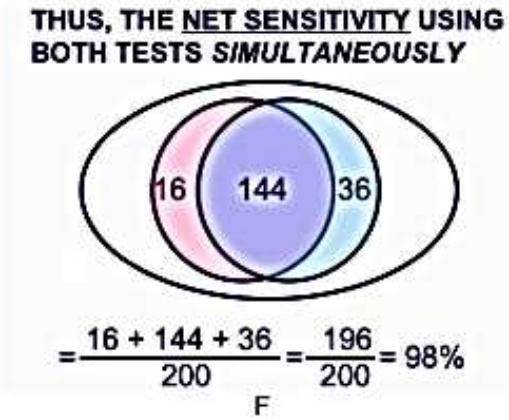












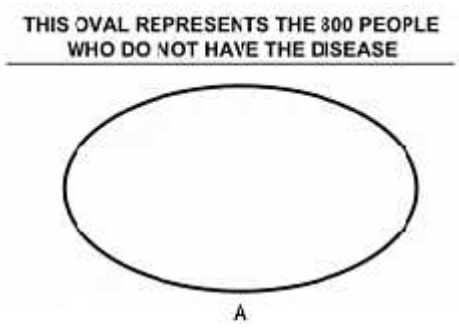
Net Specificity Using Two Simultaneous Tests

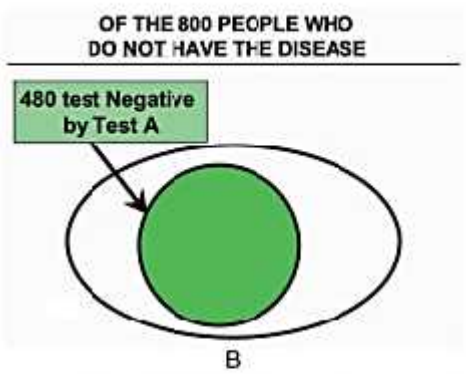
TABLE 5-5 -- Results of Screening with Test A

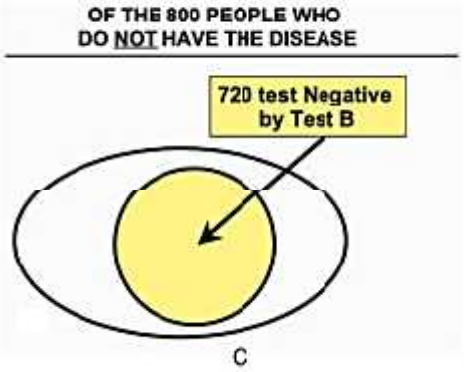
	POPULATION	
Results of Screening	**Disease**	**No Disease**
Positive	160	320
Negative	40	480
Total	200	800
	Sensitivity = 80%	
	Specificity = 60%	

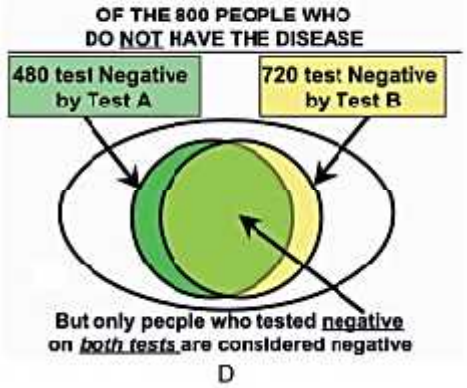
TABLE 5-6 -- Results of Screening with Test B

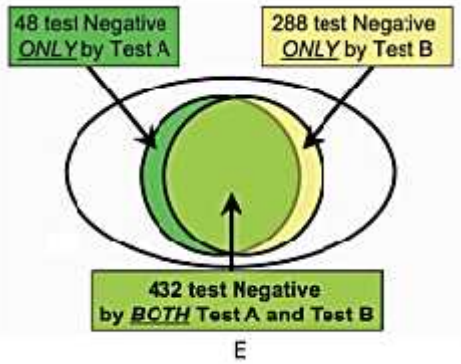
	POPULATION	
Results of Screening	**Disease**	**No Disease**
Positive	180	80
Negative	20	720
Total	200	800
	Sensitivity = 90%	
	Specificity = 90%	

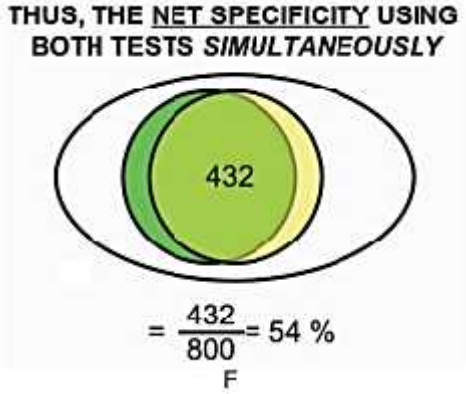












Tests done In :	Test1	Test2	Interpretation
	+	+	+
	+	-	+
Parallel	-	+	+
	-	-	-
	+	+	+
Series	+	-	-
	-	Not necessary	-

“Schematic Diagram of the Combination of Screening tests”

B .Treatment :

The effectiveness of treatment is measured through :

1. **Efficacy(theoretic effectiveness) is a measure in a situation in which all conditions are controlled to maximize the effect of the agent.**

2. **Effectiveness(practical effectiveness)**

Efficacy is established by restricting patients in a study (those who will

cooperate fully) with certain method of treatment under ideal conditions.

The method will do a better performance is more efficacious.

Effectiveness: (If we administer the agent in a "real-life" situation,is it effective?) is established by offering a treatment or a programme to patients and study the outcome under practical conditions.

Efficiency:
If an agent is shown to be effective, what is the cost benefit ratio? (not only money, but also discomfort)

C . Prognosis:

When people they have many questions about their illness ? how it will

affect them ? is it dangerous? Could it be fatal? Will there be pain?

Prognosis is a prediction of the future course of disease following its

onset.

It can be measured in several ways e.g. case fatality rate or probability of

survival(5 year survival rate)